INTERNATIONAL JOURNAL OF

Cardiovascular SCIENCES

Volume 33 - Number 1 | January / February | ISSN 2359-4802 | ISSN online 2359-5647

INTERNATIONAL JOURNAL OF
Cardiovascular
SCIENCES

Call for Papers

International Journal of Cardiovascular Sciences - Special Issue

Translational Cardiology

Special Invited Editor - Protásio Lemos da Luz

The term "translational research" first appeared in PubMed in 1993. By 2019 one can find 4,677 articles containing the words "cardiology" and "translational" as keywords. The main mission of translational cardiology is to assist basic science turn into cardiovascular therapy. In order to make the nomenclature clearer the Medical Institute created the main statements of the research: T1: transfer of new knowledge of disease mechanisms to new tests, treatments, and prevention methods, and T2: translation of clinical results to practice and to decision making. Thus, T1 is patient-focused research while T2 is population-focused.

This Special Issue of the International Journal of Cardiovascular Sciences is dedicated to the new and flourishing evidence of the impact of basic science in the practice of cardiology. Novel studies of mechanisms, interventions, and populations are of particular interest and encouraged to advance our understanding and development of translational cardiology for society's improved cardiovascular health. Further, it will provide an opportunity for researchers and practitioners to engage with new up-to-date and ever-evolving practices. Researchers are invited to submit original and review manuscripts on translational cardiovascular sciences.

Special Invited Editor – **Protásio Lemos da Luz**
Editor-in-Chief - **Claudio Tinoco Mesquita**

Authors can submit their manuscripts through the Manuscript Tracking System. To submit your paper click here:

SCHOLARONE™

Submission Deadline	**February 28th, 2020**
Publication Date	**June 2020**

INTERNATIONAL JOURNAL OF
Cardiovascular
SCIENCES

SUMARY

INTERNATIONAL JOURNAL OF

Cardiovascular SCIENCES

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

Exterior

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

BIENNIUM BOARD 2020/2021

SOCIEDADE BRASILEIRA DE CARDIOLOGIA/ BRAZILIAN SOCIETY OF CARDIOLOGY

President
Marcelo Antônio Cartaxo Queiroga Lopes

Vice President
Celso Amodeo

Financial Director
Ricardo Mourilhe Rocha

Scientific Director
Fernando Bacal

Managing Director
Olga Ferreira de Souza

Service Quality Director
Sílvio Henrique Barberato

Communication Director
Harry Corrêa Filho

Information Technology Director
Leandro Ioschpe Zimerman

Governmental Relations Director
Nasser Sarkis Simão

State and Regional Relations Director
João David de Souza Neto

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

Director of Specialized Departments
Andréa Araujo Brandão

Research Director
David de Pádua Brasil

Coordinator of Science, Technology and Innovation
Ludhmila Abrahão Hajjar

Coordinator of Continued Medical Education
Brivaldo Markman Filho

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

Coordinator of Compliance and Transparency
Marcelo Matos Cascudo

Coordinator of Strategic Affairs
Hélio Roque Figueira

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

Editor do IJCS
Claudio Tinoco Mesquita

Coordinator of the University of the Heart
Evandro Tinoco Mesquita

Coordinator of Standards and Guidelines
Paulo Ricardo Avancini Caramori

PRESIDENTS OF STATE AND REGIONAL BRAZILIAN SOCIETIES OF CARDIOLOGY

SBC/AL – Carlos Romerio Costa Ferro

SBC/AM – Kátia do Nascimento Couceiro

SBC/BA – Gilson Soares Feitosa Filho

SBC/CE – Gentil Barreira de Aguiar Filho

SBC/DF – Alexandra Oliveira de Mesquita

SBC/ES – Tatiane Mascarenhas Santiago Emerich

SBC/GO – Leonardo Sara da Silva

SBC/MA – Mauro José Mello Fonseca

SBC/MG – Henrique Patrus Mundim Pena

SBC/MS – Gabriel Doreto Rodrigues

SBC/MT – Marcos de Thadeu Tenuta Junior

SBC/NNE – Nivaldo Menezes Filgueiras Filho

SBC/PA – Dilma do Socorro Moraes de Souza

SBC/PB – Lenine Angelo Alves Silva

SBC/PE – Fernando Ribeiro de Moraes Neto

SBC/PI – Luiz Bezerra Neto

SBC/PR – Raul DAurea Mora Junior

SBC/RN – Maria Sanali Moura de Oliveira Paiva

SBC/SC – Amberson Vieira de Assis

SBC/SE – Eryca Vanessa Santos de Jesus

SOCERGS – Mario Wiehe

SOCERJ – Wolney de Andrade Martins

SOCERON – Daniel Ferreira Mugrabi

SOCESP – João Fernando Monteiro Ferreira

PRESIDENTS OF DEPARTAMENTS AND STUDY GROUPS

SBC/DA – Antonio Carlos Palandri Chagas

SBC/DCC – Bruno Caramelli

SBC/DCC/CP – Klebia Magalhães Pereira Castello Branco

SBC/DCM – Celi Marques Santos

SBC/DECAGE – Izo Helber

SBC/DEIC – Evandro Tinoco Mesquita

SBC/DERC – Gabriel Leo Blacher Grossman

SBC/DFCVR – Antoinette Oliveira Blackman

SBC/DHA – Audes Diógenes de Magalhães Feitosa

SBC/DIC – Carlos Eduardo Rochitte

SBCCV – Eduardo Augusto Victor Rocha

SOBRAC – Ricardo Alkmim Teixeira

SBHCI – Ricardo Alves da Costa

DCC/GAPO – Danielle Menosi Gualandro

DCC/GECETI – Luiz Bezerra Neto

DCC/GECO – Roberto Kalil Filho

DCC/GEMCA – Roberto Esporcatte

DCC/GERTC – Adriano Camargo de Castro Carneiro

DEIC/GEICPED – Estela Azeka

DEIC/GEMIC – Marcus Vinicius Simões

DERC/GECESP – Clea Simone Sabino de Souza Colombo

DERC/GECN – Lara Cristiane Terra Ferreira Carreira

DERC/GERCPM – Carlos Alberto Cordeiro Hossri

GECIP – Marcelo Luiz da Silva Bandeira

GEECG – Carlos Alberto Pastore

DCC/GETA – Carlos Vicente Serrano Junior

DCC/GECRA – Sandra Marques e Silva

Volume 33, Nº 1, January/February 2019
Indexing: Index Medicus Latino-Americano – LILACS and Scientific Electronic Library Online - SciELO

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

Editorial Production
SBC - Gerência Científica - Núcleo de Publicações

Desktop Publishing and Graphic Design
Primita Assessoria Produções e Serviços Artísticos

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

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

INTERNATIONAL JOURNAL OF
Cardiovascular
SCIENCES

O International Journal of Cardiovascular Sciences (ISSN 2359-4802)
é editado bimestralmente pela SBC:
Av. Marechal Câmara, 160 - 3º andar - Sala 330
20020-907 • Centro • Rio de Janeiro, RJ • Brasil
Tel.: (21) 3478-2700
e-mail: revistaijcs@cardiol.br
<www.onlineijcs.org>

International Journal of Cardiovascular Sciences. 2020;33(1):1-2

EDITORIAL

Coarctation of the Aorta: Its Importance for Pediatricians and Cardiologists

Gesmar Volga Haddad Herdy

Universidade Federal Fluminense, Niterói, RJ - Brazil

Coarctation of the aorta is a congenital defect that affects 5-8% of live births, with different degrees of severity. It may remain unnoticed throughout childhood or, in contrast, progress to heart failure and cardiogenic shock.[1-3] The most common location for coarctation of the aorta is near the ductal remnant and left subclavian artery.[4]

The main clinical signs of coarctation of the aorta are heart murmur, diminished pulses in lower extremities, arterial hypertension, left ventricular hypertrophy. It is commonly associated with a bicuspid aortic valve. In adults, in addition to hypertension with increased systemic vascular resistance, retinal arteriolar abnormality and lower extremity claudication may also occur.[5]

The first surgical treatment for coarctation of the aorta was proposed by Craford in 1945 at Mayo Clinic.[6] The surgery remains the gold standard treatment, with good results. In 1982, an endovascular treatment was proposed in an experimental study, the balloon angioplasty.[7] Since then, several reports have shown positive results of this less invasive technique, including in children. A long-term follow-up is mandatory, due to potential complications after open surgeries and angioplasties, such as recurrent coarctation, aneurysm or pseudoaneurysm and valve dysfunction.[5,8] In a multicenter study, Erben et al.[5] reported the cases of 93 adult patients undergoing endovascular treatment. Thirty-two patients were newly diagnosed, 61 were endovascular reintervention (50 recurrent coarctation and 11 aneurysmal degeneration). Endovascular treatment was mostly performed using balloon-expandable and stent grafts. Freedom from reintervention at 5 years was 85%.[5] Between 1946 and 2005, 819 patients with isolated coarctation of the aorta underwent surgical repair at the Mayo Clinic.[9] End-to-end anastomosis (n = 632) was performed in most cases, followed by other techniques including patch angioplasty and interposition grafting. Long-term survival was decreased, and many patients required reoperation, especially when the primary operative repair was performed in patients younger than 20 years old. Children younger than 9 years of age at repair had lower complications.[9]

In Brazil, Coimbra et al.[10] reported the results of angioplasty in 10 children aged 51.1 ± 30.8 years weighing less than 25 kg, eight of them with recurrent coarctation and two with native coarctation. Angioplasty was performed using stents or balloons.[10] In the study by Chamié et al.,[11] covered stent implantation was performed in 14 patients (adults and children), 10 with native coarctation and four as a second device. Patients were followed for 51.7 ± 29.8 months, without complications or deaths.[11]

In a study conducted in Australia involving 140 children with coarctation of aorta, 112 underwent surgical or endovascular repair as follows: end-to-end anastomosis (n = 43), subclavian flap aortoplasty (n = 28), percutaneous repair (n = 6) and interposition tube grafts (n = 4). During a follow-up of 20 years, patients with end-to-end repair had lower rates of recoarctation or aneurysms.[12] In a Canadian study, Rodes-Cabau et al.[13] compared surgical repair versus transcatheter treatment in 80 patients of different ages, including children under one year of age. Fifty patients underwent percutaneous angioplasty, with stent implantation in 19 of them. The other 30 patients underwent surgical repair. Angioplasty reduced morbidity and hospitalization length but was associated with a higher rate of reintervention and aneurysm occurrence.[13]

Keywords

Heart Defects, Congenital; Aortic Coarctation/surgery; Shock, Cardiogenic; Hypetrophy, Left Ventricular.

Mailing Address: Gesmar Volga Haddad Herdy
Universidade Federal Fluminense - Hospital Universitário Antonio Pedro - Rua Marques de Paraná, 303. Postal Code: 24033-900, Niterói, Rio de Janeiro, RJ - Brazil
E-mail: gesmarhaddad@gmail.com

DOI: https://doi.org/10.36660/ijcs.20190159

The American Heart Association statement recommends that percutaneous transcatheter interventions should be performed, whenever possible, for treatment of congenital repair, including coarctation and recoarctation, regardless of age.[14]

The study by Barreto et al.,[15] published in this issue, describes the outcome of 72 patients with coarctation of aorta, who underwent end-to-end anastomosis in a single center, during a 20-year follow-up. Surgery was performed at different ages (0.1-27 years). In a mean follow-up of 5.8 years, the most common complications were arterial hypertension (39.2%) and recoarctation (28.6%).[15] These results were similar to previous studies on surgical repair of coarctation of the aorta.

In conclusion, pediatricians should carefully examine newborns and infants for the presence of decreased pulse in lower extremities and systolic heart murmurs, which are the main signs of malformation at this age, for an early diagnosis of coarctation of aorta. In adolescents and adults, treatment for this condition may lead to higher morbidity and recoarctation rates. Studies have shown that a lifetime follow-up of patients with coarctation of the aorta undergoing open surgical treatment or percutaneous intervention is strongly recommended to treat potential complications. In general, although percutaneous procedure is associated with lower morbidity and lower hospitalization length, it may lead to more complications.

References

1. Anderson RH, Baeker EJ, Mackartney FJ, Rigby ML, Shinebourne EA, Tynan M, editores. Paediatric cardiology. 2nd ed. London: Churchil Lingstone; 2002.
2. Samanek M, Voriskova M. Congenital heart disease among 815.569 children born between 1980-1990 and their 15 year survival. a prospective Bohemian survival study. Pediatr Cardiol. 1999;20(6):411-7.
3. Herdy GVH, Araújo e Silva. Cardiopatias congênitas. In: Dutra A. Medicina Neonatal. 2a ed. Rio de Janeiro: Rubio; 2016. p. 116-25.
4. Warnes CA, Williams RC, Bashore TM, Child JS, Connolly HM, Dearani JA, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;52(23):e143-e263.
5. Erben Y, Oderich GS, Verhagen HJM, Witsenburg M, van den Hoven AT, Debus ES, et al. Multicenter experience with endovascular treatment of aortic coarctation in adults. J Vasc Surg. 2019;69(3):671-9.
6. Craford C, Nylin G. Congenital coarctation of the aorta and its surgical treatment. J Cardiovasc Surg. 1945;14:347-61.
7. Lock JE, Niemi T, Burke BA, Einzig S, Castaneda-Zuniga WR. Transcutaneous angioplasty of experimental aortic coarctation. Circulation. 1982;66(6):1280-6.
8. Torok RB, Campbell MJ, Fleming GA, Hill KD. Coarctation of the aorta: management from infancy to adulthood. World J Cardiol. 2015;7(11):765-75.
9. Brown ML, Burkhart HM, Connoly HM, Dearani JA, Cetta F, Li Z, et al. Coarctation of the aorta: lifelong surveillance is mandatory following surgical repair. J Am Coll Cardiol. 2013;62(11):1020-5.
10. Coimbra G, Duarte EV, Kajita LJ, Lemos P, Arrieta R. Aortic coarctation in children weighing less than 25 kg: percutaneous axillary artery approach. Rev Bras Cardiol Invasiva. 2014;22(3):271-4.
11. Chamié F, Chamié D, Simões LCN, Silva RM. Use of covered stents in the treatment of aorta coarctation. Rev Bras Cardiol Invasiva. 2015;23(2):139-44.
12. Choudhary P, Canniffe C, Jackson DJ, Tanous D, Walsh K, Celermajer DS. Late outcome in adults with coarctation of the aorta. Heart. 2015;101(15):1190-5.
13. Rodes-Cabau J, Miró J, Dancea A, Ibrahim R, Piette E, Lapierre C, et al. Comparison of surgical and transcatheter treatment of native coarcation of the aorta in patients ≥ one year old. The Quebec Native Coarctation of the Aorta Study. Am Heart J. 2007;154(1):186-92.
14. Feltes TF, Bacha E, Beekman RH 3rd, Cheatham JP, Feinstein JA, Gomes AS, et al. Indications for cardiac catheterization and intervention in pediatric cardiac disease: a scientific statement from the American Heart Association. Circulation. 2011;123(22):2607-52.
15. Barreto J, Roda J, Germano AW, Damião AP, Quinaglia T. Coarctation of the aorta: a case series from Tertiary Care Hospital. Int J Cardiovasc Sci. 2020;33(1):3-11.

International Journal of Cardiovascular Sciences. 2020;33(1):3-11

ORIGINAL ARTICLE

Coarctation of The Aorta: A Case-Series from a Tertiary Care Hospital

Joaquim Barreto,[1] Juliana Roda,[2] Carlos Wustemberg Germano,[1] Ana Paula Damiano,[1] Thiago Quinaglia[1]

Universidade Estadual de Campinas (UNICAMP),[1] São Paulo, SP - Brazil
Pontifícia Universidade Católica de Campinas (PUC-Camp),[2] São Paulo, SP - Brazil

Abstract

Background: Coarctation of the aorta is a congenital segmental narrowing of the aortic arch with severe hemodynamic repercussions and increased cardiovascular mortality. Early surgical correction and life-time echocardiographic follow-up must be performed to improve prognosis. However, this goal has been challenged by high rates of underdiagnosis, which delay surgical correction, and by recoarctation in up to one third of operated patients.

Objectives: The objectives of this study were: (i) to register the frequency of common clinical signs at diagnosis of coarctation of the aorta; (ii) to describe the course of echocardiographic parameters before and during the follow-up of coartectomized subjects; (iii) to analyze the clinical prognosis of patients according to baseline characteristics, occurrence of recoarctation and associated malformations.

Methods: Case-series of 72 patients coarctectomized between June 1996 and November 2016 in a tertiary care hospital. Clinical, echocardiographic and surgical variables were considered. All patients were submitted to coarctectomy by posterolateral thoracotomy and end-to-end anastomosis. Data were classified as parametric or non-parametric by Kolmogorov-Smirnov test. Parametric data were expressed as mean and standard deviation, and non-parametric data as median and interquartile range. Continuous variables were analyzed using paired t-tests, and categorical variables were compared by chi-square test. For all analysis, a p-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS, version 20.0 (IBM, Chicago, IL, USA).

Results: The mean follow-up time was 5.8 years (range: 0-20 years). At diagnosis, most patients had heart murmur (88%), non-palpable pulse in the lower limbs (50%), left ventricular hypertrophy (78%), and bicuspid aortic valve (33%), with a mean aortic peak gradient of 55 mmHg. After surgical correction, those without recoarctation were less symptomatic (60 vs 4.5%; $p < 0.001$), had lower aortic peak gradient (54 ± 3.8 vs 13 ± 0.8; $p = 0.01$) and left ventricle mass (95 ± 9.2 vs. 63 ± 11; $p = 0.01$), and the most common complications were late hypertension (39.2%), and recoarctation (27.6%). Recoarcted patients did not show improvement of neither clinical nor echocardiographic variables. Age at repair and bicuspid aortic valve groups had comparable results with controls. Surgical procedure was safe; mean time of hospitalization was 10 days and mean surgery time 2.3 hours.

Conclusions: Coarctectomy improves cardiac symptoms and left ventricular hypertrophy, with a slight effect on the incidence of hypertension. Recoarctation occurs in one-third of patients and draws attention for the need of lifelong surveillance by echocardiography. (Int J Cardiovasc Sci. 2020;33(1):3-11)

Keywords: Heart Defects, Congenital; Aortic Coarctation/surgery; Hypertrophy, Left Ventricular; Echocardiography/methods; Hypertension.

Introduction

Coarctation of the aorta (CoA), first described over 200 years ago, has for long been considered as a simple mechanical obstruction caused by a segmental narrowing of the aortic arch.[1] It was only in the last decades that staggering results revealed that, beyond the anatomical malformation, CoA answers for a systemic vasculopathy with irreversible effects on endothelial function, arterial stiffness and left ventricular remodeling.[2-4] As a

Mailing Address: Joaquim Barreto
Rua Denir Dias da Silva, 199. Postal Code: 13092-610, Parque da Hípica, Campinas, São Paulo, SP - Brazil.
E-mail: joaquimbarretoantunes@gmail.com, joaquimbarretoantunes@hotmail.com

DOI: 10.5935/2359-4802.20190067

Manuscript received February 16, 2018; revised manuscript January 19, 2019; accepted January 22, 2019.

result, although resection of the coarcted segment may prevent patients from dying by age of 30, even after this procedure, subjects remain at higher risk of hypertension and premature cardiovascular death.[5,6]

This challenging phenomenon has led to an intense search for predictors of worse prognosis in repaired patients. In this direction, some have claimed that late repair is among the main risk factor for all-cause mortality in subjects undergoing resection of aorta coarctation.[7] Importantly, late correction frequently occurs as a result of an underdiagnosis rate of over 62%, placing CoA as the most frequently misdiagnosed critical congenital heart disease.[8] Besides, recoarctation occurs in one-third of patients, leading to a regression of the benefits of first surgical correction and, often, requiring reintervention. This complication demands a life-long surveillance by regular echocardiography in repaired patients.[5] Finally, hypertension stands as the main complication in repaired subjects, hence representing a known risk factor for cardiovascular disease from an early age, with important long-term repercussions on mortality.[9-11]

In this study, we retrospectively analyzed data of patients operated for CoA at a tertiary care hospital. The main goals of this study were: (i) to register the frequency of common clinical signs at diagnosis; (ii) to describe the course of echocardiographic parameters before and during the follow-up of coartectomized subjects; (iii) to analyze the clinical prognosis of patients according to baseline characteristics, occurrence of recoarctation and associated malformations. A total of 417 patient-years follow-up was studied, revealing hypothesis-generating results.

Materials and methods

Study population

Data were collected from medical records of patients operated for native coarctation of the aorta between June 1996 and November 2016 at the University of Campinas General Hospital (HC-UNICAMP), a tertiary care hospital in Brazil. The last visit to outpatient clinic occurred in November 2016. We compared clinical and echocardiographic data collected at the time of diagnosis and at the last outpatient clinic visit (in November 2016). Diagnosis of coarctation of the aorta was defined as a peak aortic gradient greater than 20 mmHg with compatible clinical history.

Clinical variables

Clinical variables included age, gender, antihypertensive medications and symptoms. Hypertension was defined as the use of antihypertensive drugs. Symptoms were classified according to the New York Heart Association (NYHA) criteria, and all other variables obtained from medical records. During follow-up, recoarctation was defined as a peak descending aorta gradient (DAG) greater than 20 mmHg after successful surgical correction at baseline.

Echocardiographic

Echocardiographic measurements were obtained by trained cardiologists using Vivid S6 (GE Vingmed Ultrasound, Horten, Norway) and EchoPAC version 8.0 (GE Healthcare). The following parameters were considered: left ventricular (LV) end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), posterior wall diastolic thickness (PW), aortic root diameter (ARD), peak DAG, left atrial diameter (LAD) and LV mass (LVM). All variables, except for DAG and ejection fraction (EF), were indexed by body surface calculated by DuBois formula. LV hypertrophy was defined as LV mass values above the 95th percentile for respective age and gender, according to validated guidelines.[12] For comparative purposes, we considered the first echocardiographic test performed before surgical correction as "baseline", and the last echocardiographic examination after surgery as the "last" examination.

Operative technique

Medical registries including operative notes, data on perioperative hemodynamics and complications of all patients operated at our hospital were collected for analysis. In our study, all patients have undergone coartectomy by posterolateral thoracotomy and an end-to-end anastomosis as previously described.[13] Briefly, in this procedure, a left posterolateral thoracotomy is completed with sparing of the serratus anterior muscle in the third to fourth intercostal space. Then, the lung is retracted inferiorly and medially, exposing the aorta which is further mobilized. Then, a proximal clamp is placed at the base of the left subclavian artery or proximal to the carotid bifurcation, and a distal clamp is placed below the second intercostal space. Finally, the narrowed segment is resected, and an end-to-end anastomosis performed.

Complications include injury to adjacent structures, such as the common thoracic duct, leading to chylothorax.[13] Also, paraplegia may occur in 0.5% of cases, especially in those requiring prolonged cross-clamping time or presenting with distal hypotension.[13] Lately, up to one-third of operated patients may develop recoarctation, which worsens the prognosis and require prompt intervention. If uncomplicated, the procedure should take from 2 to 3 hours, with a mean cross-clamping time of 17 minutes.[14]

Missing data

Only data collected from the medical records of our hospital and only tests performed at our institution were considered for analysis. Therefore, patients diagnosed or followed in other centers and referred to the HC-UNICAMP for surgical correction, had missing data and were lost to follow-up. To tackle this issue, data is presented according to the total number of tests available.

Statistical analysis

Kolmogorov-Smirnoff test was applied to classify data as parametric or non-parametric. Parametric data were expressed as mean and standard error, and non-parametric data as median and interquartile range. Categorical variables were expressed as number of cases and prevalence (%). Continuous variables were analyzed using paired t-tests, and categorical variables were compared by chi-square test. For all analysis, a p-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS, version 20.0 (IBM, Chicago, IL, USA).

Results

We identified 72 patients who underwent CoA surgical correction at the HC-UNICAMP between June 1996 and November 2016. Patients were followed for a mean time of 5.82 years, ranging from 0 to 20 years. The mean age at surgery was 5.64 ± 1.31 years, ranging from 0.1 to 27 years, and 51.6% of patients were operated in their first year of life. Demographic data is summarized in Table 1.

At diagnosis, 51 (87.9%) patients had a heart murmur and 23 (48.9%) had no palpable pulse in the lower limbs. Out of the 18 electrocardiographic tests performed, 12 (67%) patients with LV overload were detected, and of 14 patients who underwent complementary cardiovascular imaging investigation beyond echocardiogram, two (14%) had a chest X-ray, one (7%) had a chest computed tomography and six (43%) underwent computed tomography angiography. Besides, among those taking antihypertensive medications at baseline (58%), the most frequent classes were thiazide diuretics (35.6%), beta-blockers (27.1%) and inhibitor of angiotensin-converting enzyme inhibitors (22%). Use of vasodilators (5.1%) and angiotensin receptor blocker (1.7%) were far less common (Table 2).

Table 1 - Baseline characteristics of patients (n = 72) who underwent surgical correction of coarctation of the aorta at the HC-UNICAMP between June 1996 and November 2016

Demographic data	
Age at surgery, years	5.64 ± 1.31 (0.1 to 27)
Male, %	41/ 72 (56.9)
Follow-up time, years	5.82 ± 0.86 (0.02 to 20)
Clinical data	
Symptomatic, %	36/60 (60)
Hypertensive, %	27/46 (58.7)
Heart murmur, %	51/58 (87.9)
Absence of lower limbs pulse, %	23/47 (48.9)
Surgical data	
Hospitalization, days	10.3 ± 1.07 (4 to 32)
Surgery time, hours	2.3 ± 0.09 (1.5 to 3.5)
Clamping time, min	15.9 ± 6 (8 to 38)

Data expressed as mean ± SE (range) or n/total (%).

At baseline, the mean peak DAG was 55 mmHg, and 19 (78%) of patients had LV hypertrophy. The most common echocardiographic findings were bicuspid aortic valve (BAV) (32.8%), persistent arterial duct (31%) and interventricular communication (19%). Mitral valve insufficiency was present in 13.8% of patients. Noteworthy, pulmonary artery hypertension occurred in 12.1% of patients. Less common findings are summarized in Table 3.

All patients underwent surgical correction of CoA by left thoracotomy followed by end-to-end anastomosis. The mean time of surgery and hospitalization was 2.3 hours and 10 days, respectively, and mean cross-clamping time was 15.9 minutes. Of 51 patients operated,

Table 2 - Number of antihypertensive medications

	Baseline (n = 46)	Last exam		
		Control[a] (n = 34)	Recoarctation[b] (n = 14)	Bicuspid aortic valve[c] (n = 16)
0	19 (41.3)	21 (61.8)	3 (21.4)*	7 (43.8)#
1	15 (32.6)	8 (23.5)	6 (42.9)	6 (37.5)
2	5 (10.9)	3 (8.8)	3 (21.4)	2 (12.5)
3	7 (15.2)	2 (5.9)	2 (14.3)	1 (6.3)

*Values are n (%). *p = 0.011 compared with control; chi-square test; #p = 0.53 compared with control; chi-square test; [a] Patients without bicuspid aortic valve (BAV) at diagnosis and without recoarctation in the last echocardiographic test; [b] absence of BAV at diagnosis, and presence of recoarctation in the last echocardiographic test; [c] BAV at diagnosis, and absence of recoarctation in the last echocardiographic test; NYHA: New York Heart Association classification for heart failure symptoms; BAV: bicuspid aortic valve.*

Table 3 - Baseline echocardiographic variables

Findings	
Peak aortic gradient, mmHg	55 ± 3.2 (20 to 103)
Left ventricular hypertrophy, %	19/25 (76)
Bicuspid aortic valve, %	19/58 (32.8)
Persistent arterial duct, %	18/58 (31)
Interventricular communication%	11/58 (19)
Patent foramen ovale, %	9/58 (15.5)
Mitral valve insufficiency, %	8/58 (13.8)
Interatrial communication, %	7/58 (12.1)
Aortic valve insufficiency, %	7/58 (12.1)
Pulmonary artery hypertension, %	7/58 (12.1)
Tricuspid valve insufficiency, %	6/58 (10.3)
Aortic stenosis, %	3/58 (5.2)

Data expressed as mean ± SE (range) or n/total (%)

three patients had chylothorax, with no other surgical complications being reported. Among those who did not have recoarctation during follow-up, surgical correction greatly decreased peak DAG (54 vs 13 mmHg; p < 0.001) and symptoms (60 vs 4.5%; p < 0.001), but not hypertension (58 vs 38%; p = 0.17) (Figure 1). Besides, a significant reduction in LVM, LVEDD, LVESD, PW, ARD and LAD was observed in these patients when compared to baseline values (Figure 2 and Table 4).

Importantly, during follow-up, 16 (27.6%) patients had recoarctation (Figure 3). The mean follow-up period before detection of recoarctation was 5.6 years, and half of the cases occurred after 3.6 years of follow-up. Last recoarctation event was identified after 15 years of follow-up. Overall, patients with recoarctation were more likely to be symptomatic (4.5 vs 64%; p < 0.001) and hypertensive (38 vs 78%; p = 0.011) when compared to those without recoarctation (Table 5). In addition, compared to baseline, there was no significant change in peak gradient or in LVM (Table 5).

Noteworthy, patients with BAV at diagnosis had comparable results with controls during follow-up. Also, age at surgery and gender did not affect the outcomes (data not shown).

Discussion

In this case series, we evaluated data from 72 patients operated for coarctation of the aorta and followed for up to 20 years in tertiary hospital in Brazil. Our main objectives were to identify the most frequent clinical findings that could benefit from early diagnosis, to describe the course of echocardiographic measures following surgical correction, and to detect the occurrence of recoarctation and its impact on prognosis. Our main findings were the following: (i) heart murmur is present in most patients; (ii) in addition to peak DAG, LV mass and diameters also decreased after surgical correction; (iii) recoarctation is a late finding in operated subjects and significantly impacts prognosis.

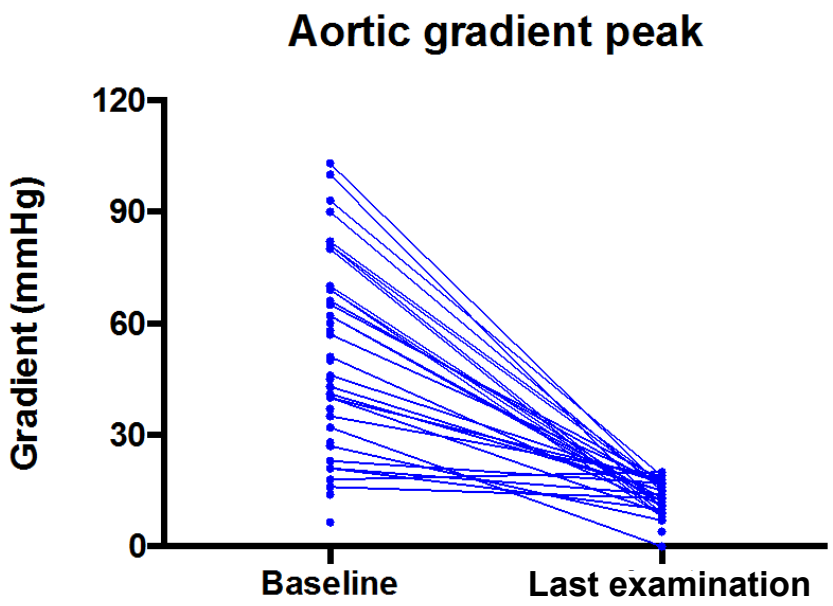

Figure 1 - Graphical representation of the changes in peak gradient measured by echocardiography before surgery and in the last echocardiographic examination after the surgery. Patients without recoarctation showed a mean improvement of 44 mmHg after the surgery ($p < 0.001$).

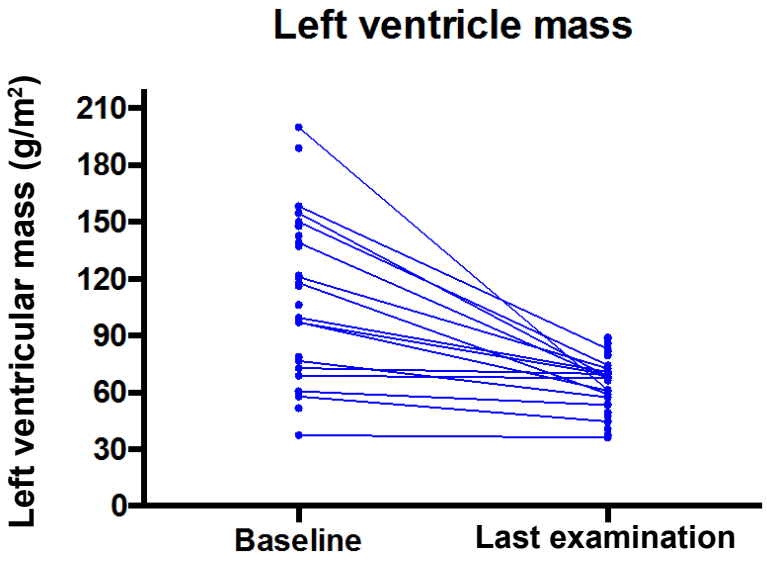

Figure 2 - Graphical representation of changes in indexed left ventricular mass measured by echocardiography before surgery and in the last echocardiographic examination after the surgery. Patients without recoarctation showed a mean improvement of 36 g/m² after surgery ($p = 0.005$).

Table 4 - Echocardiographic measures before and after surgical correction according to groups

	Baseline (n = 40)	Last exam		
		Control (n = 40)	Recoarctation (n = 16)	Bicuspid aortic valve (n = 11)
DAG, mmHg	54 ± 3.8	13 ± 0.8**	35 ± 5.9	11 ± 1.1**
LVM, g/m²	95 ± 9.2	63 ± 11**	56 ± 5.1	55 ± 3.8
LVEDD, cm/m²	72 ± 5.5	41 ± 3.2**	46 ± 7.3*	49 ± 6.3*
LVESD, cm/m²	45 ± 3.7	25 ± 2.2**	29 ± 5.6*	29 ± 4.2*
PW, cm/m²	15 ± 1.8	8 ± 0.7**	10 ± 2.1	9 ± 1.6**
ARD, cm/m²	35 ± 2.3	23 ± 1.5**	26 ± 3.4	26 ± 2.7**
LAD, cm/m²	48 ± 3.8	28 ± 2.5**	33 ± 5	36 ± 5.7
LV hypertrophy, %	22/28 (78.6)	0/27 (0)	0/7 (0)	0/6 (0)

*Values are mean ± SE. *p < 0.05; **p < 0.01 compared with baseline; paired T-test. DAG: peak descending aorta gradient; LVM: left ventricular mass; LVEDD: LV end-diastolic diameter; LVESD: LV end-systolic diameter; PW: posterior wall diastolic thickness; ARD: aortic root diameter; LAD: left atrial diameter.*

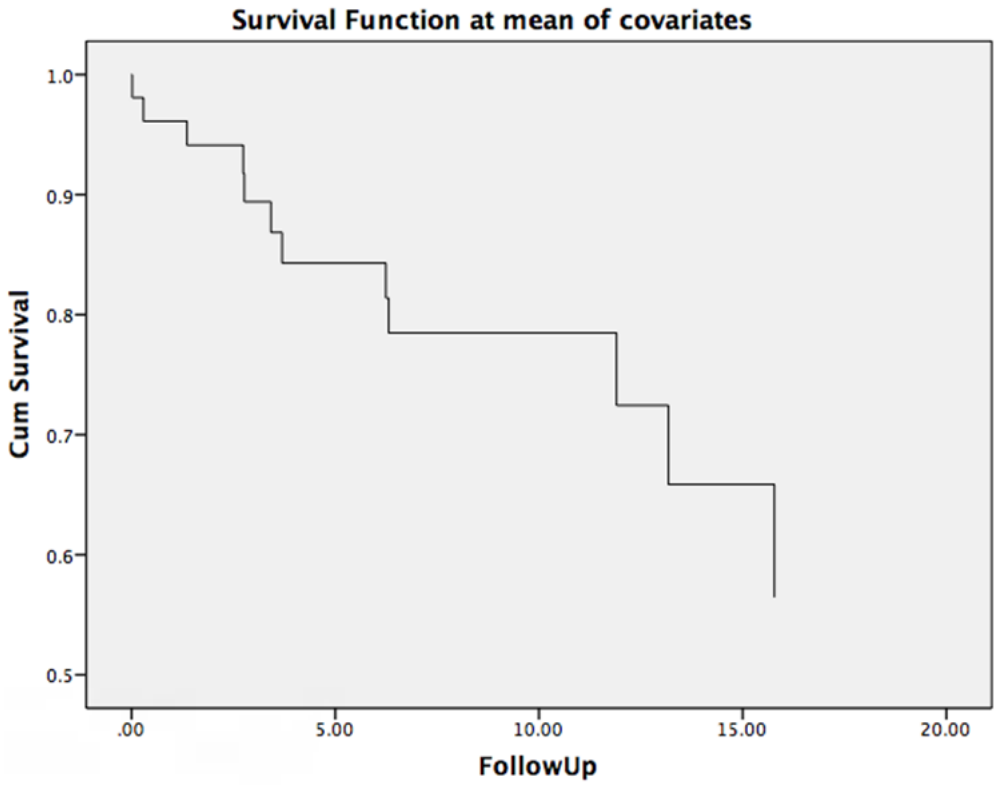

Figure 3 - Graphical representation of recoarctation episodes during follow-up. Values are presented as cumulative survival (%) and follow up (years after surgery).

Table 5 - Clinical variables before and after surgical correction

NYHA	Baseline (n = 60)	Last exam		
		Control[a] (n = 22)	Recoarctation[b] (n = 14)	Bicuspid aortic valve[c] (n = 11)
I	24 (40)	21 (95.5)[#]	5 (35.7)*	10 (90.9)[#]
II	14 (23.2)	1 (4.5)	8 (57.1)	1 (9.1)
III	12 (20)	-	1 (7.1)	-
IV	10 (16.7)	-	-	-

*Values are n (%). #p < 0.001 compared with baseline; chi-square test; *p < 0.001 compared with control; chi-square test; [a] patients without bicuspid aortic valve at diagnosis and without recoarctation in the last echocardiographic test; [b] absence of BAV at diagnosis, and presence of recoarctation in the last echocardiographic test; [c] BAV at diagnosis, and absence of recoarctation in the last echocardiographic test; NYHA: New York Heart Association classification for heart failure symptoms; BAV: bicuspid aortic valve.*

In our study, most patients who underwent CoA surgical correction had systolic heart murmur with posterior radiation at diagnosis, and half of them had hypertension, cardiac symptoms, and no palpable pulse in the lower limbs. Of note, these findings were achieved by proper physical examination and history-taking, which can guide complementary investigation focused on early diagnosis. Yet, half of patients were lately diagnosed in our follow-up, which is in accordance with previous large population-based studies showing late diagnosis rates of over 62%.[8]

Whether late correction constitutes an independent risk factor for poor prognosis remains a matter of debate, with some suggesting a relationship of late correction with re-coarctation rates[6] and others with long-term cardiovascular mortality. In our study, neither re-coarctation nor clinical outcomes differed in a significant manner between age groups. Still, an earlier surgical treatment of comorbidities that are known to have an impact on cardiovascular mortality would presumably improve long-term survival. This hypothesis is supported by the absence of LV hypertrophy and cardiac symptoms in operated patients in our analysis.

It is of note that more than one third of patients remained hypertensive after surgical correction. This finding is in accordance with previous studies suggesting hypertension as the main late complication in operated patients, even in the absence of residual obstruction.[9,11] Although the exact mechanism for this phenomenon remains unclear, a role of arterial stiffness, endothelial dysfunction and altered autonomic cardiac modulation has been proposed.

In this matter, post-coartectomy subjects have impaired endothelial function, which, in turn, increases peripheral vascular resistance, leading to increased blood pressure.[10] Moreover, coarctation leads to deposition of collagen and depletion of smooth muscle in the aortic wall. This negatively affects aortic distensibility and the sensitivity of aortic arch baroreceptors, thereby impairing arterial compliance with substantial effects on blood pressure.[15,16] Finally, it has been conjectured that hypertension results from compensatory sympathetic stimuli in response to acute unloading of the baroreceptors following surgery.[10] Importantly, these features are not prevented by surgical correction, reinforcing that coarctation is a generalized vasculopathy far beyond the narrowing of the aortic arch.

Our study found a high prevalence of LV hypertrophy at baseline, which markedly decreased after surgical correction. Noteworthy, in coarctation, an increase in LV mass occurs in spite of elevated blood pressure, which may be explained by the "ventricular-arterial coupling" hypothesis, that postulates that aortic stiffness increases wave reflection pressure, leading to LV afterload.[17] Importantly, such phenomenon leads to diastolic dysfunction and changes in LV morphology, which are partially reversed by surgery, as demonstrated in the present study and in previous ones.[4,18-20] In fact, in our follow-up we found a significant reduction of indexed LV diameters, LV mass and posterior wall thickness in operated patients who did not manifest recoarctation.

Finally, pulmonary hypertension occurred in 12% of patients in our follow-up, which is in accordance with previous studies. Mechanistically, it is assumed that endothelial dysfunction and arterial stiffness are the

most likely causes of pulmonary hypertension in these patients, though a role for vascular reactivity has been also proposed.[20] Moreover, BAV was the most common associated malformation in our analysis, which is in agreement with previous studies showing a common genetic mutation for both congenital heart diseases.[21] Noteworthy, it has been proposed that such phenomenon would lead to greater hemodynamic changes, which could plausibly lead to worsen prognosis.[22] In our study, patients with isolated and complex coarctation had comparable results, although larger studies are required to correctly address this issue.

Limitations

Our study has some limitations that are inherent to retrospective case series. Also, since we collected data from a tertiary care hospital, the possibility of a selection bias cannot be excluded, favoring those with more complex presentations of the disease. Finally, we did not register any hard endpoint, which weaken the capacity of identifying predictive risk factors for a worse prognosis.

Conclusions

Coarctectomy improves cardiac symptoms and LV hypertrophy, with a slight effect on the incidence of hypertension. Age at surgical repair and complex malformations were not related to a worse prognosis. In our study, recoarctation had a negative impact on the benefit of surgery in one-third of patients, which reinforces the need for lifelong surveillance by echocardiography.

Author contributions

Conception and design of the research: Barreto J, Roda J, Germano CW, Quinaglia T. Acquisition of data: Barreto J, Roda J, Germano CW, Damiano AP, Quinaglia T. Analysis and interpretation of the data: Barreto J, Quinaglia T. Statistical analysis: Barreto J, Quinaglia T. Writing of the manuscript: Barreto J, Quinaglia T. Critical revision of the manuscript for intellectual content: Barreto J, Roda J, Germano CW, Damiano AP, Quinaglia T.

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. Yokoyama U, Ichikawa Y, Minamisawa S, Ishikawa Y. Pathology and molecular mechanisms of coarctation of the aorta and its association with the ductus arteriosus. J Physiol Sci. 2017;67(2):259-70.
2. Lee MG, Allen SL, Kawasaki R, Kotevski A, Koleff J, Kowalski R, et al. High prevalence of hypertension and end-organ damage late after coarctation repair in normal arches. Ann Thorac Surg. 2015;100(2):647-53.
3. Quail MA, Short R, Pandya B, Steeden JA, Khushnood A, Taylor AM, et al. Abnormal wave reflections and left ventricular hypertrophy late after coarctation of the aorta repair. Hypertension. 2017;69(3):501-9.
4. Lombardi KC, Northrup V, McNamara RL, Sugeng L, Weismann CG. Aortic stiffness and left ventricular diastolic function in children following early repair of aortic coarctation. Am J Cardiol. 2013;112(11):1828-33.
5. Brown ML, Burkhart HM, Connolly HM, Dearani JA, Cetta F, Li Z, et al. Coarctation of the aorta: lifelong surveillance is mandatory following surgical repair. J Am Coll Cardiol. 2013;62(11):1020-5.
6. Choudhary P, Canniffe C, Jackson DJ, Tanous D, Walsh K, Celermajer DS. Late outcomes in adults with coarctation of the aorta. Heart. 2015;101(15):1190-5.
7. Farag ES, Kluin J, de Heer F, Ahmed Y, Sojak V, Koolbergen DR, et al. Aortic coarctation repair through left thoracotomy: results in the modern era. Eur J Cardiothorac Surg. 2019;55(2):331-7.
8. Peterson C, Ailes E, Riehle-Colarusso T, Oster ME, Olney RS, Cassell CH, et al. Late detection of critical congenital heart disease among US infants: estimation of the potential impact of proposed universal screening using pulse oximetry. JAMA Pediatr. 2014;168(4):361-70.
9. Canniffe C, Ou P, Walsh K, Bonnet D, Celermajer D. Hypertension after repair of aortic coarctation--a systematic review. Int J Cardiol. 2013;167(6):2456-61.
10. Kenny D, Polson JW, Martin RP, Paton JF, Wolf AR. Hypertension and coarctation of the aorta: an inevitable consequence of developmental pathophysiology. Hypertens Res. 2011;34(5):543-7.
11. Rinnstrom D, Dellborg M, Thilen U, Sörensson P, Nielsen NE, Christersson C, et al. Hypertension in adults with repaired coarctation of the aorta. Am Heart J. 2016 Nov;181:10-5.
12. Khoury PR, Mitsnefes M, Daniels SR, Kimball TR. Age-specific reference intervals for indexed left ventricular mass in children. J Am Soc Echocardiogr. 2009;22(6):709-14.

13. Jaquiss RDB. Coarctation of the aorta: end-to-end anastomosis. Oper Tech Thorac Cardiovasc Surg. 2002;7(1):2-10.

14. Wright GE, Nowak CA, Goldberg CS, Ohye RG, Bove EL, Rocchini AP. Extended resection and end-to-end anastomosis for aortic coarctation in infants: results of a tailored surgical approach. Ann Thorac Surg. 2005;80(4):1453-9.

15. Kuhn A, Baumgartner D, Baumgartner C, Hörer J, Schreiber C, Hess J, et al. Impaired elastic properties of the ascending aorta persist within the first 3 years after neonatal coarctation repair. Pediatr Cardiol. 2009;30(1):46-51.

16. Kenny D, Polson JW, Martin RP, Caputo M, Wilson DG, Cockcroft JR, et al. Relationship of aortic pulse wave velocity and baroreceptor reflex sensitivity to blood pressure control in patients with repaired coarctation of the aorta. Am Heart J. 2011;162(2):398-404.

17. O'Sullivan J. Late hypertension in patients with repaired aortic coarctation. Curr Hypertens Rep. 2014;16(3):421.

18. Murakami T, Takeda A, Yamazawa H, Tateno S, Kawasoe Y, Niwa K. Aortic pressure wave reflection in patients after successful aortic arch repair in early infancy. Hypertens Res. 2013;36(7):603-7.

19. Menting ME, van Grootel RW, van den Bosch AE, Eindhoven JA, McGhie JS, Cuypers JA, et al. Quantitative assessment of systolic left ventricular function with speckle-tracking echocardiography in adult patients with repaired aortic coarctation. Int J Cardiovasc Imaging. 2016;32(5):777-87.

20. Oliver JM, Gallego P, Gonzalez AE, Sanchez-Recalde A, Bret M, Aroca A. Pulmonary hypertension in young adults with repaired coarctation of the aorta: an unrecognised factor associated with premature mortality and heart failure. Int J Cardiol. 2014;174(2):324-9.

21. Quintero-Rivera F, Xi QJ, Keppler-Noreuil KM, Lee JH, Higgins AW, Anchan RM, et al. MATR3 disruption in human and mouse associated with bicuspid aortic valve, aortic coarctation and patent ductus arteriosus. Hum Mol Genet. 2015;24(8):2375-89.

22. Abdulkareem N, Smelt J, Jahangiri M. Bicuspid aortic valve aortopathy: genetics, pathophysiology and medical therapy. Interact Cardiovasc Thorac Surg. 2013;17(3):554-9.

EDITORIAL

Diabetes Mellitus, Insulin Use, and Infective Endocarditis

Rubens Antunes Cruz Filho

Hospital Universitário Antonio Pedro, Universidade Federal Fluminense, Niterói, RJ – Brazil

The prevalence of diabetes mellitus (DM) is very high in Brazil and worldwide. It is estimated that there are now more than 12 million diabetics in Brazil, not counting those who already have the disease but have not yet been diagnosed. Since the introduction of insulin, the treatment of DM has been constantly changing, according to treatment guidelines proposed by diabetes societies, from the diagnosis to more advanced stages of the disease. More stable insulins, as well as incretin-based therapy for subcutaneous use, have been proposed in the treatment of type 2 DM patients. These therapies have not only contributed to the better treatment of the most prevalent type of diabetes, but also introduced the use of a parenteral medication other than insulin.

Infective endocarditis (IE) is a relatively rare, serious cardiovascular disease with a hospital mortality rate of 17-25%, despite all therapeutic advances.[1] In an observational study by Bezerra et al.,[2] published in this issue of the IJCS, the association between the use of insulin and IE is discussed. In this retrospective study involving 211 patients, 17 with DM (nine insulin users), there was a higher proportion of S. aureus infection in diabetics using insulin. However, mortality rate was not higher among diabetics when compared to non-diabetics. There is a lack of studies on IE in DM and regarding the use of insulin and IE, data are even more scarce. So, the study by Bezerra et al.,[2] assumes an importance in this area of knowledge, since we are talking about a highly prevalent disease (DM) and a serious comorbidity (IE) with a still high risk of mortality.

Keywords

Diabetes Mellitus/physiopathology; Infectious Endocarditis; Insuli; Staphylococcus Aureus; Mortality/Morbidity.

Today there are more pure and more stable insulin preparations, which allied to modern applicators, produce virtually no reaction. Also, the risk of infection (and complications including the formation of abscess and hematogenous spread of the infection) is lower. However, the higher prevalence of S. aureus infection found in diabetics calls attention to a possible entry point via cutaneous route. In a recent observational study by Lin et al.,[1] who assessed the risk of in-hospital mortality between diabetics and non-diabetics with IE, S. aureus was also the most frequent pathogen in endocarditis in diabetics, but only 15% of these patients used insulin.

Another important and controversial aspect is the association of in-hospital mortality with DM and IE. In the studies by Bezerra et al.,[2] and Olmos et al.,[3] no difference was observed in mortality between diabetics and non-diabetics, although an independent association of DM and septic shock was reported.[3] On the other hand, in the study by Lin et al.,[1] DM was independently associated with mortality and was a factor of poor prognosis in IE. In another study, Duval et al.,[4] showed that the in-hospital mortality was higher in diabetic patients, especially in those using insulin.

The study by Bezerra et al.,[2] also showed a greater impairment of tricuspid valve in diabetic patients using insulin (compared with non-users), which resembles the pattern found in IE in injecting drug users. This is not corroborated by results of previous studies on DM, as in the study by Duval et al.,[4] who evaluated subgroups of patients with DM by the use or not of insulin. Larger studies evaluating diabetic patients of several centers should be done to enhance our understanding about IE in DM. Several questions remain to be solved, for example, which heart valve is most commonly affected in diabetic patients. Greater involvement of the tricuspid valve would allow us to infer that the site of insulin application could be the source of bacterial skin infection.

Mailing Address: Rubens Antunes Cruz Filho
Marques do Paraná, 300. Postal Code: 24033-900, Niterói, Rio de Janeiro, RJ - Brazil.
E-mail: rubensacfilho@gmail.com

DOI: 10.5935/2359-4802.20190087

Given the increase of the diabetic population, mainly type 2 diabetic patients, and advances in the knowledge of pathophysiological mechanisms and therapeutic options, which has led to an increase in the life expectancy of these patients, improving the knowing of the development of IE in DM is justified. It is important to elucidate the possible increased risk of patients on insulin or other subcutaneous medication to have IE compared with non-diabetics or diabetic patients on oral medications. Also, the reports showing that S. aureus is the main pathogen responsible for IE, in addition to the increasing number of diabetic patients, call for the need to develop prophylactic measures against this pathogen.

References

1. Lin CJ, Chua S, Chung SY, Hang CL, Tsai TH. Diabetes mellitus: an independent risk factor of in-hospital mortality in patients with infective endocarditis in a new era of clinical practice. Int J Environ Res Public Health. 2019;16(12):2248-58.
2. Bezerra RL, Carvalho TF, Batista RS, Silva YM, Campos BF, Castro JHM, et al. Association between insulin use and infective endocarditis: an observational study. Int J Cardiovasc Sci. 2020;33(1):14-21.
3. Olmos C, Vilacosta I, Pozo E, Fernández C, Sarriá C, López J, et al. Prognostic implications of diabetes in patients with left-sided endocarditis: findings from a large cohort study. Medicine (Baltimore). 2014;93(2):114-9.
4. Duval X, Alla F, Doco-Lecompte T, Lemoing V, Delahaye F, Mainardi JL, et al. Diabetes mellitus and infective endocarditis: the insulin factor in patient morbidity and mortality. Eur Heart J. 2007;28(1):59-64.

ORIGINAL ARTICLE

Association between Insulin use and Infective Endocarditis: An Observational Study

Renato Lott Bezerra,[1,4] Thales Figueiredo de Carvalho,[1] Ricardo dos Santos Batista,[1] Yago Machado da Silva,[1] Bruno Fiuza Campos,[1] João Henrique Máximo de Castro,[1] Matheus de Carvalho Alves,[1] Pedro Ivo Palhares Monteiro,[1] Raimundo Matos Bezerra Filho,[2] Eduardo Luis Guimarães Machado[1,3]

Faculdade de Ciências Médicas de Minas Gerais,[1] Minas Gerais, MG - Brazil
Hospital Márcio Cunha, Fundação São Francisco Xavier,[2] Ipatinga, MG - Brazil
Santa Casa de Misericórdia de Belo Horizonte,[3] Belo Horizonte, MG - Brazil
Hospital João XXIII, Fundação Hospitalar do Estado de Minas Gerais,[4] Belo Horizonte, MG - Brazil

Abstract

Background: The association between Diabetes Mellitus (DM) and Infective Endocarditis (IE) is controversial in the literature, since many controversial results have been published. However, when evaluating specifically the evidence on IE and individuals with DM using insulin, we found only two observational studies that considered this variable, with discordant results regarding the prognosis and prevalence of *Staphylococcus sp* in insulin users compared to non-users. Despite the lack of evidence, in clinical practice the insulin use could be interpreted as minor criteria "injection drug use", using the modified Duke criteria for IE diagnosis.

Objectives: To compare the microbiological and valvar profile, as well as the outcome of non-diabetic and diabetic patients with IE who were insulin users or not.

Methods: This was an observational, analytical and retrospective study of patients diagnosed with IE between 2003 and 2015 in three tertiary care centers. A total of 211 patients were included, of which 17 were diabetics and 9 were insulin users. Patients were compared using the Shapiro-Wilk normality test and Fisher's exact test, with a significance level of 5%.

Results: The mortality from IE in diabetic individuals was higher than that of non-diabetic patients, but with no statistical significance (35.29% vs. 21.1%; p = 0.221), even when the groups were divided into insulin-user diabetic, non-insulin user diabetic and non-diabetic patients (33.3% vs. 37.5% vs. 21.1%, p = 0.229). There was a difference regarding the prevalence of IE caused by *S. aureus* (57.1% vs. 14.3% vs. 17.4%, p = 0.029) and the involvement of the tricuspid valve (33.3% vs. 0.00% vs. 10.0%, p = 0.034) among insulin users.

Conclusion: In our sample, insulin use or the presence of DM did not mean higher in-hospital mortality from IE. It is not possible to generalize the microbiological and valvar findings due to the lack of studies evaluating insulin users in IE; however, particularities have been previously reported and may indicate a different behavior of IE in these patients. New studies considering the insulin use variable are required to elucidate the association between DM and IE. (Int J Cardiovasc Sci. 2020;33(1):14-21)

Keywords: Diabetes Mellitus; Insulin; Inyeccion; Infections; Heart Valve Diseases; Endocarditis, Bacterial.

Introduction

Infective Endocarditis (IE) is an infectious condition with high mortality that develops when bacteremia and endocardial tissue invasion occurs, usually in previously damaged cardiac valves. Several conditions have been associated with IE, such as congenital and rheumatic heart diseases, presence of prosthetic valves, prior IE and Diabetes Mellitus (DM).[1-4] DM is a high-prevalence disease, with an estimated 11.9 million affected individuals in Brazil and 387 million in the worldwide population.[5] It is a condition that leads to immunosuppression and, therefore, predisposes to several infectious complications.[6]

Mailing Address: Renato Lott Bezerra
Rua Professor Morais, número 210, apartamento 303. Postal Code: 30150-370. Funcionários, Belo Horizonte, MG - Brazil.
E-mail: lott.renato@gmail.com

DOI: 10.5935/2359-4802.20190049

Manuscript received on May 22, 2018, revised manuscript on September 11, 2018, accepted on November 01, 2018.

The association between DM and IE is still controversial in the literature. DM has been indicated as an independent predictor of in-hospital mortality in the studies by Chu et al.[3] and Chrillo et al.,[7] and according to Movahed et al.,[8] IE was more prevalent in patients with Type II DM, when compared to non-diabetic patients. On the other hand, although Moreno et al.[9] and Wallace et al.[10] found higher mortality values in diabetic patients with IE in relation to non-diabetic ones, there was no statistical significance to corroborate this association. Other authors have shown that DM was associated with a higher risk of septic shock in IE, but an association with higher mortality was not observed.[11]

However, regarding the use of insulin by diabetic patients and a possible association with IE, there was little evidence in the literature that considered this variable; only two observational studies did it, one carried out by Duval et al.[12] and another by Olmos et al.[11] The first one showed that insulin users showed significant differences regarding in-hospital mortality and the proportion of IE by *Staphylococcus sp* when compared to DM patients receiving an exclusive oral hypoglycemic drug and non-diabetic patients. The results of the second study were discordant, since there were no differences in prognosis and microbiology. It should be noted that the study by Olmos et al.[11] included only cases of IE in the left heart chamber.

For the diagnosis of IE, the Duke Criteria were proposed by Durack et al.[13] in 1994, which represented an advance in the understanding of IE and which included "intravenous drug use" as a minor criterion. However, Li et al.,[14] in 2000, proposed changes that gave rise to the modified Duke Criteria, with the minor criterion "intravenous drug use" being replaced by "injectable drug use".

Therefore, by definition,[15] any subcutaneous, intramuscular or intravenous injectable substance would also be considered a minor and predisposing criterion for IE, such as insulin. We emphasize that the reason for the change was not addressed by Li et al.[14]

Moreover, considering the pathophysiological aspects of IE, in which bacteremia has an essential role, it is possible that the use of subcutaneous insulin has characteristics that are close to those of the group of patients who use intravenous drugs. The correlation between intravenous drug use and IE is explained by the introduction of microorganisms and particles into the circulation during the injection, which damage and colonize the heart valves.[16]

In the case of insulin use, despite the subcutaneous route of administration, it would be plausible the hypothesis of bacteremia occurring in certain situations, such as hematoma at the injection site, a frequently described complication[17-19] with the use of inadequate techniques and one that represents vascular damage associated with a solution of continuity with the skin microbiota. In fact, Tuazon et al.[20] have shown that insulin use increases the risk of mucocutaneous colonization by *S. aureus*.

Skin infections such as abscesses have also been described in injection sites in insulin users, and according to Binswanger et al.,[21] the subcutaneous space can be colonized by multiple microorganisms that are introduced by non-sterile drug injections. The study by Lipsky et al.[22] demonstrated bacteremia in 15 to 19% of patients with this type of infection and the most often involved microorganism was *S. aureus*.

Patients who are insulin-users also have the concomitant need for frequent self-monitoring of blood glucose levels through finger blood collection, which could facilitate bacteremia, as the capillary bed is exposed to the external environment. Cases of sepsis and osteoarthritis due to abscess focus in the fingers of patients who were inadequately self-monitoring blood glucose have already been reported.[23,24,25]

Thus, the aim of the study is to evaluate and compare the microbiological, valvular and outcome aspects of IE in diabetic patients who are insulin users or non-insulin users or are not diabetic, in addition to comparing the results with the current literature.

Method

Study population

The population consisted of 211 patients with probable or definitive IE admitted at in three tertiary care centers in the municipalities of Belo Horizonte and Ipatinga, state of Minas Gerais, Brazil, between 2003 and 2015.

The inclusion criteria were: patients admitted between 2003 and 2015 in three hospitals, who were diagnosed with definitive or probable IE, according to the modified Duke criteria.[13] Patients who met the criteria for Definitive or Probable IE were included in the database. The exclusion criteria were: patients who were transferred to another tertiary care center or who were still hospitalized during the data collection period. Medical records with insufficient data were also excluded.

The Free and Informed Consent was waived, considering the retrospective design of the study, which was approved by the Research Ethics Committee of *Faculdade Ciências Médicas de Minas Gerais*, under number CAEE 1.856.064.

Study design

This is an observational, retrospective and cross-sectional study. It has an analytical aspect,[26] as it compares and applies statistical tests to diabetic patients who are insulin users, non-insulin users and non-diabetic patients. A microbiological profile was collected according to the blood culture or valvular culture results that were described in the medical records. The site of EI involvement was collected according to transthoracic, transesophageal echocardiography or perioperative findings.

Patients who used insulin only during hospital stay were not included in the insulin-user group. Any type of subcutaneous insulin used by the patients was considered (NPH, Regular, Glargine, Ultra-fast, Lispro, Aspart, etc.). The medical records that showed any doubts, of any nature, were evaluated again by the author. All data collected were entered into an Excel worksheet.

Sample size

The sample was calculated to test the proportion of diabetics among patients with infective endocarditis. Considering a significance level of 5% and a minimum power of 80%, using the result of a reference study,[7] to detect a minimum difference of 6.6% in the proportion of diabetics, at least 210 patients with IE would be required.[27]

Data analysis

The categorical variables were shown as numbers and percentages, and the numerical variables as mean ± standard deviation (SD). The numerical variables were submitted to the Shapiro-Wilk normality test. The association between the analysis groups and the variables of interest was performed using a multinomial logistic model. The comparison of means was performed through one-way analysis of variance. The association between the type of diabetes and the presence of comorbidities was assessed using Fisher's exact test. The analyses were carried out using the free program R, version 3.3.2, with a significance level of 5%.

Results

Epidemiological and prognostic aspects are shown in Table 01. A total of 211 patients were included in our analysis, 110 from Belo Horizonte and 101 from Ipatinga. The mean age of the patients was 46.6 ± 18.8 years and 70.6% of the them were males. Regarding the outcome, the number of deaths was 47, representing a mortality rate of 22.3%. When analyzing the patients from Belo Horizonte and Ipatinga separately, it can be observed that the mortality rate was 20% and 20.7%, respectively.

Table 2 shows the results regarding the microbiological profile of our sample. Considering the positive blood

Table 1 - Epidemiological and prognostic aspects of hospitalized patients with Infective Endocarditis

Characteristic	IUD (n = 9)	NIUD (n = 8)	ND (n = 194)	Total (n = 211)	p-value
Age	56.9 ± 13	56.3 ± 9.7	45.7 ± 19.1	46.6 ± 18.8	0.071*
Male gender	4 (44.4%)	5 (62.5%)	140 (72.2%)	149 (70.6%)	0.066†
Definitive IE	6 (66.6%)	6 (75%)	106 (54.6%)	118 (55.9%)	0.277†
Blood cultures performed	9 (100%)	8 (100%)	160 (82.5%)	177 (83.9%)	-
Positive blood culture	7 (77.8%)	7 (87.5%)	92 (47.4%)	106 (50.2%)	0.057†
Defined location	9 (100%)	6 (75%)	192 (99%)	208 (98.6%)	-
Deaths[L]	3 (33.3%)	3 (37.5%)	41 (21.1%)	47 (22.3%)	0.229†

*ND: non diabetics; NIUD: non-insulin-user diabetics; IUD: insulin-user diabetics. The superscripts indicate the method used for the association analysis: * One-way analysis of variance; † multinomial logistic model. [L]Comparing the mortality of diabetics and non-diabetics, there was no statistical significance according to Fisher's exact test (p = 0.221).*

cultures, our results showed a higher prevalence of the *Staphylococcaceae genus* (37.7%), almost equally distributed as 19.8% *S. aureus* and 17.9% of coagulase-negative *Staphylococcus*.

We emphasize that the prevalence of *S. aureus* was similar when we evaluated the two cities separately, with 18.6% in Ipatinga and 20.6% in Belo Horizonte. *Streptococcus spp* represented the second most prevalent genus, estimated at 29.2%, followed by *Enterococcus spp* with 13.2% and other microorganisms in 9.4% of the time. The blood culture was shown to be positive in the medical records, but without specifying the microorganism in 13.2% of the patients.

The location of the IE is shown in Table 3. The native valves were the most affected site in the general sample, representing 149 (70.6%) patients, most of them in the mitral valve (41.7%), followed by the aortic valve (26.5%), tricuspid (10%) and pulmonary (1.4%) valve. The valvular prostheses were infected in 51 (24.2%) patients, pacemaker cable in 9 (4.3%) and 6 (2.8%) were infected in other places such as the right atrium, pulmonary arteries, superior vena cava ostium or interventricular septal defect.

There were 194 non-diabetic and 17 diabetic patients, of which 9 (52.9%) were insulin users and 8 (47.1%) used only oral hypoglycemic drugs. The data showed 35.29% of mortality in diabetics and 21.1% in non-diabetic patients, with no statistical difference (p = 0.221). When considering diabetics who used or did not use insulin, the observed mortality was 33.3% and 37.5%, respectively, and the statistical tests did not show a significant difference in relation to this variable (p = 0.229).

The microbiological comparison between the subgroups showed a higher proportion of *S. aureus* in insulin users than in the non-diabetic group, with a statistical significance (p = 0.029), whereas *Streptococcus spp* was the most common microorganism in the diabetic patients receiving oral medication and in non-diabetic patients.

The native mitral valve was the most often affected in patients who did not use insulin, non-diabetic or diabetic patients, with 42.8% and 25%, respectively. In the diabetic patients who used insulin, we observed that the mitral valve showed the same prevalence as the tricuspid valve, calculated as 33.3%. We emphasize there was a statistical significance between tricuspid valve involvement (p = 0.034). The aortic valve was the second most affected in the total sample, in 26.5% of the patients, which was also observed in non-diabetic patients, with 27.8%.

There was a higher prevalence of individuals with unidentified sites among diabetics who were non-insulin-users and non-diabetic patients (p = 0.031).

Table 04 shows several characteristics of the diabetic patients in our sample that could influence prognostic, microbiological and valvular aspects in the groups of insulin users or non-users. The statistical analysis showed homogeneity between the two groups, which improves the internal validity of the comparison. However, it

Table 2 - Microbiological profile of 106 patients with a positive blood culture diagnosed with Infective Endocarditis

Microorganism	IUD (n = 7)	NIUD (n = 7)*	ND (n = 92)*	Total (n = 106)*	p-value
Staphylococcus spp	5 (71.4%)	2 (28.6%)	33 (35.9%)	40 (37.7%)	0.133†
S. aureus	4 (57.1%)‡	1 (14.3%)	16 (17.4%)‡	21 (19.8%)	0.029†
Coagulase negative S§	1 (14.3%)	1 (14.3%)	17 (18.5%)	19 (17.9%)	0.723†
Streptococcus spp//	-	3 (42.9%)	28 (30.4%)	31 (29.2%)	0.217†
Enterococcus	-	-	14 (15.2%)	14 (13.2%)	-
Others¶	1 (14.3%)	1 (14.3%)	8 (8.7%)	10 (9.4%)	0.535†
Not specified#	1 (14.3%)	2 (28.6%)	11 (12%)	14 (13.2%)	0.519†

*ND: non diabetics; NIUD: non-insulin-user diabetics; IUD: insulin-user diabetics. * Some patients had more than one microorganism growing in the blood culture; † Association evaluated via multinomial logistic model; ‡ Indicates pairs with significant difference (p < 0.05); §S. epidermidis, S. warneri, S. haemoliticus, S. lugdunensis, S. capitis; //S. pneumoniae, S. pyogenes, S. sanguinis, S. mitis; ¶ Haemophillus spp, Candida spp, Proteus mirabilis, Proteus penneri, E. coli, Enterobacter sp, Klebsiella sp,, Achromobacter xylosoxidans, Morganella morganii, Stenotrophomonas maltophilia, Facklamia hominis; # Blood culture was positive, but the microorganism was not specified.*

Table 3 - Cardiac structures affected in 211 patients with Infective Endocarditis

Location	IUD (n = 9)	NIUD (n = 8)	ND (n = 194)*	Total (n = 211)*	p-value
Native valves	7 (77.8%)	3 (37.5%)	139 (71.6%)	149 (70.6%)	0.642†
Mitral	3 (33.3%)	2 (25%)	83 (42.8%)	88 (41.7%)	0.369†
Aortic	1 (11.1%)	1 (12.5%)	54 (27.8%)	56 (26.5%)	0.168†
Tricuspid	3 (33.3%)‡	-	18 (9.3%)‡	21 (10%)	0.034†
Pulmonary	-	-	3 (1.5%)	3 (1.4%)	-
Prosthetic valves	1 (11.1%)	3 (37.5%)	47 (24.2%)	51 (24.2%)	0.640†
Pacemaker cable	-	-	9 (4.6%)	9 (4.3%)	-
Others §	1 (11.1%)	-	5 (2.6%)	6 (2.8%)	0.237†
Unidentified location	-	2 (25%)‡	1 (0.5%)‡	3 (0.1%)	0.031†

*IUD: insulin-user diabetics; NIUD: non-insulin-user diabetics; ND: non diabetics; *Some patients showed lesions in more than one place; †Association evaluated via multinomial logistic model; ‡Indicates pairs with significant difference (p < 0.05); § Right Atrium, Pulmonary Arteries, Ostium of the interventricular defect, Ostium of Superior Vena Cava.*

Table 4 - Characteristics of diabetic individuals with Infective Endocarditis according to insulin use

Aspect	IUD (n = 9)	NIUD (n = 8)	p-value
Health care related IE†	2 (22.2%)	3 (37.5%)	0.620
Systemic arterial hypertension	9 (100%)	7 (87.5%)	0.471
Dyslipidemia	5 (55.5%)	4 (50%)	1.000
CHF NYHA III*	3 (33.3%)	2 (25%)	1.000
Valvulopathy	2 (22.2%)	3 (37.5%)	0.620
Coronary artery disease	2 (22.2%)	3 (37.5%)	0.620
Dialytic chronic kidney disease	2 (22.2%)	2 (25%)	1.000
Non-dialytic chronic kidney disease	1 (11.1%)	1 (12.5%)	1.000
Smoking	3 (33.3%)	4 (50%)	0.637
Alcohol consumption	3 (33.3%)	2 (25%)	1.000

*† According to the definition used by Yang et al.28. We included in this group 4 patients undergoing kidney dialysis and 1 patient in long-term care. It was not possible to evaluate hospitalizations up to 90 days prior to IE manifestations, so this criterion was not used. NIUD: non-insulin-user diabetics; IUD: insulin-user diabetics. The p-values refer to Fisher's exact test. * NYHA Class III Congestive Heart Failure.*

was not possible to reliably collect these same variables for non-diabetic patients in our sample, which could represent a limitation in the comparison with this group.

Discussion

When considering the general data of all 211 patients with IE in our population, regardless of whether or not they were diabetics, findings consistent with large observational studies in the literature can be observed. The multicenter study by Murdoch et al.,[1] with 2781 patients with IE, showed a mortality rate of 18.0%, comparable to the 22.3% in our results. Moreover, the proportion of diabetic patients with IE was 8.0% (n = 17), similar to the 10.0% found by the same study by Murdoch et al.,[1] when only South America was considered.

The microbiological profile evaluated in the literature shows differences according to the affected site. The findings were proportional to those in the study by Murdoch et al.,[1] when considering only South America (n = 254), which showed a predominance of *Streptococcus sp.* in 26.0%, followed by *S. aureus* in 17%, whereas ours results showed 25.0% and 18.0%, respectively. In contrast, Nunes et al.[29] (n = 62) and Ruiz et al.[30] (n = 159), in Belo Horizonte, state of Minas Gerais and Ribeirão Preto, state of São Paulo, respectively, found a higher prevalence of *S. aureus* (32.0% and 27.0%).

In our sample, mortality was higher in diabetic patients, when compared to non-diabetic ones, 35.29% of mortality in diabetics and 21.1% in non-diabetic patients, with no statistical difference (p = 0.221), as reported by Wallace et al.[10] with 36% and 16% and Moreno et al.[9] with 31% and 15%. That is in disagreement with the results of Chrillo et al.[7] and Movahed et al.,[8] who indicated an association between DM and the outcome of IE.

When we attempted to separate the diabetic patients between those who used or did not use insulin, mortality persisted without a statistically significant difference between the two groups, as demonstrated by Olmos et al.[11] On the other hand, Duval et al.[12] obtained a different result, showing that insulin use was a strong and independent predictor of mortality in IE.

According to Wang,[31] the higher mortality rate observed in insulin users reported by Duval et al.[12] occurred because generally there is a higher prevalence of complications in patients with DM, such as coronary artery disease, renal failure, among others. In our sample, the groups of diabetic patients who were insulin users and non-insulin users were similar regarding these characteristics and there was no difference in the outcome, which may corroborate the hypothesis by Wang,[31] i.e., that the clinical evolution is more related to the state of vulnerability associated with DM complications. It is also possible that the type of treatment implemented is a determinant for prognosis, but this variable was not collected in our study and it was not possible to evaluate whether there was any difference between the groups.

We observed specific and relevant characteristics of the IE in insulin users in comparison to the other patients, related to the high prevalence of IE by *S. aureus* and the involvement of the tricuspid valve. In the study by Duval et al.,[12] *S. aureus* also represented the majority of insulin users, but the statistical significance was only observed when the entire *Staphylococcus spp* genus was considered. As for the results of Olmos et al,[11] which studied only cases of left-chamber IE, *S. aureus* was also more prevalent, with 27.6% of cases, but there was no statistical significance.

From the point of view of valvular involvement, the higher prevalence of IE in the tricuspid valve was not consistent with the findings of Duval et al.,[12] since there was no statistical significance in relation to this variable. It should be noted that in the study by Olmos et al.,[11] patients with right-chamber IE were excluded from the sample, which makes this comparison impossible and also raises the question whether this fact could have underestimated the proportion of IE caused by *S. aureus* among insulin users in their study.

It can be observed that the higher prevalence of IE by *S. aureus* and the significant tricuspid involvement among insulin users are similar characteristics to what is described in IE observed in intravenous drug users, a known and well established risk factor for IE. Our results showed 57.1% of IE by *S. aureus* in insulin users, whereas this rate has already been described in the literature as ranging from 64.2% to 82% among intravenous drug users.[1,30,32,33]

Regarding the tricuspid valve involvement,[32,34] rates have been reported as raging from 44% to 46% among intravenous drug users, and a rate of 33.3% was observed in the present study, which is in contrast with that observed in the general population, with 10% in our sample and 7% in South America, according to Murdoch et al.[1]

Study limitations

The present study has several limitations regarding its retrospective design. First, the difficulty in obtaining some information that would be relevant for sample characterization. It was not possible to obtain information on specific characteristics of non-diabetic patients, such as the proportion of patients with health-care related IE[28], which would attenuate the bias of the comparison of the *S. aureus* proportion in this group of patients. It was possible to collect specific characteristics in diabetic patients, but the criterion of previous hospitalization related to health-care related IE[28] was not used.

It was not possible to control for the quality, interval and location of blood collection for cultures, and sometimes the information on how many samples showed bacterial growth was not reported and, therefore, it is believed that some positive blood cultures, especially those in the ones that showed growth of coagulase-negative *Staphylococcus*, the result may be due to contamination.

Blood culture was not performed in 34 patients, which received empirical treatment or who had already started antibiotic therapy at the health services that referred them. It was not possible to collect data regarding the time of DM, glycemic control and quality of IE treatment received, whether surgical or not, which are information that directly reflect the prognosis of these patients.

Additionally, the sample size may be considered insufficient, since there is a considerable difference between the number of non-diabetic and diabetic patients

in our sample. The initial search for medical records through the International Classification of Diseases codes may have underestimated the total number of IE cases that occurred in these hospitals during the assessed period, considering the records may not have been performed in the presence of other diagnoses.

Conclusion

According to our results, diabetic patients did not show higher mortality rates in comparison to the others, even those who used insulin. In turn, we observed a statistically significant difference regarding the higher prevalence of IE by *S. aureus* and the greater involvement of the tricuspid valve among insulin users. Only two studies separately analyzed diabetics with IE who used or did not use insulin, and some of our results are in agreement and others in disagreement with these studies, which makes it difficult to generalize the results.

Nevertheless, it is reasonable to infer that these microbiological and valvular characteristics found in the insulin users of our sample may signal a particular IE profile in these patients. New observational studies considering the insulin use variable are necessary to understand whether these characteristics are identified in observational studies with significant samples and in different locations. Thus, by establishing and controlling the previous insulin use variable, it may be possible to obtain a better understanding of the factors involved in the association between DM and IE, aiming to clarify the current controversy.

Despite the limitations of observational and retrospective studies to confirm causal inferences, the analogy between the microbiological and valvular profile of the insulin user and the intravenous drug user is notable. The analogy is a piece of evidence of contestable strength; however, when associated with the fact that both are injectable substances and could share the same pathophysiological mechanism, it raises a hypothesis to be confirmed or rejected in future studies.

Acknowledgments

We thank Isabel Cristina Gomes for statistical support; Luiz Wellington Pinto, Maria do Carmo Pereira Nunes, Teresa Cristina de Abreu Ferrari, Milton Henriques Guimarães Junior and Beatriz Pinto Coelho Lott for technical-scientific support; Gilmar Alves Costa, Flávia Martins Alves Godinho, Jéssica Paula Gonçalves, Elcy de Oliveira Silva and Mirian Gonçalves Soares from Santa Casa BH; David da Silva from Hospital Universitario Ciências Médicas; Vivian Ribeiro Miranda, Alessandra Barbosa de Oliveira Andrade and Kenia Coeli Patrício Viana from Hospital Márcio Cunha.

Author contributions

Conception and design of the research: Bezerra R. Acquisition of data: Bezerra RL, Carvalho TF, Batista RS, Silva YM, Fiuza-Campos B, Castro JHM, Filho RMB, Monteiro PIP. Analysis and interpretation of the data: Bezerra RL, Carvalho TF, Batista RS, Silva YM, Fiuza-Campos B, Castro JHM, Filho RMB, Monteiro PIP. Statistical analysis: Bezerra RL, Alves MC. Obtaining financing: Bezerra RL, Batista RS, Monteiro PIP, Machado ELG. Writing of the manuscript: Bezerra RL. Critical revision of the manuscript for intellectual content: Bezerra RL, Machado ELG, Batista RS, Silva YM, Carvalho TF, Alves MC, Castro JHM.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by CNPq and FAPEMIG.

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 *Pesquisa da Ciências Médicas – MG* (CEPCM-MG) under the protocol number 1.856.064. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

References

1. Murdoch DR, Corey GR, Hoen B, Miró JM, Fowler VG Jr, Bayer AS, et al. Clinical presentation, etiology and outcome of infective endocarditis in the 21st century: the international collaboration on endocarditis-prospective cohort study. Arch Intern Med. 2009;169(5):463-73.
2. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015;132(15):1435-86.
3. Chu VH, Cabell CH, Benjamin DK Jr, Kuniholm EF, Fowler VG Jr, Engemann J, et al. Early predictors of in-hospital death in infective endocarditis. Circulation. 2004;109(14):1745-9.
4. 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.
5. Iser BPM, Stopa SR, Chueiri PS, Szwarcwald CL, Malta DC, Monteiro HOC, et al. Self-reported diabetes prevalence in Brazil: results from National Health Survey 2013. Epidemiol Serv Saúde. 2015;24(2):305-14.
6. Chirillo F, Bacchion F, Pedrocco A, Scotton P, De Leo A, Rocco F, et al. Infective endocarditis in patients with diabetes mellitus. J Heart Valve Dis. 2010;19(3):312-20.
7. Joshi N, Caputo GM, Weitekamp MR, Karchmer AW. Infections in patients with diabetes mellitus. N Engl J Med.1999;341(25):1906-12.
8. Movahed MR, Hashemzadeh M, Jamal MM. Increased prevalence of infective endocarditis in patients with type II diabetes mellitus. J Diabetes Complications. 2007;21(6):403-6.
9. Moreno R, Zamorano J, Almería C, Villate A, Rodrigo JL, Herrera D, et al. Influence of diabetes mellitus on short- and long-term outcome in patients with active infective endocarditis. J Heart Valve Dis. 2002;11(5):651-9.
10. Wallace SM, Walton BI, Kharbanda RK, Hardy R, Wilson AP, Swanton RH. Mortality from infective endocarditis: clinical predictors of outcome. Heart. 2002;88(1):53-60.
11. Olmos C, Vilacosta I, Pozo E, Fernández C, Sarriá C, López J, et al. Prognostic implications of diabetes in patients with left-sided endocarditis: findings from a large cohort study. Medicine (Baltimore). 2014;93(2):114-9.
12. Duval X, Alla F, Doco-Lecompte T, Le Moing V, Delahaye F, Mainardi JL, et al. Diabetes mellitus and infective endocarditis: the insulin factor in patient morbidity and mortality. Eur Heart J. 2007;28(1):59-64.
13. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med. 1994;96(3):200-9.
14. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30(4):633-8.
15. Hutin Y, Hauri A, Chiarello L, Catlin M, Stilwell B, Ghebrehiwet T, et al. Best infection control practices for intradermal, subcutaneous, and intramuscular injections. Bull World Health Organ. 2003;81(7):491-500.
16. Moss R, Munt B. Injection drug use and right sided endocarditis. Heart. 2003;89(5):577-81.
17. Camata DG. Local complications in the skin related to the administration of insulin. Rev Lat Am Enfermagem. 2003;11(1):119-22.
18. Kahara T, Kawara S, Shimizu A, Hisada A, Noto Y, Kida H. Subcutaneous hematoma due to frequent insulin injections in a single site. Intern Med. 2004;43(2):148-9.
19. Fleming DR, Jacober SJ, Vandenberg MA, Fitzgerald JT, Grunberger G. The safety of injecting insulin through clothing. Diabetes Care. 1997;20(3):244-7.
20. Tuazon CU, Perez A, Kishaba T, Sheagren JN. Staphylococcus aureus among insulin-injecting diabetic patients: an increased carrier rate. JAMA. 1975;231(12):1272.
21. Binswanger IA, Kral AH, Bluthenthal RN, Rybold DJ, Edlin BR. High prevalence of abscesses and cellulitis among community-recruited injection drug users in San Francisco. Clin Infect Dis. 2000;30(3):579-81.
22. Lipsky BA, Kollef MH, Miller LG, Sun X, Johannes RS, Tabak YP. Predicting bacteremia among patients hospitalized for skin and skin-structure infections: derivation and validation of a risk score. Infect Control Hosp Epidemiol, 2010;31(8):828-37.
23. Monami M, Mannucci E, Masotti G. Finger sepsis in two poorly controlled diabetic patients with reuse of lancets. Diabetes Care. 2002;25(6):1103.
24. Ryan EA, Miller J, Skyler JS. Finger sepsis: possible complication of self monitoring of blood glucose concentrations. Br Med J (Clin Res Ed). 1983;286(6378):1614-5.
25. Suzuki Y, Atsumi Y, Matsnoka K. Finger infection resulting from self-monitoring of blood glucose and a new aid for reducing risk. Diabetes Care. 1998;21(8):1373-4.
26. Hochman B, Nahas FX, Oliveira Filho RS, Ferreira LM. Research designs. Acta Cir Bras. 2005;20(suppl 2):2-9.
27. Miot HA. Sample size in clinical and experimental trials. J Vasc Bras. 2011;10(4):275-8.
28. Yang F, Zhang B, Yu J, Lingyun Shao, Pu Zhou, Liping Zhu, et al. Epidemiology and the prognosis of healthcare-associated infective endocarditis in China: the significance of non-nosocomial acquisition. Emerg Microbes Infect. 2015;4(7):e38.
29. 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.
30. Ruiz Jr E, Schirmbeck T, Figueiredo LTM. A study of infective endocarditis in RibeirãoPreto, SP - Brazil. Analysis of cases occurring between 1992 and 1997. Arq Bras Cardiol. 2000;74(3):217-31.
31. Wang A. Diabetes mellitus and insulin therapy in infective endocarditis. Eur Heart J. 2007;28(1):3-4.
32. Mathew J, Addai T, Anand A, Morrobel A, Maheshwari P, Freels S. Clinical features, site of involvement, bacteriologic findings, and outcome of infective endocarditis in intravenous drug users. Arch Intern Med. 1995;155(15):1641-8.
33. Hecht S, Berger M. Right-sided endocarditis in intravenous drug users. Prognostic features in 102 episodes. Ann Internal Med. 1992;117(7):560-6.
34. Dressler FA, Roberts WC. Infective endocarditis in opiate addicts: analysis of 80 cases studied at necropsy. Am J Cardiol. 1989;63(17):1240-57.

EDITORIAL

Pain after Cardiac Surgery

Tirone E. David

Division of Cardiac Surgery of the Peter Munk Cardiac Centre at Toronto - General Hospital and the University of Toronto, Toronto, Ontario - Canada

Most cardiac operations are performed via median sternotomy and cardiopulmonary bypass. Both thoracic incision and cardiopulmonary bypass cause major disturbances in the homeostasis of the patient. Disruption of the tissues by the incision initiates an immediate neurological reaction perceived as pain and an intense biochemical and cellular response to repair the wound. Cardiopulmonary bypass causes far more serious systemic changes in homeostasis than pain, and that is probably the main reason why cardiac surgery is behind other surgical specialties in the development of minimally invasive procedures. Pain associated with surgical incision is largely self-limited and resolves with time and, luckily, so do the changes caused by cardiopulmonary bypass. Obviously, surgical incisions that cause less tissue damage are associated with lower degrees of pain and metabolic disturbance than larger and more traumatic incisions.

In this issue of the International Journal of Cardiovascular Sciences, Silva and colleagues,[1] from the University of Fortaleza, Brazil, report a comparative study on postoperative pain following conventional median sternotomy and right mini-thoracotomy. The study has limitations because of the sample size (there were only 17 patients in each arm), the endpoint of the study was largely subjective, and patients were not randomized. However, as one would expect, both groups of patients complained of pain in the first three days but fewer patients with mini-thoracotomy complained of pain by the seventh postoperative day. In addition, mini-thoracotomy was associated with pain of lower intensity, fewer sites, and shorter duration than median sternotomy.

Minimally invasive cardiac surgery was developed in the early 1990's consisting of partial or transverse sternotomy. The benefits, however, were largely cosmetic because of the length of time it took for the sternum to heal. Soon after, small thoracotomies were introduced for performance of coronary artery bypass, heart valve repair and replacement, and repair of congenital heart defects. The development of new surgical instruments and enhanced visualization including 3-D endoscopes have facilitated the performance of these operations. There have been many comparative studies on the early outcomes of heart surgery with conventional sternotomy and small thoracotomy but few randomized studies and no multicenter study. Case-control studies have consistently shown less pain and faster recovery compared with the conventional approach. Other advantages of minimally invasive surgery are less blood loss and lower transfusion rate and lower risk of postoperative atrial fibrillation, a common complication of heart surgeries that frequently prolongs hospital stay and requires hospital readmission. The incidence of stroke and occurrence of other neurological disturbances are often higher with minimally invasive approaches largely because of the need for peripheral arterial cannulation. In many centers, a computed tomography scan of the aorta is obtained before offering minimally invasive surgery to older patients.

The use of minimally invasive techniques has been lower than expected, even for procedures that can be safely performed through a small right thoracotomy such as isolated mitral valve surgery. A recent report from the Society of Thoracic Surgeons National Database on isolated mitral valve surgery in the United States showed that only 23% were performed using minimal invasive approaches including partial sternotomy.[2] Mean age of the patients was 64 years and this may be an influencing

Keywords

Minimally Invasive Surgical Procedures; Cardiovascular Surgical Procedures; Sternotomy; Postoperative Care.

Mailing Address: Tirone E. David
200 Elizabeth St. 4N453, Toronto, Ontario M5G 2C4 - Canada
E-mail: tirone.david@uhn.ca

DOI: https://doi.org/10.36660/ijcs.20190188

factor for the decision to perform a minimally invasive approach. But more importantly, I believe, is the fear of failure. Today, elective cardiac surgery is expected to be performed with very low operative mortality and morbidity, and experienced cardiac surgeons are reluctant to change. The ingrained "do no harm" prevents us from adopting newer surgical approaches than the ones we have mastered. Innovation and progress require that we step out of our comfort zone while keeping patients safe.

References

1. Silva JF, Cavalcante MP, Montenegro RB, Lira R, Melo EC, Castro JV. Minimally invasive cardiac surgery versus sternotomy - Pain investigation. Int J Cardiovasc Sci. 2020;33(1):24-33.
2. Gammie JS, Chikwe J, Badhwar V, Thibault DP, Vemulapalli S, Thourani VH, et al. Isolated Mitral Valve Surgery: The Society of Thoracic Surgeons Adult Cardiac Surgery Database Analysis. Ann Thorac Surg. 2018;106 (3):716-27.

SBC2020
Fortaleza

75° CONGRESSO BRASILEIRO DE CARDIOLOGIA

Agende esta data!

25 a 27 de setembro de 2020

Centro de Eventos do Ceará

SOCIEDADE BRASILEIRA DE CARDIOLOGIA
SBC
1943

International Journal of Cardiovascular Sciences. 2020;33(1):24-33

ORIGINAL ARTICLE

Minimally Invasive Cardiac Surgery versus Sternotomy - Pain Investigation

Juliana Fernandes Silva, Marcela Paula Cavalcante, Roger Benevides Montenegro, Romulo Lira, Emanuel Carvalho Melo, Josue Viana Castro

Universidade de Fortaleza (UNIFOR), Fortaleza, CE - Brazil

Abstract

Background: Treatment of postoperative (PO) pain is essential after surgery, as it contributes to a faster rehabilitation. Assessment of PO pain after minimally invasive (MI) surgery has not been regularly addressed, especially when compared with median sternotomy (MS).

Objective: This study aims to evaluate the intensity of thoracic pain in the PO period in patients subjected to MI surgery and MS.

Methods: This study compared the intensity of thoracic pain in 34 patients subjected to minimally invasive (MI; n = 17) and median sternotomy (MS; n = 17) from June 2015 to June 2016. The intensity and sites of pain in the PO period, assessed using the visual numeric pain scale, and the need for pain medications were analyzed using the Student's t-test and the z test, with confidence level of 95% ($p < 0.05$).

Results: Almost all patients reported pain on the third PO day (MS = 94.1% and MI = 88.2%; p = 0.5410). On the seventh PO day, there were significantly more patients free of pain in the group of patients subjected to the MI procedure (MS = 94.1% and MI = 64.7%; p = 0.0341). also, these patients reported fewer pain sites (3rd PO day: MS = 3.2 ± 1.5; MI = 1.5 ± 1.2; p = 0.001; 7th PO day: MS = 3.1 ± 1.4; MI = 0.9 ± 0.9; p = 0.000). Patients undergoing MS reported higher pain intensity and longer lasting pain (3rd PO: MS = 4.8 ± 2.2; MI = 3.0 ± 1.6; 7th PO: MS = 5.3 ± 2.0; MI = 1.2 ± 1.3; p = 0.001), with no difference in pain intensity between the third and the seventh PO days (p = 0.4931). In addition, patients subjected to MI procedure had a significant decrease in pain intensity from the third to the seventh PO days (p = 0.001).

Conclusion: According to these results, we concluded that a MI procedure leads to lower intensity of pain in the PO period (from the third PO day on) when compared to a MS; also, patients undergoing MI patients reported fewer pain sites. (Int J Cardiovasc Sci. 2020;33(1):24-33)

Keywords: Minimally Invasive Surgical Procedures; Cardiovascular Surgical Procedures; Sternotomy; Postoperative Care.

Introduction

Minimally invasive (MI) cardiac surgery is a safe procedure with similar mortality and morbidity, but better surgical outcomes compared with conventional sternotomy (MS) in some groups of patients.[1–4] The potential benefits of MI procedures include better stability of the sternum in the postoperative period, with implications on deep infection prevention, improvement of respiratory function, mobility and bleeding.[5] The MI approach was introduced to reduce surgical trauma with better cosmetic results; this approach is currently applied to procedures including valve and septal defect surgeries.[6,7]

Pain has been shown to be one of the primary sources of concern in surgical patients,[8] even though it is expected in the postoperative (PO) period. Inadequate management of pain can have profound clinical (deep vein thrombosis, pulmonary embolism, coronary ischemia, myocardial infarction, pneumonia, and poor wound healing) and

Mailing Address: Juliana Silva
Av. Washington Soares, 1321. Postal Code: 60811-905, Edson Queiroz, Fortaleza, CE – Brazil.
E-mail: s.juliana.fernandes@gmail.com

DOI: 10.5935/2359-4802.20190048

Manuscript received on March 20, 2018, revised manuscript on December 02, 2018, accepted on February 17, 2019.

psychological (insomnia) implications that increase morbidity and mortality.[8,9]

In the last few years, there has been a significant increase in knowledge about PO pain and tissue trauma that influence the choice for MI surgical procedures.[1,9] Although a median sternotomy (MS) remains the main access in cardiac surgeries, the intercostal access combined with a MI approach has been progressively used.[2,3,5,6,10] Systematic assessment and treatment of pain is essential after cardiac surgery and can contribute to a faster recovery and rehabilitation of patients.[11] Some studies have reported less PO pain and shorter in-hospital stays after a MI procedure,[1,3,12–14] but the literature lacks a comparative study between MS and MI procedures regarding pain intensity (PI). This prospective observational study aims to evaluate the PO thoracic PI by comparing patients subjected to a MI and MS procedures. We evaluated if patients with valve and septal defects subjected to MI procedure have less PO pain compared with those undergoing MS.

Materials and methods

Study population

We evaluated PO thoracic pain in 34 patients who were subjected to MS or MI procedure between June 2015 and June 2016. The Institutional Review Board of the university approved this prospective observational comparative study (approval number 1104.606). We included symptomatic patients presenting with mitral valve (MV) disease or an atrial septal defect (ASD). Exclusion criteria were patients older than 60 years old, patients with body mass index (BMI) (for the MI group only) greater than 32 kg/m^2, chronic obstructive lung disease, previous heart or thoracic interventions, renal failure, interstitial or inflammatory lung disease, thoracic deformities, mitral valve or aortic calcifications, systolic pulmonary pressure greater than 80 mmHg, coronary artery disease, severe tricuspid valve insufficiency, femoral vessel calcification, femoral artery smaller than 5 mm, moderate or severe aortic valve insufficiency, requirement for re-intervention for any cause after the end of surgical procedure, communication impairments, pain syndrome before the procedure, and patients who withdrew consent at any moment throughout the study. The surgical access technique was chosen according to the pathoanatomical characteristics of each patient and the recommended surgical protocol. The patients were divided in two groups: MS (n = 17) and MI (n = 17). Written informed consent was obtained from all patients before treatment.

Surgical technique

The surgical procedures were all carried out by the same surgeon (JVC). The patients underwent surgical interventions under general anesthesia and a cardiopulmonary bypass with moderate hypothermia and cold crystalloid cardioplegic arrest.

Description of the MS procedure: a main incision of twenty centimeters was performed followed by bone division from the manubrium to xiphoid. A sternal retraction was made to provide a 12-centimeter working space, with full vision of the heart and vessels. The second incision was made two centimeters below main incision for placement of a chest tube drain. Arterial perfusion was achieved by direct cannulation of the ascending aorta. Systemic venous return was achieved with two individual caval cannulas. The aortic occlusion was made by direct clamping of the aorta. Usual techniques and instruments were applied for the procedure.

Minimally invasive procedure: main surgical access was a right minithoracotomy (5 centimeters) into the fourth intercostal space. A periareolar incision and a submammary incision were made for men and women, respectively, between the midclavicular and the anterior axillary line for valve surgery and on the midclavicular line for atrial septal defect closure. The main incision was enlarged with a wound protector and soft tissue retractor (ALEXIS™), and a steel retractor was used as necessary during the procedure. Three auxiliary 5 mm ports were placed in the anterior axillary line. In the second space, the port was used for placement of a transthoracic aortic cross-clamp to obtain an aortic occlusion. In the fourth space, a 30-degree high definition camera was placed. In the seventh space, the port was used for atrial venting and CO_2 flow in the operative field at 2 L/min. This port was also used for placement of a 24 F BlakeTM drain at the end of the procedure An atrial lift retractor system was positioned at the fourth intercostal space near the sternum, when required. Femoral arterial perfusion was performed using a cannula adjusted for patient's body surface and internal diameter of the femoral artery. The cannula was inserted by direct puncture using the Seldinger`s technique. The vacuum assisted venous return with a single right femoral venous cannula was associated or not with a right jugular venous cannula. Patients

were monitored by a transesophageal echocardiogram. Specific instruments for minimally invasive surgery were used.

Management of postoperative thoracic pain

The same protocol for induction and maintenance of anesthesia was followed in all patients. All of them were intubated with a single lumen endotracheal tube that remained until extubation criteria were met. In the first 48 hours, the patients received 1 g of dipyrone every 6 hours and 100 mg of tramadol every 8 hours for pain relief. According to each patient's needs, 2 mg of morphine was administered. After this initial management, 500 mg of dipyrone were administered orally every 6 hours with or without 50 mg of tramadol, if necessary.

Thoracic pain evaluation

Thoracic pain was assessed using the Visual Numeric Scale (VNS).[15] Patients were instructed on the use of the VNS before the surgery. In the VNS, pain is rated from zero to 10, where zero indicates no pain and 10 the maximum pain level tolerated by the patient. Pain data were obtained on the third and seventh PO days. All patients were free of chest tubes at the moment of data collection. Patients were asked about the presence of pain, and for positive responses, pain location was registered, and PI rated on the scale. This was repeated for each pain site, if there was more than one. The pain drugs were then verified and registered.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Science (SPSS) software for Windows™, version 17.0 or the Statistica 12. A power of 80% was calculated for 34 patients (17 in each group). Normality of the data was determined using the Kolmogorov-Smirnov test, and homogeneity of the variance was assured by the Levene's test. Results were expressed as mean and standard deviation (mean ± SD) for continuous variables; categorical data were summarized by frequencies and percentages and compared by a z test for two proportions. Data were parametric and compared using paired (within group comparisons) and unpaired (between group comparison) Student's t test, with a confidence level of 95% ($p < 0.05$).

Results

Demographic and clinical data, including the presence of cardiovascular risks factors in the study groups are described in Table 1. Most patients were women, and age was not different between the groups. Weight and BMI were different between the groups, probably due to the non-inclusion of patients with BMI > 32 kg/m^2 in the MI group. The prevalence of comorbidities was not relevant, except for systemic arterial hypertension. Mitral valve insufficiency was the main diagnosis, followed by *ostium secundum* atrial septal defects, mitral valve stenosis, and *ostium primum* atrial septal defects.

Patients were subjected to mitral valve surgical repair or replacement (MS n = 11 and MI n = 9) or surgical closure of an atrial septal defect (MS–n = 6 and MI-n = 8). Procedures for mitral correction included bioprosthetic replacement (7 in the MS group and 8 in the MI group) and mitral valve repair (4 in the MS group and 1 in the MI group). Valve resection, valve reconstruction, and semi-rigid ring annuloplasty were the main procedure for mitral repair. In the MS group, one patient required a Neochord placement, and no patient was subjected to pulmonary vein isolation. Regarding the procedures for atrial septal defect closure, there were one suture closure and five patch closures in the MS group and three suture closures and five patch closures in the MI group.

Table 2 lists the PO data for the MS and MI groups. The MS procedure time was shorter than MI procedures. No difference was observed in mean aortic cross-clamping time or cardiopulmonary bypass time between the groups. Despite longer procedural times, MI patients needed less intensive care unit time for recovery in comparison with MS patients (Table 2). Mean hospital stay after the procedure was longer in the MS than in MI group. None of the patients had major complications, stroke or death after the surgery.

The PO pain evaluation indicated that most of the patients reported pain on the third PO day (MS = 94.1% and MI = 88.2%; p = 0.5410). On the seventh PO day, significantly more patients were free of pain in the MI group compared with the MS group (MS = 94.1% and MI = 64.7%; p = 0.0341). The patients in the MI group reported fewer pain sites than the patients in the MS group (Figure 1) on the third (MS = 3.2 ± 1.5; MI = 1.5 ± 1.2; p = 0.001) and seventh (MS = 3.1 ± 1.4; MI = 0.9 ± 0.9; p = 0.000) PO day.

Table 1 - Demographic and clinical characteristics of patients enrolled in the study

Characteristics	MS group (n = 17)	MI group (n = 17)	p-value
Age (years)	47.60 ± 15.10	40.10 ± 13.90	0.100
Gender (n/%)			
Male	6/35.30%	3/17.60%	0.200
Female	11/64.70%	14/82.4%	
Weight (kg)	71.90 ± 13.40	60.70 ± 10.1	0.010*
Hight (cm)	1.62 ± 0.09	1.61 ± 0.06	0.600
BMI (kg/m^2)	27.10 ± 3.70	23.30 ± 3.90	0.007*
Diagnosis (n/%)			
Mitral insufficiency	10/58.80%	6/35.30%	0.400
OSASD	4/23.50%	6/35.30%	
OPASD	1/5.90%	1/5.90%	
SVASD	1/5.90%	0/0.00%	
PFO	0/0.00%	1/5.90%	
Mitral stenosis	1/5.90%	3/17.60%	
Comorbidities (n/%)			
Smoking	1/5.90%	1/5.90%	1.000
Drinking	0/0.00%	2/11.80%	0.300
Systemic arterial hypertension	10/58.80%	3/17.60%	0.010*
Diabetes mellitus	1/5.90%	1/5.90%	1.000
Stroke	1/5.90%	0/0.00%	1.000
Transient ischemic attack	0/0.00%	1/5.90%	1.000
COPD	0/0.00%	0/0.00%	
Dyslipidemia	1/5.90%	0/0.00%	1.000
Thrombolysis	1/5.90%	0/0.00%	1.000

*MS: median sternotomy; MI: minimally invasive; n: number of patients; %: frequency; OSASD: ostium secundum atrial septal defect; OPASD: ostium primum atrial septal defect; SVASD: sinus venosus atrial septal defect; PFO: patent foramen ovale; COPD: chronic obstructive pulmonary disease. *p < 0.05 between groups by unpaired Student's t-test for continuous variables and z test for categorical variables.*

The main sites of pain were those related to the surgical incision site. The upper area of the sternum (around the manubrium) was more painful for the MS group and the right submammary region was more painful for the MI group (Table 3). PI was different between the groups. The MS group had more intense pain than the MI group on the third PO day and on the seventh PO day. The MS group showed a mean of 5.3 ± 2.0 of maximal PO thoracic PI three days after the procedure, which was not significantly decreased on the seventh day after the surgical procedure (4.8 ± 2.2; p = 0.4931). The maximum PI reported by MI patients was significantly (p = 0.001) decreased from the third (3.0 ± 1.6) to the seventh PO day (1.2 ± 1.3). The comparison between groups demonstrated that the postoperative PI was higher and lasted longer in the MS group than in the MI group (p = 0.001) (Figure 2).

These data were in accordance with the medical necessity to control the symptoms. On the 3rd PO day, all

Table 2 - Postoperative data of the patients

	MS group (n = 17)	MI group (n = 17)	p-value
Surgery (n/%)			
Mitral valve replacement	7/41.2	8/47.1	
Atrial septal defect closure	6/35.3	8/47.1	0.300
Mitral reconstruction	4/23.5	1/5.9	
Procedure time (minutes)	194.7 ± 60	251.0 ± 52.3	0.006*
Extracorporeal circulation time (minutes)	101.8 ± 35.4	118.4 ± 26.1	0.100
Cross-clamp time (minutes)	78.2 ± 33.5	88.5 ± 21.9	0.300
ICU time (hours)	52.2 ± 16.8	33.7 ± 12.7	0.001*
Hospital length of stay (days)	6 ± 1.4	3.5 ± 0.9	0.001*

*MS: median sternotomy; MI: minithoracotomy; n: number of patients; %: frequency; ICU: intensive care unit. *p < 0.05 between groups, unpaired Student's t-test for continuous variables and z test for categorical variables; 95% confidence level.*

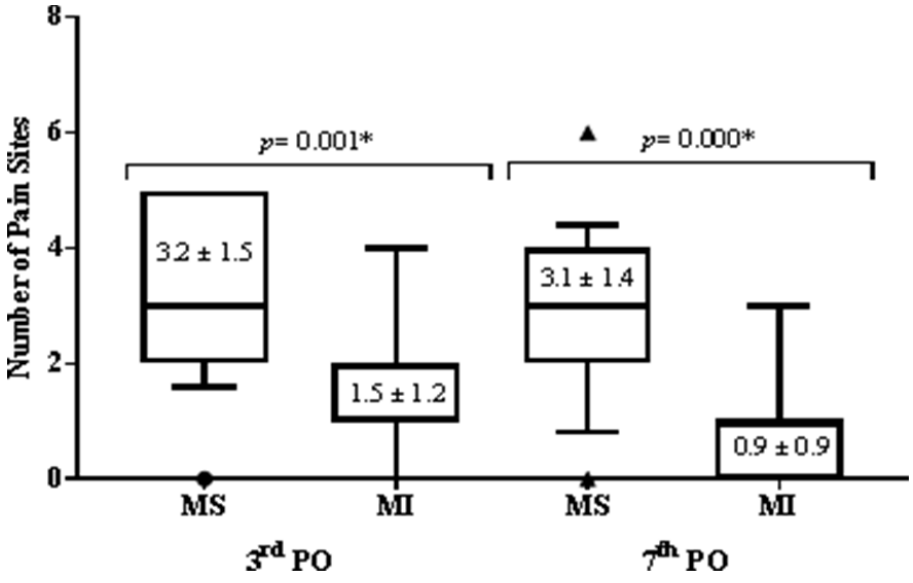

Figure 1 - Number of pain sites in patients undergoing minimally invasive cardiac surgery and median sternotomy on the third and seventh postoperative days. Box plot of the number of pain sites reported by 34 patients (17 patients subjected to minimally invasive cardiac surgery, MI, and 17 to median sternotomy, MS) on the third (3rd) and seventh (7th) postoperative days. Circles and triangles represent outliers.
**p < 0.05 between groups, unpaired Student's t-test at 95% confidence level.*

patients in the MS group and 16 patients in the MI group were receiving pain medications (p = 0.3052). On the 7th PO day, 16 patients in the MS group and only six in the MI group were receiving pain medications (p = 0.0003).

Discussion

The present study showed that, in patients undergoing surgical treatment for mitral valve and septal defects,

Table 3 - Pain intensity according to patients' body area

	MS group (n = 17)		p-value*	MI group (n = 17)		p-value*
Body region	3rd PO	7th PO		3rd PO	7th PO	
Right periclavicular	0.7 ± 2.0	0.7 ± 2.0	1.000	0.0	0.0	1.000
Left periclavicular	0.4 ± 1.6	0.2 ± 1.2	0.300	0.0	0.0	1.000
Intersection between 2nd right intercostal space and right anterior axillary line	0.0	0.0	1.000	0.4 ± 1.0	0.0	0.100
Intersection between 4th right intercostal space and right anterior axillary line	0.0	0.0	1.000	0.0	0.0	1.000
Intersection between 7th right intercostal space and right anterior axillary line	0.0	0.0	1.000	0.2 ± 1.2	0.0	0.300
Periareolar	0.4 ± 1.6	0.2 ± 1.2	0.300	0.5 ± 1.2	0.1 ± 0.5	0.300
Submammary	0.4 ± 1.6	0.2 ± 1.2	0.700	1.3 ± 1.4	0.5 ± 0.9	0.070
Upper sternal	4.0 ± 2.6	2.8 ± 2.0	0.070	0.1 ± 0.7	0.0	0.300
Lower sternal	3.5 ± 2.7	3.0 ± 1.9	0.400	0.1 ± 0.4	0.1 ± 0.7	0.700
Subxiphoid	1.4 ± 2.2	0.2 ± 8.0	0.060	0.0	0.0	1.000
Intersection between 2nd left intercostal space and left anterior axillary line	0.0	0.0	1.000	0.0	0.0	1.000
Intersection between 4th left intercostal space and left anterior axillary line	0.0	0.0	1.000	0.0	0.0	1.000
Intersection between 7th left intercostal space and left anterior axillary line	0.0	0.0	1.000	0.0	0.0	1.000
Right inguinal	0.3 ± 1.4	0.0	0.300	0.0	0.0	1.000
Left inguinal	0.0	0.0	1.000	0.0	0.0	1.000
Posterior cervical	1.0 ± 2.2	0.6 ± 1.9	0.600	0.0	0.0	1.000
Right scapular	2.5 ± 3.1	1.7 ± 3.0	0.500	0.2 ± 0.9	0.0	0.300†
Left scapular	1.4 ± 2.4	2.5 ± 3.3	0.100	0.8 ± 1.6	0.2 ± 0.6	0.100†
Vertebral	0.8 ± 1.9	1.2 ± 2.5	0.600	0.0	0.0	1.000
Right infrascapular	0.0	0.0	1.000	0.2 ± 1.2	0.4 ± 1.1	0.500
Left infrascapular	0.4 ± 1.6	0.0	0.300	0.2 ± 1.2	0.4 ± 1.3	0.300

*Caption: MS: median sternotomy; MI: minithoracotomy; n: number of patients; %: frequency; PO: postoperative; *within group by paired Student's t-test for continuous variables and z test for categorical variables; †p < 0.05 between groups by unpaired Student's t-test for continuous variables and z test for categorical variables; 95% confidence level.*

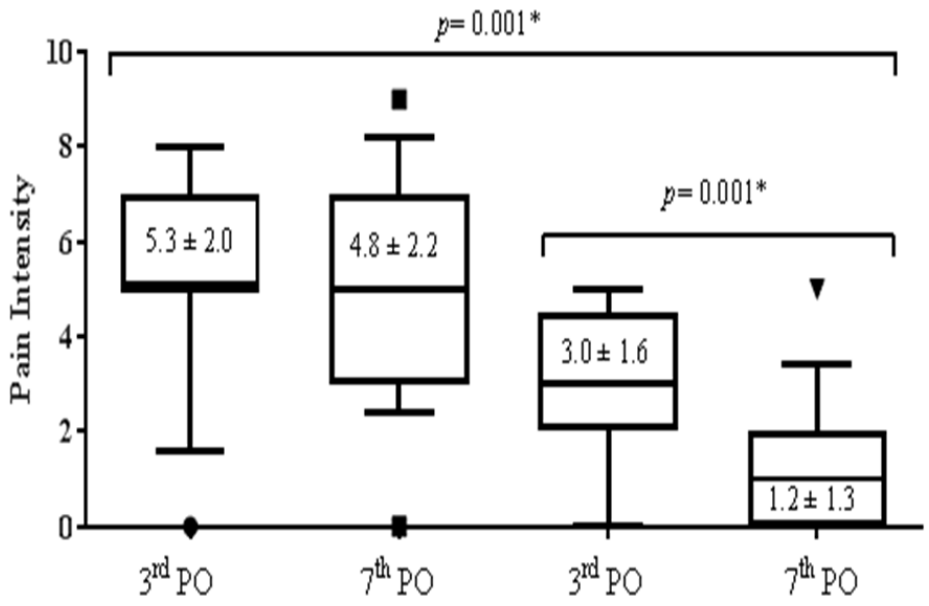

Figure 2 - Pain intensity levels for patients undergoing minimally invasive cardiac surgery and median sternotomy on the third and seventh postoperative days. Box plot of pain intensity reported by the 34 patients (17 patients subjected to minimally invasive cardiac surgery, MI, and 17 to median sternotomy, MS) on the third (3rd) and seventh (7th) postoperative days. Squares, circles and triangles represent outliers.
** p < 0.05 between groups (unpaired Student's t-test) and within group (paired Student's t-test).*

those subjected to MI procedure had less pain from the third PO day on and fewer sites of pain than the patients who underwent a sternal procedure. Our findings showed that a reduction in PI can lead to better recovery, indicated by shorter ICU and hospital stays as well as a diminished need for pain relief medications.

In the 1990s, MI techniques were initially used in cardiac surgeries.[7,16–18] Meanwhile, Carpentier et al.,[19] Chitwood et al.,[20] Vanermen et al.,[21] and Mohr et al.,[22] established the MI approach for mitral valve surgery, and numerous studies started to report the feasibility, safety and efficacy of these procedures.[1–5] However, although many studies have evaluated the advantages of MI cardiac procedures, including pain sites and PI, in addition to hospital stay duration,[1–3,5,6,10,23] none of them performed a systematic comparison between MI and MS procedures regarding PO pain.

In the current investigation, we studied patients with mitral valve disease and patients with septal defects, since these are among the most prevalent cardiovascular diseases among Brazilian adults[24] that can be addressed by either MI or MS procedure. The main surgical procedure was valve replacement followed by valve reconstruction, and the most common cause of valve dysfunction was inflammatory in both groups.

The procedure time was longer in the MI group in comparison to the MS group, as reported in many other studies.[6,7,10,18,22,25–29] This difference was due to intrinsic characteristics of the MI procedure, which demands a femoral incision for echo-guided cannulation before the insertion of chest ports. Although a longer cardiopulmonary bypass and cross-clamp times may lead to higher mortality and morbidity,[30] Raja et al.,[7] demonstrated that these adverse outcomes were not evident in the MI group. Differently from other studies on MI procedures,[28,31–33] we observed similar circulatory support and clamp times between the groups. These surgical variables are related to the complexity of the surgical procedure (mainly valve replacement) as well as the surgeon's experience. In addition, the time for cardiopulmonary bypass could be reduced by percutaneous insertion of the cannula. Of note, the higher weight and body surface in the MS group was due to the exclusion criterion of a BMI greater than 32 kg/m^2 in the MI group. Despite this, we do not believe that BMI is directly related to PI in the PO period, as we do not report any complication related to higher BMIs in this period.

Table 4 - Assessment of pain medications in the postoperative of patients undergoing minimally invasive cardiac surgery and median sternotomy

	MS group (n = 17)		p-value*	MI group (n = 17)		p-value*
	3rd PO day	7th PO day		3rd PO day	7th PO day	
Pain drugs (n/%)	17.0/100.0	15.0/88.3	0.600	16.0/94.1	6.0/35.3†	0.010*
Daily prescriptions	1.1 ± 0.3	1.0 ± 0.8	0.600	0.9 ± 0.2	0.3 ± 0.4	0.010*
Daily frequency	4.4 ± 1.8	3.0 ± 1.6	0.040*	3.1 ± 1.2	0.8 ± 1.4†	0.001*

*MS: median sternotomy; MI: minithoracotomy; n: number of patients; %: frequency; PO: postoperative; *: p < 0.05 within group by paired Student's t-test for continuous variables and z test for categorical variables; † p<0.05 between groups by unpaired Student's t-test for continuous variables and z test for categorical variables; 95% confidence level.*

In addition, the number and sites of the incisions differed between the groups. The MS group had two thoracic incisions (main and chest tube incisions). The MI group had two incisions (thoracic and inguinal) and at least three right thoracic punctures. For the main incision, we used a wound protector for soft tissue[34] to diminish intercostal retraction that could lead to nerve stimulation[11,35] during the procedure (e.g. valve replacement), which could be a cause of pain. We observed moderate to intense pain after both surgical approaches (MS and intercostal). According to the literature, at least 60% of the patients who underwent MS and MI procedures report moderate to severe pain in the early PO days.[1] As expected, the main sites of pain were directly related to the surgical incision, i.e., the sternal wound for MS patients and the inframammary area for patients who underwent MI procedure, although the MS group also reported extra-wound pain sites (posterior thoracic area). Although MI procedure involves a higher number of incision/punctures, these patients did not report more pain sites as compared with those undergoing MS procedure.

Regarding PI, we observed that the most remarkable differences between the groups occurred on the seventh PO day. There were no significant differences in PI between the third and the seventh PO days in the MS group. This data agrees with the study by Mueller et al.,[27] that indicated a slow reduction of thoracic pain following a sternal based procedure. On the other hand, there was a statistically significant reduction in PI from the third to the seventh PO days in the MI group. The presence of moderate to severe pain on the third PO day for both groups was in accordance with previous studies.[1,11,23,35,36] Landrenaeu et al.,[37] and Nagahiro et al.,[38] compared conventional posterolateral thoracotomy with MI (video-assisted) thoracotomy procedures and verified that the MI approach promoted less postoperative PI. The advantages regarding PI and length of hospital stay for the MI procedures are well established[1] and were corroborated in our study. In patients subjected to MI procedure, there was lower PO pain and need for pain medication, and shorter ICU and hospital stay (19 hours shorter and two and a half days shorter, respectively). It is worth mentioning that although the group differed in the presence of comorbidities, no PO complications related to these conditions were found in neither of the groups, such as hypertensive crisis or pulmonary complications.

This work resulted in important findings regarding PO pain, a symptom often overlooked by healthcare professionals dealing with cardiac surgery. Wildgaard et al.,[11] noted that the strategies for PO pain control after thoracic procedures has evolved in the last years. However, inadequate pain management still affects the quality of life and postoperative outcomes of cardiac surgery patients,[8,9] whereas adequate pain control results in better rehabilitation after a cardiovascular surgical procedure. Thus, pain management is a challenging task, as it demands attention by health professionals in making correct decisions towards medications and PI ratings, considering patients' pain tolerance and differences between protocols.

Despite all advances in the diagnosis and management of PO pain, accurate evaluation of this symptom is still very difficult, since the perception of pain and the response to pain medications vary widely between individuals. Also, the experience of the surgical team on MI procedures reduces possible complications of this type of surgery. A multicenter study involving larger

number of patients should be performed to confirm the differences in PI reported in our study and to overcome the limitations of this study.

Conclusion

Patients subjected to a MI cardiac procedure reported lower PI and fewer pain sites from the third PO day on, and showed lower need for pain medication and shorter ICU stay when compared to those subjected to a MS procedure. Based on these results, our study reinforces the advantages of a MI procedure for valve surgery.

Author contributions

Conception and design of the research: Silva JF, Castro JV, Montenegro RB, Lira R and Melo EC. Acquisition of data: Silva JF and Cavalcante, MP. Analysis and interpretation of the data: Silva JF, Castro JV and Melo EC. Writing of the manuscript: Silva JF, Cavalcante MP, Montenegro RB, Lira R, Melo EC, Castro JV.Critical revision of the manuscript for intellectual content: Silva JF, Cavalcante MP, Montenegro RB, Lira R, Melo EC, Castro JV.

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 Juliana Fernandes Silva, from *Universidade de Fortaleza* (UNIFOR).

Ethics approval and consent to participate

This study was approved by the Human Research Ethics Committee of *Universidade de Fortaleza* (Coética) under the protocol number 1104.606. 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. Walther T, Falk V, Metz S, Diegeler A, Battellini R, Autschbach R, et al. Pain and quality of life after minimally invasive versus conventional cardiac surgery. Ann Thorac Surg. 1999;67(6):1643-7.
2. Mihaljevic T, Cohn LH, Unic D, Aranki SF, Couper GS, Byrne JG. One thousand minimally invasive valve operations. Ann Surg. 2004;240(3):529-34.
3. Soltesz EG, Cohn LH. Minimally invasive valve surgery. Cardiol Rev. 2007;15(3):109-15.
4. Castro Neto JV, Melo EC, Silva JF, Rebouças LL, Corrêa C, Germano AQ, et al. Minimally invasive procedures – direct and video-assisted forms in the treatment of heart diseases. Arq Bras Cardiol. 2014;102(3):219-25.
5. Tabata M, Umakanthan R, Cohn LH, Bolman RM, Shekar PS, Chen FY, et al. Early and late outcomes of 1000 minimally invasive aortic valve operations. Eur J Cardio-Thoracic Surg. 2008;33(4):537-41.
6. Sündermann SH, Sromicki J, Rodriguez Cetina Biefer H, Seifert B, Holubec T, Falk V, et al. Mitral valve surgery: right lateral minithoracotomy or sternotomy? A systematic review and meta-analysis. J Thorac Cardiovasc Surg. 2014;148(5):1989-95.e4.
7. Raja SG, Navaratnarajah M. Impact of minimal access valve surgery on clinical outcomes: current best available evidence. J Card Surg. 2009;24(1):73–9.
8. Carr DB, Goudas LC. Acute pain. Lancet. 1999;353(9169):2051-8.
9. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg. 2003;97(2):534-40.
10. Iribarne A, Russo MJ, Easterwood R, Hong KN, Yang J, Cheema FH, et al. Minimally invasive versus sternotomy approach for mitral valve surgery: a propensity analysis. Ann Thorac Surg. 2010;90(5):1471-7.
11. Wildgaard K, Ravn J, Kehlet H. Chronic post-thoracotomy pain: a critical review of pathogenic mechanisms and strategies for prevention. Eur J Cardio-thoracic Surg. 2009;36(1):170-80.
12. Cremer JT, Böning A, Anssar MB, Kim PY, Pethig K, Harringer W, et al. Different approaches for minimally invasive closure of atrial septal defects. Ann Thorac Surg. 1999;67(6):1648-52.
13. Black MD, Freedom RM. Minimally invasive repair of atrial septal defects. Ann Thorac Surg. 1998;65(3):765-7.
14. Chang CH, Lin PJ, Chu JJ, Liu HP, Tsai FC, Chung YY, et al. Surgical closure of atrial septal defect. Minimally invasive cardiac surgery or median sternotomy? Surg Endosc. 1998;12(6):820-4.
15. McCormack HM, Horne DJ, Sheather S. Clinical applications of visual analogue scales: a critical review. Psychol Med. 1988;18(4):1007-19.
16. Cosgrove DM 3rd, Sabik JF, Navia JL. Minimally invasive valve operations. Ann Thorac Surg. 1998;65(6):1535-8.
17. Navia JL, Cosgrove DM 3rd. Minimally invasive mitral valve operations. Ann Thorac Surg. 1996;62(5):1542-4.
18. Langer NB, Argenziano M. Minimally invasive cardiovascular surgery: incisions and approaches. Methodist Debakey Cardiovasc J. 2016;12(1):4-9.
19. Carpentier A, Loulmet D, Carpentier A, Le Bret E, Haugades B, Dassier P, et al. Open heart operation under videosurgery and minithoracotomy.

First case (mitral valvuloplasty) operated with success. C R Acad Sci III. 1996;319(3):219-23.

20. Chitwood WR Jr, Wixon CL, Elbeery JR, Moran JF, Chapman WH, Lust RM. Video-assisted minimally invasive mitral valve surgery. J Thorac Cardiovasc Surg. 1997;114(5):773-80.

21. Vanermen H, Wellens F, De Geest R, Degrieck I, Van Praet F. Video-assisted Port-Access mitral valve surgery: from debut to routine surgery. Will Trocar-Port-Access cardiac surgery ultimately lead to robotic cardiac surgery? Semin Thorac Cardiovasc Surg. 1999;11(3):223-34.

22. Mohr FW, Falk V, Diegeler A, Walther T, van Son JAM, Autschbach R. Minimally Invasive port-access mitral valve surgery. J Thorac Cardiovasc Surg. 1998;115(3):567-74.

23. Mueller XM, Tinguely F, Tevaearai HT, Revelly JP, Chioléro R, Von Segesser LK. Pain location, distribution, and intensity after cardiac surgery. Chest. 2000;118(2):391-6.

24. Ribeiro AL, Duncan BB, Brant LC, Lotufo PA, Mill JG, Barreto SM. Cardiovascular health in Brazil:trends and perspectives. Circulation. 2016;133(4):422-33.

25. Dogan S, Aybek T, Risteski PS, Detho F, Rapp A, Wimmer-Greinecker G, et al. Minimally invasive port access versus conventional mitral valve surgery: prospective randomized study. Ann Thorac Surg. 2005;79(2):492-8.

26. Santana O, Reyna J, Grana R, Buendia M, Lamas GA, Lamelas J. Outcomes of minimally invasive valve surgery versus standard sternotomy in obese patients undergoing isolated valve surgery. Ann Thorac Surg. 2011;91(2):406-10.

27. Mueller XM, Tinguely F, Tevaearai HT, Ravussin P, Stumpe F, von Segesser LK. Impact of duration of chest tube drainage on pain after cardiac surgery. Eur J Cardiothorac Surg. 2000;18(5):570-4.

28. Raanani E, Spiegelstein D, Sternik L, Preisman S, Moshkovitz Y, Smolinsky AK, et al. Quality of mitral valve repair: median sternotomy versus port-access approach. J Thorac Cardiovasc Surg. 2010;140(1):86-90.

29. Glower DD, Landolfo KP, Clements F, Debruijn NP, Stafford-Smith M, Smith PK, et al. Mitral valve operation via Port Access versus median sternotomy. Eur J Cardiothorac Surg. 1998;14(Suppl 1):S143-7.

30. Loulmet DF, Carpentier A, Cho PW, Berrebi A, D'Attellis N, Austin CB, et al. Less invasive techniques for mitral valve surgery. J Thorac Cardiovasc Surg. 1998;115(4):772-9.

31. Speziale G, Nasso G, Esposito G, Conte M, Greco E, Fattouch K, et al. Results of mitral valve repair for Barlow disease (bileaflet prolapse) via right minithoracotomy versus conventional median sternotomy: A randomized trial. J Thorac Cardiovasc Surg. 2011;142(1):77-83.

32. Downs EA, Johnston LE, LaPar DJ, Ghanta RK, Kron IL, Speir AM, et al. Minimally invasive mitral valve surgery provides excellent outcomes without increased cost: a multi-institutional analysis. Ann Thorac Surg. 2016;102(1):14-21.

33. Ryan WH, Brinkman WT, Dewey TM, Mack MJ, Prince SL, Herbert MA. Mitral valve surgery: comparison of outcomes in matched sternotomy and port access groups. J Heart Valve Dis. 2010;19(1):51-8.

34. Horiuchi T, Tanishima H, Tamagawa K, Sakaguchi S, Shono Y, Tsubakihara H, et al. A wound protector shields incision sites from bacterial invasion. Surg Infect (Larchmt). 2010;11(6):501-3.

35. Rogers ML, Henderson L, Mahajan RP, Duffy JP. Preliminary findings in the neurophysiological assessment of intercostal nerve injury during thoracotomy. Eur J Cardiothorac Surg. 2002;21(2):298-301.

36. Watt-Watson J, Stevens B. Managing pain after coronary artery bypass surgery. J Cardiovasc Nurs. 1998;12(3):39-51.

37. Landreneau RJ, Hazelrigg SR, Mack MJ, Dowling RD, Burke D, Gavlick J, et al. Postoperative pain-related morbidity: video-assisted thoracic surgery versus thoracotomy. Ann Thorac Surg. 1993;56(6):1285-9.

38. Nagahiro I, Andou A, Aoe M, Sano Y, Date H, Shimizu N. Pulmonary function, postoperative pain, and serum cytokine level after lobectomy: a comparison of VATS and conventional procedure. Ann Thorac Surg. 2001;72(2):362-5.

International Journal of Cardiovascular Sciences. 2020;33(1):34-35

EDITORIAL

Biological and Mechanical Heart Valves Under a New Spotlight: Paradigm Shift and New State of the Art

Domingo Marcolino Braile[1,2] and Idiberto José Zotarelli Filho[1]

Domingo Braile Institute of São José do Rio Preto (SP),[1] São José do Rio Preto, SP - Brazil
Braile Biomédica,[2] São José do Rio Preto, SP - Brazil

With the growth in life expectancy observed in recent decades in Brazil and worldwide, implantation of cardiac valve prostheses has been one of the recommended procedures for patients with valve diseases. In Brazil, this approach is the second most performed surgery among highly complex cardiovascular procedures. According to DATASUS, between January 2008 and May 2018, 900 implants were performed.[1]

The 2017 European Society of Cardiology / European Association for Cardio-Thoracic Surgery (ESC/EACTS3) guidelines established that the choice between a mechanical (MV) and biological valve (BV) in adults is primarily determined by estimating the risk of bleeding related to anticoagulation, thromboembolism, and the risk of structural deterioration of BV, considering the patient's lifestyle and preferences.[2] This risk/benefit ratio of MV and BV led the US and European guidelines to recommend the use of prostheses in patients under 60 years of age. Nevertheless, the use of BV has increased significantly in all age groups in recent decades.[2]

The recently published paper entitled "Bioprosthesis versus Mechanical Valve Heart Prosthesis: Assessment of Quality of Life"[3] assessed the quality of life (QoL) using the short form (SF)-36 questionnaire of 36 consecutive patients (16 men), mean age 51 years, who underwent heart valve replacement. After an average time of 32.5 months, the study showed that the type of prosthesis did not seem to influence patients' QoL. Also, another study on QoL (SF-36) included 121 consecutive patients undergoing BV (76.5%) and MV (86,3,1%). No significant differences were found between valve groups for any aspects of QoL.[4]

Kottmaier et al.,[5] compared QoL and anxiety of 56 patients after mechanical aortic valve replacement (AVR) (mean age: 64.4 ± 8.17 years) and 66 patients after biological AVR (mean age: 64.8 ± 11.05 years. After 5.66 (± 2.68) years of surgery, patients received the SF-36 to assess QOL, the fear of progression questionnaire (FOP), and the cardiac anxiety questionnaire (CAQ) to assess general anxiety. No significant differences were found for all categories of the SF-36. The FOP showed significantly favorable values for the biological AVR group. The CAQ showed a tendency towards more favorable values in the subscales "avoid" (i.e, avoid pulse increase) and "attention" for the biological AVR group.[5]

A systematic review and meta-analysis were performed to compare long-term survival, major prosthetic-related events, anticoagulant-related events, major bleeding, reoperation, and structural valve degeneration in middle-aged patients who received BV or MV. Results from patients under 70 years of age undergoing AVR with BV or MV were included. A total of 12 studies involving 8,661 patients was analyzed. There was no significant difference in long-term survival between patients 50 to 70 or 60 to 70 years. BV patients had significantly fewer long-term anticoagulant-related events. Also, studies have supported the use of BV in patients over 60 years of age.[6]

In this sense, scientific progress may increase the acceptance level for conservative aortic valve surgery using bovine pericardium valve (BPV). One study reported a long-term follow-up (23 years) of a patient who underwent surgery on the BPV cusp extension.[7]

Keywords

Heart Valve Diseases/surgery; Heart Valve Prosthesis Implantation/methods;Trancathter Aortic Valve Replacement (TAVR)/methods; Minimally Invasive Surgical Procedures/trends.

Mailing Address: Idiberto José Zotarelli Filho
Rua Luiz Vaz de Camões, 3111. Postal Code: 15015-750, Vila Redentora, São José do Rio Preto, SP - Brazil.
E-mail: m.zotarelli@gmail.com

DOI: https://doi.org/10.36660/ijcs.20190202

Increasing confidence in the effectiveness of the operation has allowed a faster indication for surgical treatment, as is already the case in mitral valve repair. This change of attitude will allow patients with mild aortic valve regurgitation to be referred for surgery, which can positively alter the natural history of aortic valve insufficiency.[7]

In the setting of transcatheter AVR (TAVR) as a minimally invasive alternative to surgical AVR (SAVR), Chakravarty et al.,[8] aiming to elucidate the greater propensity of using bioprostheses in relation to anticoagulation, evaluated the impact of anticoagulation after aortic valve replacement. Echocardiograms were performed 30 days and 1 year after TAVR. A total of 4,832 patients underwent TAVR (3,889) and SAVR (943). In the short term, early anticoagulation after biological AVR did not result in adverse clinical events, did not significantly affect aortic valve hemodynamics and was associated with decreased rates of stroke after SAVR.

In this context, transcatheter valve-in-valve (ViV) implantation has been increasingly used in recent years, especially with BPV. A 2019 study evaluated 30-day and 1-year mortality and the incidence of adverse outcomes in patients receiving ViV or re-SAVR. Despite a higher risk profile in ViV, 30-day and 1-year mortality rates were no different compared to re-SAVR, which may be explained by a higher rate of re-SAVR complications. Therefore, ViV seems to be a safe and viable therapeutic option for patients with degenerated aortic bioprosthesis.[9]

Also, two randomized clinical trials have been published, the Evolut Low-Risk study[10] and the PARTNER 3 study compared TAVR and SAVR in patients who are low surgical risk.[11] The mean age in both trials was 74 years. Patients who had undergone TAVR showed lower rate of death, stroke, rehospitalization or complications than surgery. Altogether, these results indicate that TAVR may be indicated not only for patients with lower surgical risk, but also for younger patients.

Thus, TAVR and ViV procedures are advancing, and in the coming years, there will likely be an even stronger change in the treatment of patients with valve diseases, in operating rooms and cath labs. Recent findings in the literature corroborate a shift in the paradigm to the use of bioprostheses, especially with the advent of PBV and advances in ViV implantation for aortic valve prosthesis failure, recognizing them as state-of-the-art therapies.

References

1. Brasil. Ministério da Saúde [Internet]. DATASUS. Procedimentos hospitalares do SUS - por gestor – Brasil [acesso em 17 jul 2018]. Disponível em: http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sih/cnv/qgbr.def.
2. Head SJ, Çelik M, Kappetein AP. Mechanical versus bioprosthetic aortic valve replacement. Eur Heart J. 2017;38(28):2183-91.
3. Molero Junior JC, Raimundo RD, Amaral JAT, Abreu LC, Breda JR. Bioprosthesis versus Mechanical Valve Heart Prosthesis: Assessment of Quality of Life. Int J Cardiovasc Sci. 2020;33(1):36-42.
4. Repack A, Ziganshin BA, Elefteriades JA, Mukherjee SK. Comparison of quality of life perceived by patients with bioprosthetic versus mechanical valves after composite aortic root replacement. Cardiology. 2016;133(1):3-9.
5. Kottmaier M, Hettich I, Deutsch MA, Badiu C, Krane M, Lange R, et al. Quality of life and anxiety in younger patients after biological versus mechanical aortic valve replacement. Thorac Cardiovasc Surg. 2017;65(3):198-205.
6. Zhao DF, Seco M, Wu JJ, Edelman JB, Wilson MK, Vallely MP, et al. Mechanical versus bioprosthetic aortic valve replacement in middle-aged adults: a systematic review and meta-analysis. Ann Thorac Surg. 2016;102(1):315-27.
7. Evora PRB, Arcêncio L, Evora PM, Menardi AC, Chahud F. Bovine pericardial patch augmentation of one insufficient aortic valve cusp with twenty-three-year positive clinical follow-up independent of the patch degeneration. Braz J Cardiovasc Surg. 2017;32(1):49-52.
8. Chakravarty T, Patel A, Kapadia S, Raschpichler M, Smalling RW, Szeto WY, et al. Anticoagulation after surgical or transcatheter bioprosthetic aortic valve replacement. J Am Coll Cardiol. 2019;74(9):1190-1200.
9. Stachel G, Woitek FJ, Holzey D, Kiefer P, Haussig S, Leontyev S, et al. Treatment of degenerated aortic bioprostheses: a comparison between conventional reoperation and valve-in-valve transfemoral transcatheter aortic valve replacement. Eur Heart J. 2018;39(suppl 1):ehy564.234.
10. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med. 2019;380(18):1706-15.
11. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019;380(18):1695-705.

International Journal of Cardiovascular Sciences. 2020;33(1):36-42

ORIGINAL ARTICLE

Bioprosthesis *versus* Mechanical Valve Heart Prosthesis: Assessment of Quality of Life

José Carlos Molero Junior,[1] Rodrigo Daminello Raimundo,[1] Joice Anaize Tonon do Amaral,[2] Luiz Carlos de Abreu,[1] João Roberto Breda[1]

Centro Universitário Saúde ABC,[1] Santo André, SP - Brazil
Faculdade de Medicina da Universidade de São Paulo (FMUSP),[2] São Paulo, SP - Brazil

Abstract

Background: The aim of this study was to evaluate the QoL of patients undergoing heart valve replacement using the SF-36 questionnaire, compare it between patients with mechanical prosthesis and patients with bioprosthesis, and correlate the results with sociodemographic variables.

Objective: To assess the QoL of patients undergoing heart valve replacement and compare it between patients with bioprosthetic valves and patients with mechanical prosthetic valves.

Methods: We included 36 consecutive patients (16 men) with a mean age of 51 years and six months, who underwent mitral or aortic valve replacement from September 2007 to December 2011. The study was conducted between March and May 2012 and involved the application of the SF-36 survey and a sociodemographic questionnaire. Statistical tests were performed, and data are expressed as absolute frequency and percentile, and median and interquartile range (P25 and P75) (Mann-Whitney test), considering a significance of 95%.

Results: The average time of surgery was 32.5 months (8-61 months). Participants were asked about the practice of physical activity, and 41.7% were physically active. For the SF-36 domains, the highest scores were observed for the social domain whereas the lowest scores were found for mental health, with a mean of 89.25 and 54.44, respectively. In the statistical analysis, we found statistically higher values in emotional functional for patients with mechanical valve prosthesis (p = 0.0084).

Conclusion: The QoL of the patients undergoing heart valve replacement improves considerably after the surgery, except for the mental health domain, probably due to the low practice of physical activity. The type of prosthesis seems not to influence the QoL or the patients in the late postoperative period. (Int J Cardiovasc Sci. 2020;33(1):36-42)

Keywords: Quality of Life; Sickness Impact Profile; Stress, Psychological; Heart Valve Prosthesis; Mitral Valve; Aortic Valve.

Introduction

Heart valve diseases cause substantial impairment in daily life due to symptoms like angina, dyspnea, and tiredness during normal activities. It is considered a disabling condition as it is one of the main causes of heart failure, with a negative impact on quality of life (QoL).[1] The treatment of heart valve disease is surgical repair or replacement of the affected valve, which can significantly increase survival and control and reduce the symptoms of the disease.[1,2]

Despite advances in the development of valvular prothesis over the years, current devices have some drawbacks, including the need of anticoagulation in patients with mechanical prostheses.[3] According to a review conducted in 2011, the choice of the prosthesis should be made with caution, based on the best alternatives for each patient. There is currently no

Mailing Address: Rodrigo Daminello Raimundo
Centro Universitário Saúde ABC - Avenida Príncipe de Gales, 667. Postal Code: 09060-590, Bairro Príncipe de Gales - Santo André, SP – Brazil.
E-mail: rodrigo.raimundo@fmabc.br

DOI: 10.5935/2359-4802.20190074

Manuscript received on March 03, 2018, revised manuscript on January 22, 2019, accepted on March 18, 2019.

valvular prosthesis available with all the characteristics of an ideal prosthesis.[4]

Most complications of valvular prosthesis implantation are probably related to the patient rather than the prosthesis per se.[5] In recent years, studies on QoL have been one the main objects of health studies, and has been the focus of discussion forums, lay press, and marketing of products and services.[6,7]

One of the methods for assessing QoL is the Medical Outcomes Study (MOS) 36-Item Short Form Health Survey (SF-36), which was validated in Portuguese by Ciconelli et al.,[8] This is a generic tool for assessing QoL, easy to apply and understand and relatively short when compared to others. The instrument can be used in individuals older than 12 years and administered either individually or in groups and evaluate physical and mental health in clinical practice. For each question of the SF-36, a score from 0 to 100 is assigned, where a low score indicates poor health perception, loss of function and pain, and a high score indicates good health perception, preserved function and absence of pain.[9-11]

The main of this study was to assess the QoL of patients undergoing heart valve replacement and compare it between patients with bioprosthetic valves and patients with mechanical prosthetic valves.

Methods

The study was approved by the Ethics Committee of the ABC Medical School (approval number 043/2011). Between September 2007 and December 2011, 36 patients underwent mitral and/or aortic valve replacement and were invited to participate in a descriptive study about QoL, using the SF-36 health survey and a sociodemographic questionnaire.

The convenience sample was composed of 16 men and 20 women, consecutively included in the study. All participants signed the informed consent form.

SF-36 health survey

The SF-36 survey is a generic questionnaire that assesses multiple dimensions of health-related QoL, which is widely used due to its high applicability and practicality. It is composed of 36 items grouped in eight scales or domains: functional capacity, physical functioning, pain, vitality, social functioning, emotional role and mental health. Among the 36 items, one item specifically compares current with previous (one year or more) perception of health status.[8]

Responders are asked to assign a rate from 0 to 100, where 0 denotes the worst health status and 100 denotes the best health status.[8]

Sociodemographic questionnaire

This questionnaire was used to evaluate personal data (age, sex, height, weight, marital status), diagnosis (type of valve replacement), educational background, occupation, risk factors (including chronic obstructive pulmonary disease, COPD, systemic arterial hypertension, smoking and diabetes mellitus) and income of the patients.

All interviews were conducted by the main researcher. The interviews were scheduled individually, by telephone, and lasted approximately 30 minutes.

Statistical analysis

Due to non-normality of data distribution (Shapiro-Wilk test, $p < 0.05$), data were presented as median and 25th and 75th percentiles. The Mann-Whitney test was used for comparisons of independent, quantitative variables between two unpaired samples. All analyses were performed using the Stata 11.0 software package, and significance level was set at 5%.

Results

A total of 36 patients (16 men) were interviewed. Age varied between 19 and 76 years (51.6 ± 15.2 years), 11 were older than 60 years, 14 were aged between 45 and 59 years and the others were younger than 44 years. Almost half of them were overweight (BMI > 25). With respect to educational attainment, 69.44% had some or completed primary education (Table 1).

With respect to the types of surgeries performed, 18 (50%) patients underwent mitral valve replacement, 16 (44.4%) patients underwent aortic valve replacement and 2 (5.6%) underwent mitral and aortic valve replacement, concomitantly. Nineteen patients (52.8%) received bioprosthesis and 17 (47.2%) mechanical prosthesis %). The causes of valve replacement are described in Table 2. Mean postoperative period, which corresponded to the day of the questionnaire, was 32.5 ± 15.5 months (8 - 61 months).

In our population, 27.8% of patients were working, and 72.2% were retired, out of work or housewives. Regarding

Table 1 – Distribution (absolute and relative frequencies) of demographic data by sex

Categories	Variables	Sex					
		Women	%	Men	%	Total	%
Marital status	Single	4	11.11	2	5.55	6	16.66
	Married	9	24.99	13	36.11	22	61.11
	Divorced/separated	4	11.11	1	2.77	5	13.88
	Widow(er)	3	8.33	0	0	3	8.33
	Total	20	55.55	16	44.44	36	100
Education	Illiterate	2	5.55	2	5.55	4	11.11
	Primary	13	36.11	8	22.22	21	58.33
	Secondary and higher education	5	13.88	6	16.66	11	30.55
	Total	20	55.55	16	44.44	36	100
BMI	Normal	6	16.66	6	16.66	12	33.33
	Overweight	8	22.22	9	24.99	17	47.22
	Obesity	6	16.66	1	2.77	7	19.44
	Total	20	55.55	16	44.44	36	100
Age	< 44 years	8	22.22	3	8.33	11	30.55
	45 - 59 years	6	16.66	8	22.22	14	38.88
	> 60 years	6	16.66	5	13.88	11	30.55
	Total	20	55.55	16	44.44	36	100

Table 2 – Distribution of the types and causes of heart valve replacement

Valve replacement	Material	Valve failure	Stenosis	Double replacement	Total
Mitral	Tissue	5	1	1	7
	Metallic	10		1	11
Aortic	Tissue	5		6	11
	Metallic	2	3		5
Mitral + aortic	Tissue		1		1
	Metallic		1		1
Total		22	6	8	36
%		61.1%	16.7%	22.2%	100%

the family income, 55.6% received less than Brazilian reals (BRL) 1,000; 33.3% gained from BRL 1,000 to BRL 2,000; 8.3% from BRL 2.000 to 3.000; and 2.8% received more than BRL3,000.

All patients reported performing physiotherapy during hospitalization, only 2.8% underwent cardiac rehabilitation in the postoperative period, 100% reported to perform clinical tests periodically and 41.7%

practiced physical exercise regularly, mostly walking, 2-3 times a week.

With respect to the SF-36 domains, the highest scores were found for social functioning (mean of 89.25), and the lowest scores for mental health (mean of 54.4). Comparisons of SF-36 results and sociodemographic data between mechanical prosthetic valves and bioprostheses are found in Table 3.

Comparison of SF-36 scores by the type of prosthesis implanted showed that emotional functioning scores were significantly higher in the emotional functional domain for patients with mechanical prosthesis compared with those with bioprosthesis (0.0084) (Table 3). In the analysis by valve replaced, patients with aortic valve replacement showed significantly higher scores for the functional capacity domain (p = 0.0047). In addition, significantly higher scores were found in the functional capacity domain for men compared with women (p = 0.0264). Considering the marital status, married patients showed significantly higher scores in the general health (p = 0.0287) and social functioning (p = 0.0063) domains compared with single patients.

Regarding the income of participants, those who received more than BRL1,000 showed significantly higher mean scores for the pain (p = 0.0375) and general health (0.0078) domains. Working patients showed significantly higher scores in functional capacity (p = 0.0112) compared with non-working patients. Finally, considering physically active versus physically inactive individuals, mean scores of physical functioning (p = 0.0385), general health (p = 0.0371) and social functioning (p = 0.0069) domains were significantly higher in physically active individuals.

No difference in SF-36 scores was found between individuals according to race/ethnicity, educational attainment, age, or BMI.

The item of the SF-36 questionnaire that compares current QoL of patients with the QoL one year before showed that, as compared with the QoL one year before, 22.2% of the patients reported that current QoL is much better; 33.33% a little better and 36.1% reported that current QoL is almost the same; 8.33% a little worse, and 0% much worse.

When analyzed by gender, in general, male patients reported a better QoL – 62.5% of men reported that current QoL is a little or much better than one year before. When analyzed by the type of valve implanted (mechanical vs. bioprosthetic valves and aortic vs. mitral), patients with bioprosthesis and patients with aortic prosthesis referred a better QoL nowadays compared with one year before.

Table 3 – Comparison between mechanical and bioprosthetic valves of the SF-36 scores in each domain

Domain	Type of prosthesis						p
	Mechanical			Bioprosthesis			
	Median	25th percentile	75th percentile	Median	25th percentile	75th percentile	
Functional capacity	65	55	75	75	60	80	0.12
Physical functioning	75	75	100	100	75	100	0.46
Pain	84	62	84	84	62	100	0.59
General health	72	67	82	72	62	82	0.93
Vitality	70	65	75	70	60	75	1
Social functioning	100	75	100	100	75	100	0.44
Emotional functioning	100	100	100	67	67	100	0.0084*
Mental health	60	52	60	56	44	60	0.66

*Mann-Whitney test; *p < 0.05.*

Discussion

The results of the present study indicate that the patients undergoing heart valve replacement reported a satisfactory QoL according to the scores achieved in most of the SF-36 domains. Similar findings were reported by Grady et al.[11] that evaluated 2,524 patients undergoing several cardiac surgeries and showed that the QoL of patients undergoing replacement of heart valve improved from baseline to six months after surgery and remained relatively stable through 3 years. This result demonstrates that the QoL of these patients markedly improves after valve replacement surgery compared with the preoperative period.

Except for the SF-36 domains functional capacity, physical functioning and mental health, the SF-36 scores of our population were similar to the mean scores obtained from residents of Sao Paulo city, previously published.[12] This is in agreement with another study showing that patients undergoing cardiac operations reported comparable or even higher SF-36 scores compared with the general population of the same area.[11]

In the analysis of the type of heart valve implanted (biological versus mechanical), we found a statistically significant difference only for the emotional functioning domain ($p = 0.0084$). Vicchio et al.,[13] also concluded in a study about the QoL of octogenarians who had undergone heart valve replacement that the type of the valve had no influence on their QoL.

In addition, our results were similar to those reported in a study that evaluated the QoL of 136 patients assessed two years after aortic valve replacement. The authors compared the QoL of patients with bioprostheses and patients with mechanical prostheses and found no statistically significant difference.[14] Compared with this study, our group reported higher mean scores for all SF-36 domains, except for mental health and pain.

In the mental health domain, which encompasses depression and anxiety, we found low scores, with a mean of 54.44. These data seem to differ from the results of Aboud et al.,[14] who observed higher scores in a study with a similar sample (mean of 69.6). However, our results seem to be not that different considering the mean age of our sample, 51 years and 6 months old, and considering that most of our sample had a bioprosthesis, since the mean score in the mental health domain in the equivalent group was 56.

According to Ruo et al.,[15] depression and anxiety were found in 20% of the patients with coronary artery disease. The authors suggested that efforts should be made in the treatment of depression and anxiety in cardiac patients. Although we studied a different population, heart valve replacement surgery can also have a negative impact on the perception of health and performance of physical exercise, leading to worsening physical impairment and QoL, similarly to what was reported by Ruo et al.[15]

The low score in health perception may be explained by the fact that many patients feel frustrated for not performing all the activities they wished to do, since expectations in the postoperative period may be high. Góis et al.,[16] support this theory in the study about QoL in the pre and postoperative periods of myocardial revascularization to explain the deterioration in social functioning and mental health.

These low scores can also be explained by the lack of physical activity, as 58.3% of the patients were physically inactive, which can have a negative impact on the QoL, on emotional status and on health. The positive impact of physical activity was well demonstrated in our study, as we found a statistically significant difference in three of the eight domains of the SF-36 questionnaire. Physically active individuals had better scores compared with physically inactive ones.

Exercise increases work capacity and improves the QoL.[17] Araújo et al.,[18] showed that physical activity has a positive effect on emotional health. Veigas & Gonçalves,[19] in a study on 207 individuals, reported the impact of physical activity on anxiety and stress in younger individuals and on depression in older individuals. The incidence of these conditions was lower in physically active than inactive ones.

In addition, a considerable number of patients reported to be unsatisfied with the fact that they did not return to work and to feel insecure to perform activities that require greater effort. These findings are in accordance with another study[20] on acute myocardial infarction patients which reported that an inability to return or be fit for work had a negative influence on QoL.[20]

The present study has some limitations including the different periods of time from the surgery between the patients and lack of information of ventricular function, which may have had some influence on the QoL. Also, the sample size was small due to the low adherence to the treatment by the patients during the study period.

In the present study, patients undergoing aortic valve replacement showed better scores in functional

capacity as compared with those undergoing mitral valve replacement (73.12 and 64.16, respectively, $p < 0.05$). This difference may be related to the prevalence of male patients in the aortic valve replacement group, considering the greater physical capacity of men compared with women.

Conclusion

The QoL of the patients undergoing heart valve replacement improves considerably after the surgery, except for the mental health domain, probably due to the low practice of physical activity. The type of prosthesis seems not to influence the QoL or the patients in the late postoperative period.

Author contributions

Conception and design of the research: Molero Junior JC, Breda JR. Acquisition of data: Molero Junior JC, Breda JR. Analysis and interpretation of the data: Molero Junior JC, Raimundo RD, Amaral JAT, Abreu LC, Breda JR. Statistical analysis: Raimundo RD, Amaral JAT, Abreu LC, Writing of the manuscript: Molero Junior JC, Raimundo RD, Abreu LC, Breda JR. Critical revision of the manuscript for intellectual content: Molero Junior JC, Raimundo RD, Amaral JAT, Abreu LC, Breda JR. Supervision / as the major investigador: Breda JR.

Potential Conflict of Interest

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

Sources of Funding

This article is part of the thesis of master submitted by José Carlos Molero Junior, from Faculdade de Medicina do ABC.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Faculdade de Medicina do ABC* under the protocol number 043/2011. 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. Holmes C, Briffa N. Patient-Reported Outcome Measures (PROMS) in patients undergoing heart valve surgery: why should we measure them and which instruments should we use? Open Heart. 2016;3(1):e000315. doi:10.1136/openhrt-2015-000315.
2. Pomerantzeff PM, Barbosa GV, Filho BSS, Brandão CMA, Ribeiro EJ, Costa FDA, et al. Diretrizes de Cirurgias nas Valvopatias. Arq Bras Cardiol. 2004; 82: (Supl. 5):22-33.
3. Campos NLKL, Andrade RR, Silva MAM. Anticoagulação oral em portadores de próteses valvares cardíacas mecânicas. Experiência de dez anos. Rev Bras Cir Cardiovasc. 2010;25(4):457-65.
4. Tasca R, Tasca MG, Amorim PAA. Evaluation of Prosthetic Valves with Echocardiography and Doppler Ultrasound. Rev bras ecocardiogr imagem cardiovasc. 2011;24(3):58-83
5. Almeida AS, Picon PD, Wender OCB. Resultados de pacientes submetidos à cirurgia de substituição valvar aórtica usando próteses mecânicas ou biológicas. Rev Bras Cir Cardiovasc. 2011;26(3):326-37.
6. Monteiro R, Braile DM, Brandau R, Jatene FB. Qualidade de vida em foco. Rev Bras Cir Cardiovasc. 2010;25(4):568-74.
7. Berg SK, Rasmussen TB, Thrysoee L, Lauberg A, Borregaard B, Christensen AV, et al. DenHeart: Differences in physical and mental health across cardiac diagnoses at hospital discharge. J Psychosom Res. 2017 Mar;94:1-9. doi: 10.1016/j.jpsychores.2017.01.003. Epub 2017 Jan 6.
8. Ciconelli RM, Ferraz MB, Santos W, Meinão I, Quaresma MR. Tradução para a língua portuguesa e validação do questionário genérico de avaliação de qualidade de vida SF-36 (Brasil SF-36). Rev Bras Reumatol. 1999;39(3):143-50.
9. Nogueira CRSR, Hueb W, Takiuti ME, Girardi PBMA, Nakano T, Fernandes F, et al. Qualidade de vida após revascularização cirúrgica do miocárdio com e sem circulação extracorpórea. Arq Bras Cardiol. 2008;91(4):238-44.
10. Takiuti ME, Hueb W, Hiscock SB, Nogueira CRSR, Girardi P, Fernandes F, et al. Qualidade de vida após revascularização cirúrgica do miocárdio, angioplastia ou tratamento clínico. Arq Bras Cardiol. 2007;88(5):537-44.
11. Grady KL, Lee R, Subacius H, Malaisrie SC, McGee EC, Kruse J, et al. Improvements in Health-Related Quality of Life Before and After Isolated Cardiac Operations. Ann Thorac Surg. 2011;91(3):777-83.
12. Lima MG, Barros MBA, César CLG, Goldbaum M, Carandina L, Ciconelli RM. Health related quality of life among the elderly: a population-based study using SF-36 survey. Cad Saúde Púbica. 2009;25(10):2159-67
13. Vicchio M, Corte AD, Santo LSD, Feo MD, Caianiello G, Scardone M, et al. Tissue versus Mechanical Prostheses: Quality of Life in Octogenarians. Ann Thorac Surg. 2008;85(4):1290-5.
14. Aboud A, Breuer M, Bossert T, Gummert JF. Quality of life after mechanical vs. biological aortic valve replacement. Asian Cardiovasc Thorac Ann. 2009; 17(1):35-8.
15. Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive symptoms and health-related quality of life. JAMA. 2003;290(2):215-21.

16. Góis CFL, Dantas RAS, Torrati FG. Qualidade de vida relacionada à saúde antes e seis meses após a cirurgia de revascularização do miocárdio. Rev Gaúcha Enferm. 2009;30(4):700-7.

17. Marchionni N, Fattirolli F, Fumagalli S, Oldridge N, Del Lungo F, Morosi L, et al. Improve exercise tolerance and quality of life with cardiac rehabilitation o folder patients after myocardial infarction: results of randomized, controlled trial. Circulation. 2003;107(17):2201-6.

18. Araújo SRC, Mello MT, Leite JR. Transtornos de ansiedade e exercício físico. Rev Bras Psiquiatr. 2007;29(2):164-71.

19. Veigas J, Gonçalves M. A influência do exercício físico na ansiedade, depressão e stress. Internet. [Acesso em 17 de julho 2018]. Disponível : www.psicologia.com.pt

20. Brown N, Melville M, Gray D, Young T, Munro J, Skene AM, et al. Quality of life four years after acute myocardial infarction: short form 36 scores compared with a normal population. Heart.1999;81(4):352-8.

EDITORIAL

The Ejection Fraction Returns to Hyde Park Session's Speakers' Corner

Wolney de Andrade Martins[1,2] and Antonio José Lagoeiro Jorge[1]

Universidade Federal Fluminense (UFF),[1] Niterói, RJ - Brazil
Complexo Hospitalar de Niterói (CHN),[2] Niterói, RJ - Brazil

The ejection fraction returns to Hyde Park Session's Speakers' Corner

About two decades ago, the Heart Failure Society of America created the Hyde Park Session at its annual meeting.[1] The analogy with the free and innovative proposals that took place in the historic London park were transposed to that scientific event. One of the first proposals made there was the extinction of the left ventricular ejection fraction (LVEF) as if it was an absolutist tyrant determining the life of his/her subjects. The proposition took no breath. The overwhelming majority of heart failure (HF) trials used LVEF as an inclusion criterion. The cutoff points varied. Magical numbers had little pathophysiological or clinical foundation. LVEF was measured by noninvasive methods, especially echocardiography, with high intra- and inter-examiner variability, dependent on preload and afterload changes.[2]

Later, in 2001, a clinical entity was recognized, where acute pulmonary edema of cardiogenic cause occurred despite LVEF at levels above 50%.[3] The following years saw incredulous initial acceptance until the epidemiological and clinical characterization of what we today call "heart failure with preserved ejection fraction (HFpEF)." From rare, it became frequent, especially in primary care. Considered benign, the prognosis became almost as reserved as heart failure with reduced ejection fraction (HFrEF). There were different proposals for diagnosis, prognostic scores, but such evolution in the knowledge of HFpEF resulted in a frustrating succession of negative therapeutic trials.

Keywords

Heart Failure/physiopathology; Stroke Volume/physiology; Ventricular Dysfunction; Prognosis.

In 2013, ACCF/AHA[4] re-stratified LVEF levels and created "borderline heart failure," which was in fact settled by the 2016 European guideline[5] under the "mid-range" nomenclature. Something was created that was not known in depth. The race for the demographic, clinical and prognostic characterization of the new entity began. What is heart failure with mid-range ejection fraction (HFmrEF)? Which direction of travel? HFrEF in reverse remodeling under optimal treatment? HFpEF following natural history with progressive necrosis, fibrosis and dilation vis-à-vis lack of treatment? An early manifestation of the disease? Would these different phenotypes grouped together by LVEF strata have the same clinical behavior? Tsuji et al.,[6] showed that the clinical characteristics of HFmrEF are intermediate between HFpEF and HFrEF and that HFmrEF has a dynamic transition to HFpEF or HFrEF, especially within a year, then suggesting that HFmrEF would represent a transition phenotype or an overlap zone between HFpEF and HFrEF instead of an independent heart failure entity. Currently, it is known that there are many HF phenotypes besides the simplification of LVEF strata.

There are few studies addressing the HFpEF and HFmrEF strata, either due to the relative novelty of HFrEF or the need for inclusion in clinical trials of lower LVEF patients, where the expectation of mortality and major events would increase the statistical power of the study.[2] Currently, there is a tendency for higher valuation of studies that include higher LVEF.

The paper published by Cavalcanti et al.,[7] in the International Journal of Cardiovascular Sciences draws a picture of 493 patients admitted for decompensated HF in the northeast region of Brazil over a 10-year period. Then, it compares the three strata defined by the ESC: reduced, mid-range and preserved. If we break free from the dictatorship of the p-value, we can see from the results

Mailing Address: Wolney de Andrade Martins
Rua Marques do Paraná, 303, 6º andar. Postal Code: 24030-215, Centro, Niterói, RJ - Brazil.
E-mail: wolney_martins@hotmail.com

DOI: https://doi.org/10.36660/ijcs.20190230

of the study that patients who presented themselves as HFmrEF now resemble each other's extremes. They resemble HFrEF in NYHA functional class, etiologies, chronic kidney disease, valvular heart disease, alcoholism and smoking, prevalence of atrial fibrillation, mitral and tricuspid regurgitation, and B-type natriuretic peptide levels. On the other hand, they resemble HFpEF as to age, presence of hypertension and diabetes mellitus, anemia and right ventricular remodeling. Mortality appears to be closer to HFpEF and 30-day readmission to HFrEF. These last two facts lose magnitude, since all numbers are alarming.

Cavalcanti et al.,[7] presented a frequency of 26% of patients with HFmrEF, as well as other characteristics consistent with those recently described in the literature.[6,8,9] It is very important that we know this characterization, because the answer on how to treat depends on it. The HFrEF prescription, very well grounded in large clinical trials or the therapeutic uncertainties of HFpEF. Cavalcanti et al.,[7] show data that should reflect the reality of a tertiary or quaternary referral hospital in a population with a higher socioeconomic level. We should contextualize this. It may not be reproduced in primary care or in public institutions.

The still very high 30-day mortality and readmission rates presented by Cavalcanti et al.,[7] make it mandatory that we improve the approach to HF as a whole, independent of LVEF. It is important to have the demographic and clinical portrait of HFpEF and HFmrEF. The paper presented by Cavalcanti et al.,[7] is an important contribution to one of the obscure areas of HF. We do hope that the debate at the Hyde Park session should be based on evidence such as the one presented by Cavalcanti et al.[7]

References

1. Heart Failure Society of America.(HFSA). [Internet]. [Cited in 2019 Oct 11]. Available from: https://meeting.hfsa.org/past-meetings/
2. Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. Circ Res. 2019;124(11):1598-617.
3. Gandhi SK, Powers JC, Nomeir AM, Fowle K, Kitzman DW, Rankin KM, et al. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med. 2001;344(1):17-22.
4. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62(16):e147-239.
5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS., et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(36):2129-200.
6. Tsuji K, Sakata Y, Nochioka K, Miura M, Yamauchi T, Onose T., et al. Characterization of heart failure patients with midrange left ventricular ejection fraction-a report from the CHART-2 study. Eur J Heart Fail. 2017;19(10):1258-69.
7. Cavalcanti CP, Sarteschi C, Gomes GES, Medeiros CA, Pimentel JHM, Lafayette AR, et al. Decompensated heart failure with mid-range ejection fraction: epidemiology and inhospital mortality risk factors. Int J Cardiovasc Sci. 2020;33(1):45-54.
8. Kapoor JR, Kapoor R, Ju C, Heidenreich PA, Eapen ZJ, Hernandez AF, et al. Precipitating clinical factors, heart failure characterization, and outcomes in patients hospitalized with heart failure with reduced, borderline, and preserved ejection fraction. J Am Coll Cardiol HF. 2016;4(6):464-72.
9. Lauritsen J, Gustafsson F, Abdulla J. Characteristics and long-term prognosis of patients with heart failure and mid-range ejection fraction compared with reduced and preserved ejection fraction: A systematic review and meta-analysis. ESC Heart Fail. 2018;5(4):685-94.

ORIGINAL ARTICLE

Decompensated Heart Failure with Mid-Range Ejection Fraction: Epidemiology and In-Hospital Mortality Risk Factors

Gabriela Paiva Cavalcanti, Camila Sarteschi, Glory Eithne Sarinho Gomes, Carolina de Araújo Medeiros, José Henrique Martins Pimentel, André Rabelo Lafayette, Maria Celita Almeida, Paulo Sérgio Rodrigues Oliveira, Silvia Marinho Martins

Real Hospital Português de Beneficência em Pernambuco, Recife, PE - Brazil

Abstract

Background: Recently, a new HF entity, with LVEF between 40-49%, was presented to comprehend and seek better therapy for HF with preserved LVEF (HFpEF) and borderline, in the means that HF with reduced LVEF (HFrEF) already has well-defined therapy in the literature.

Objective: To compare the clinical-therapeutic profile of patients with HF with mid-range LVEF (HFmrEF) with HFpEF and HFrEF and to verify predictors of hospital mortality.

Method: Historical cohort of patients admitted with decompensated HF at a supplementary hospital in Recife/PE between April/2007 - August/2017, stratified by LVEF (< 40%/40 - 49/≥ 50%), based on the guideline of the European Society of Cardiology (ESC) 2016. The groups were compared and Logistic Regression was used to identify predictors of independent risk for in-hospital death.

Results: A sample of 493 patients, most with HFrEF (43%), HFpEF (30%) and HFmrEF (26%). Average age of 73 (± 14) years, 59% men. Hospital mortality 14%, readmission within 30 days 19%. In therapeutics, it presented statistical significance among the 3 groups, spironolactone, in HFrEF patients. Hospital death and readmission within 30 days did not make difference. In the HFmrEF group, factors independently associated with death were: valve disease (OR: 4.17, CI: 1.01-9.13), altered urea at admission (OR: 6.18, CI: 1.78-11.45) and beta-blocker hospitalization (OR: 0.29, CI: 0.08-0.97). In HFrEF, predictors were: prior renal disease (OR: 2.84, CI: 1.19-6.79), beta-blocker at admission (OR: 0.29, CI: 0.12-0.72) and ACEI/ ARB (OR: 0.21, CI: 0.09-0.49). In HFpEF, only valve disease (OR: 4.61, CI: 1.33-15.96) and kidney disease (OR: 5.18, CI: 1.68-11.98) were relevant.

Conclusion: In general, HFmrEF presented intermediate characteristics between HFrEF and HFpEF. Independent predictors of mortality may support risk stratification and management of this group. (Int J Cardiovasc Sci. 2020;33(1):45-54)

Keywords: Heart Failure/physiopatology; Stroke Volume/physiology; Prognosis; Hospital Mortality; Epidemiology.

Introduction

Heart failure (HF) is a clinical syndrome with high global prevalence, responsible for elevated mortality and readmission rates.[1] It is often categorized according to left ventricular ejection fraction (LVEF), historically defined as heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). Unlike HFrEF, whose therapy in terms of mortality reduction has been well-defined, HFpEF remains a syndrome that still poses diagnostic challenges, with no well-established treatment.[2] Most HFrEF clinical trials have included patients with EF < 35-40%, whereas HFpEF trials used EF > 50%, EF > 45% or EF > 40% as

Mailing Adress: Sílvia Marinho Martins
Rua Manuel de Carvalho 262/601. Postal Code: 50050 – 370, Aflitos, Recife, PE – Brazil.
E-mail: s.m.martins@uol.com.br

DOI: 10.5935/2359-4802.20190075

Manuscript received December 18, 2017; revised manuscript October 23, 2018; accepted November 01, 2018.

inclusion criteria. Other HF studies reported, within large populations, a broad proportion of patients with mid-range LVEF, between 40-50% still poorly characterized.[1-4]

In 2013, the American Heart Association (AHA)[5] proposed in its guidelines the inclusion of a new group, HF with borderline EF (EF: 41-49%). Recently, the European Society of Cardiology guidelines has emphasized this new classification, recognizing a new entity of HF with mid-range ejection fraction (HFmrEF), defined as the presence of signs and symptoms of heart failure, EF: 40-49%, elevated natriuretic peptides levels and at least 1 additional criterion: structural heart disease and/or diastolic dysfunction.[6] Until now, there is no consensus on the most appropriate LVEF cut-off to differentiate the HF groups or the prognosis and the real benefits of the treatment in this particular group of HF with mid-range ejection fraction. In view of such a scenario, the objective of this study was to identify and compare the clinical and therapeutic profile of HF patients, stratifying them by LVEF, according with the 2016 European Society of Cardiology (ESC) guidelines, and to identify specific independent predictors of in-hospital mortality in each group.

Methods

Retrospective hospital-based cohort of patients admitted to a reference hospital of the Supplemental Healthcare System, in Recife/PE, between April 2007 and August 2017.

The sample included patients admitted with a diagnosis of decompensated heart failure, aged over 18 years, who had been hospitalized for at least 24 hours, in functional classes III and IV, according to the New York Heart Association (NYHA) functional classification[7] and who had undergone echocardiography at the service or had recent echocardiographic data available (obtained within less than 3 months), including a description of the LVEF.

Based on the guideline of the European Society of Cardiology (ESC) 2016[6] and on the Brazilian guidelines published in 2018,[8] patients were divided into 3 distinct groups of HF, according to LVEF on echocardiogram: HFrEF (EF<40%), HFmrEF (EF: 40 - 49%) and HFpEF (≥ 50%).

LVEF was calculated by echocardiography, using the Teichholz' M-mode volume method, or the modified Simpson's formula for measurement of LV end-systolic and end-diastolic diameter, in the 4-chamber apical plane, in accordance with current guidelines, all performed in the echocardiography sector of the hospital.[9]

Data collection included hospital admission data, in-hospital mortality data and readmission within 30 days. The information were obtained from the consultation of medical records and complemented, whenever necessary, by contact with the assisting physician. A structured questionnaire was chosen as data collection instrument, including demographic and clinical variables, clinical exam at admission, complementary exams and the treatment adopted. The outcome of interest was in-hospital mortality.

The etiology of HF and the cause of decompensation were defined by the assistant physician on medical report. Ischemic, hypertensive, valvular, idiopathic, and other etiologies (lower proportion group or with no confirmed diagnosis by the assistant physician) were investigated.

Some continuous variables were changed into categories for analytical purposes;[10] age (< 65 and ³ 65 years), systolic blood pressure (SBP < 115 mmHg and ³ 115 mmHg), heart rate (£ 80 bpm and > 80 bpm), serum creatinine (altered: > 1,3 mg/dl men and > 1,1 mg/dl women), plasma sodium (altered: < 130 mEq/l) and urea (altered: ³ 92 mg/dl). The presence of anemia was defined, according to the WHO criteria (Hb < 13.0 g/dL in men and Hb < 12.0 g/dL in women).[11]

Statistical Analysis

Demographic and clinical characteristics of patients were analyzed using descriptive statistics: mean and standard deviation (SD) for quantitative variables and absolute and relative frequencies for qualitative variables. Data normality was verified using the Kolmogorov-Smirnov test. To compare the LVEF groups, in relation to the qualitative variables, the Qui-square test was utilized, and, for quantitative variables, analysis of variance methodology was used for normal distribution, Kruskal-Wallis test for not normal. Bivariate analysis, using Pearson's Chi-square, was carried out as a strategy to assess the relation between the outcome (in-hospital death) and the independent variables, studied for each group individually. All variables related to in-hospital death with a p value < 0.20 in the bivariate analysis were considered for inclusion in multiple logistic regression model. The stepwise forward method was used to select the final model. Once the final model was chosen, calibration was assessed using Hosmer Lemeshow›s goodness of fit test. The IBM SPSS Statistics for Windows

(Version 21.0. Armonk, NY: IBM. Corp.) software was used to perform statistical analysis. The level of significance assumed was 5%.

The research project was approved by the Ethics Committee in Research of the Catholic University of Pernambuco UNICAP/PE (CAAE: 70897517.8.0000.5206). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

A sample of 599 patients was collected between January 2007 and March 2017. Out of these, 106 did not have any LVEF data available and were not included in the analysis. A total of 493 patients fulfilled the inclusion and exclusion criteria of the study.

From the sample studied, most HF individuals (43%) were classified with LVEF < 40%, followed by 30% of with LVEF ≥ 50% and 26% with LVEF 40-49%. The age of the patients varied from 20 to 99 years, with a mean of 73 (SD = 14) years, 370 (75%) were 65 years old or more, with men accounting for the majority of them (59%), Functional Class (FC) IV (52%), ischemic etiology (52%), followed by hypertensive (19%) and idiopathic (9%) etiologies. The outcome in-hospital death was 14% of the sample. Nineteen percent of patients were readmitted within 30 days.

Among the most frequent comorbidities found, we can highlight: systemic arterial hypertension (SAH) in 87% of patients; diabetes mellitus (DM) in 51% and coronary insufficiency (CI) in 59%. In a comparative analysis, the groups were significantly distinct with regard to SAH and CI, being more frequent in HFmrEF patients; valve disease and alcoholism were more common in HFpEF and HFrEF, respectively. The main cause for decompensation was acute coronary syndrome - ACS (38%), followed by infection (33%) and arrhythmia (atrial fibrillation). In relation to pharmacological therapeutics during hospitalization, the use of beta-blockers was observed in 73% of patients, angiotensin converting enzyme inhibitors (ACEi) / angiotensin II receptor blockers (ARB) in 68% and aldosterone receptor antagonist spironolactone in 42%.

When the three groups were comparatively analyzed (Table 1), HFpEF and HFmrEF patients were older, with a prevalence of female patients, compared to the HFrEF group, which had a prevalence of males (68%). Ischemic and idiopathic etiologies were observed in a higher percentage of HFrEF and HFmrEF patients, whereas the hypertensive and valve etiologies were more frequent among those with HFpEF. ACS was the main cause for decompensation, being more frequent in HFmrEF (46%), followed by HFrEF (39%). Hypertension and CI were more prevalent among HFmrEF patients (93% and 67%, respectively), whereas valve disease accounted for a higher proportion in HFpEF, and alcoholism in the HFrEF and HFmrEF groups.

In relation to systolic blood pressure (SBP) at admission, the values were lower in patients with HFrEF. As to heart rate (HR) and NYHA functional

Table 1 - Comparison of groups in relation to demographic, clinical, therapeutic, laboratory and outcome variables

Variables	Total	LVEF			p
		< 40%	40 – 49%	≥ 50%	
Age – Mean (SD)	42.9 (13.6)	70.3 (14.4)+/++	75.2 (12.4)	74.6 (12,9)	0.003*
Age ≥ 65 years (%)	75.2	67.6	80.6	81.3	
Male (%)	58.6	67.8	58.9	45.3	< 0.001*
FC IV (%)	52.3	55.3	52.4	47.9	0.392
Etiology (%)					< 0001*
Ischemic	52.3	57.1	56.3	41.8	
Hipertensive	19.5	11.3	18.0	32.9	
Idiopathic	8.6	10.4	11.7	3.4	
Valve	11.5	8.0	10.2	17.8	
Others	8.0	13.2	3.9	4.1	

Cont. Table 1 - Comparison of groups in relation to demographic, clinical, therapeutic, laboratory and outcome variables

Variables	Total	LVEF			p
		< 40%	40 – 49%	≥ 50%	
ACS-HF (%)	38.0	38.8	45.7	30.2	0.028*
Comorbidities					
DM	50.7	44.9	58.1	52.7	0.050
SAH	87.2	82.7	93.8	88.0	0.011*
IC	58.6	60.7	67.4	48.0	0.003*
Valve disease	10.3	6.1	10.1	16.7	0.005*
Kidney disease	34.5	36.0	34.9	32.0	0.729
COPD/Asma	19.5	21.0	17.1	19.3	0.666
Neoplasia	8.1	5.1	10.9	10.0	0.103
Alcoholism	18.3	22.4	20.2	10.7	0.014*
Smoking	20.1	22.4	20.2	16.7	0.401
SBP (mmHg) – Mean (SD)	136.3 (31.8)	128.5 (27.9)$^{+/++}$	139.2 (31.9)	145.0 (34.4)	< 0.001*
HR (bpm) – Mean (SD)	87,4 (20.8)	87.9 (21.6)	88,4 (20.6)	85.9 (19.6)	0.557
AF (%)	22.8	20.5	19.7	28.8	0.144
EDD – Median (P25 – P75)	58 (50-65)	65 (58 - 70)$^{+/++}$	55 (52 – 62)$^{+++}$	47 (45 – 85)	< 0.001*
SPAP - Median (P25 – P75)	46 (39-57)	45 (40 – 56)	42 (37 – 56)	48 (42 – 59)	0.870
Moderate/severe MR (%)	47.9	55.2	56.1	30.3	< 0.001*
Moderate/severe TR (%)	22.6	25.9	23.8	16.7	0.128
Increased RV (%)	19.6	30.2	12.9	11.0	< 0.001*
LVEF – Mean (SD)	43.2 (14.3)	30.2 (6.6)	44.4 (2.7)	60.7 (7,3)	-
Sodium Ad – Mean (SD)	137.2 (5.8)	137.6 (5.5)	137.1 (5.9)	136.7 (6.2)	0.387
Urea Ad – Mean (SD)	64.9 (39.6)	68.5 (42.9)	64.7 (40.7)	60.1 (32.6)	0.141
Creatinine Ad – Mean (DP)	1.5 (0.9)	1.4 (0.8)	1.4 (0.9)	1.5 (1.1)	0.681
Hb Ad – Mean (SD)	12.2 (2.3)	12.6 (2.3)$^{+/++}$	11.9 (1.9)	11.8 (2.2)	0.002*
BNP Ad Median (P_{25}–P_{75})	6,000 (2,769-15,927)	7,249 (3,473-19,610)$^{+/++}$	8,421 (5,304-22,352)$^{+++}$	2,827 (1,685-6,285)	0.015*
B-blocker (%)	73.3	77.8	72.9	67.1	0.076
ACEi /ARB (%)	66.5	69.2	64.3	68.7	0.626
Digoxin (%)	22.0	28.6	17.2	16.8	0.008*
SPIR (%)	41.7	52.8	38.8	28.2	< 0.001*
In-hospital death (%)	14.0	18.2	12.4	12.0	0.173
Readmission within 30 d (%)	19.2	19.9	22.1	15.7	0.498

** Statistically significant (p < 0.05); $^{+}$: Statistically significant difference between G1 (< 40%) and G2 (40-49%); $^{++}$: Statistically significant difference between G1 (< 40%) and G3 (≥ 50%); $^{+++}$: Statistically significant difference between G2 (40-49%) and G3 (≥ 50%); A: p-value derived from ANOVA; χ: p-value derived from Pearson's Chi-Square test; K: p-value derived from Krukal-Wallis test.*

class VI, there were no statistical differences between the categories of HF.

With regard to the laboratory variables, the groups were distinct in terms of natriuretic peptides (NT-ProBNP) levels and anaemia, which were higher among patients with HFrEF and HFmrEF. LV end-diastolic diameter (LVEDD) values were higher among HFrEF patients compared to HFpEF patients. Moderate to severe mitral regurgitation (MR) was commonly observed in HFrEF and HFmrEF.

In-hospital pharmacological treatment of patients with DHF is presented in Chart 1. Beta-blockers, ACEi/ARB and Spironolactone were used in 78%, 69% and 53% of HFrEF patients, respectively. However, statistical significance was only observed in the Spironolactone variable, which is more commonly used in patients with HFrEF. No statistical difference was observed between the groups in terms of in-hospital death and readmission within 30 days.

According to the bivariate analysis, the variables that presented a significant association with in-hospital death for patients with HFrEF were: advanced age, valve disease, kidney disease, peripheral vascular disease (PVD), urea, aneamia, beta-blocker and ACEi/ARB; for HFmrEF: kidney disease, urea at admission, aneamia and beta-blocker; and for HFpEF: kidney disease, PVD and creatinine at admission.

The independent risk factors obtained by multivariate analysis for in-hospital death are shown in Table 2. In the worst outcomes, previous kidney disease was associated with HFrEF and HFpEF. Previous valve disease was related to HFmrEF and HFpEF, and increased urea levels, exclusively in HFmrEF. The use of medication, such as beta-blockers and ACEi/ARB, were associated with a better evolution in HFmrEF and HFrEF, respectively.

It is worthy to highlight that HFrEF was associated with higher in-hospital mortality rates in patients with previous kidney disease (Odds Ratio (OR): 2.84, CI:1.19-6.79) and showed a 3.5 higher risk of in-hospital death for patients under no beta-blocker therapy and an almost 5 times higher risk for those under no treatment with ACE inhibitors or ARBs. HFmrEF was associated with higher in-hospital mortality rates for valve disease (OR: 4.17, CI: 1.01-9.13) and to altered levels of urea at admission (OR:6.18, CI:1.78-11.45), and the likelihood of death increased by 3.5 times in patients under no beta-blocker therapy. In relation to HFpEF patients, there was an

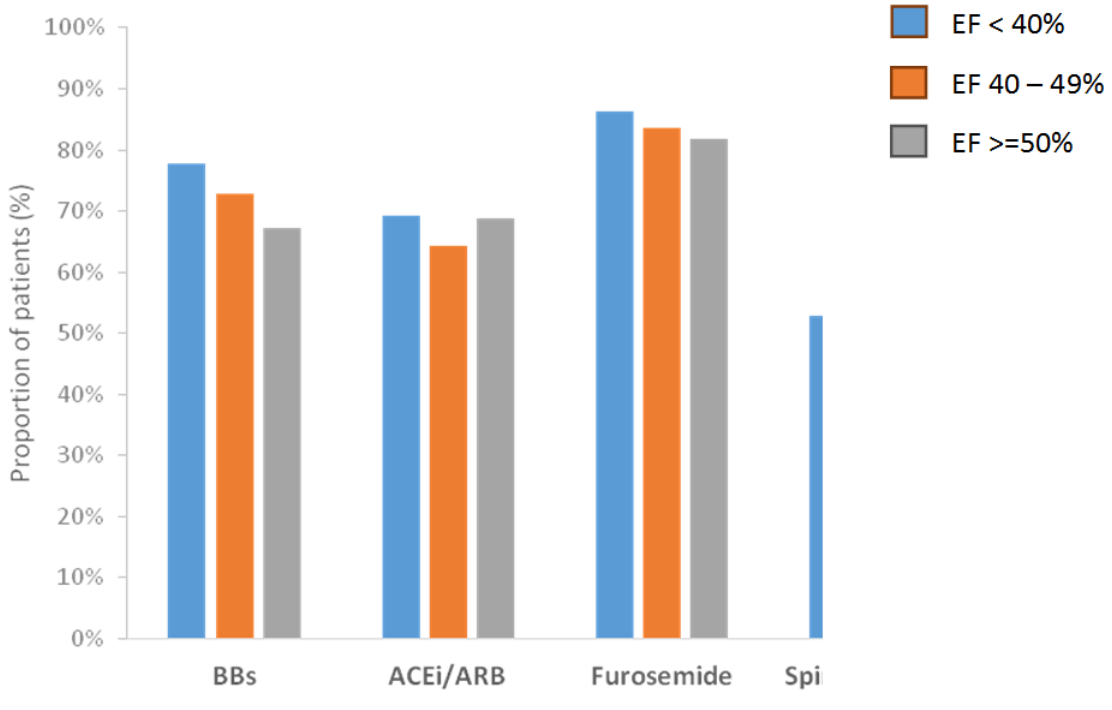

Chart 1 - Sample distribution, according to the drug administered during hospitalization.

Table 2 - Results of Multivariate analysis for the in-hospital death outcome – p-value

Variables	EF < 40%	P-value	EF 40 – 49%	p-value	EF ≥ 50%	p-value
	OR (CI95%)		OR (CI95%)		OR (CI95%)	
Sex - Male	-	-		0.373	-	-
Age ≥ 65 years		0.087	-	-		0.182
FC IV		0.223		0.090	-	-
Etiology	-	-		0.768	-	-
IC PR	-	-		0.494	-	-
Valve disease PR		0.084	4.17 (1.01-9.13)	0.047	4.61 (1.33-15.96)	0.016
Kidney disease PR	2.84 (1.9-6.79)	0.019		0.192	5.18 (1.68-11.98)	0.004
COPD/Asma PR		0.724	-	-	-	-
PVD PR		0.120	-	-		0.049
Sodium ALT		0.974		0.199	-	-
Urea ALT		0.914	6.18 (1.78-11.45)	0.004		0.911
Creatinine ALT	-	-	-	-		0.412
Aneamia		0.222		0.274	-	-
BB INT.	0.29 (0.12-0.72)	0.008	0.29 (0.08-0.97)	0.045	-	-
ACEi/ARB INT.	0.21 (0.09-0.49)	0.001	-	-	-	-
SPIR. INT		0.260		0.182	-	-
Furos. INT		0.068		0.077	-	-

Note: OR: odds ratio; CI95%: 95% confidence interval.

association with valve disease (OR: 4.61, CI: 1.33-15.96) and kidney disease (OR: 5.18, CI: 1.68-11.98).

Discussion

Clinical Profile

The ICD[12] classification is already well-defined, and its categorization according to LVEF measured by echocardiography is used to characterize the syndrome clinically and, particularly, to orientate the treatment. LVEF through echocardiography is considered easy to perform, of lower cost and can be applied at the bedside, when necessary. However, there are several limitations concerning its estimation, both technical (dependent observer, two-dimensional evaluation, intra- and inter-observer variability and inadequate acoustic window) and non-technical (mitral regurgitation, aortic stenosis, arrhythmias, myocarditis and Takotsubo syndrome), which may generate inaccurate measurements.[13] Cardiac magnetic resonance imaging is considered the gold standard for assessing left ventricular (LV) systolic function,[14] but it is not easily available in daily clinical practice. Although echocardiography does not seem to be the ideal method, it remains a practical and accessible tool for estimation of LVEF and the choice exam in all studies that have focused on HF treatment so far.[15-17] It is worthy to note that classifying HF patients is more complex than simply stratifying them by LVEF cut-off values because these patients have a high burden of cardiovascular and non-cardiovascular comorbidities, which may interact on different levels of LVEF, and may influence prognosis more than the LVEF category.

There was a discrete predominance of patients with HFrEF at this institution, in consonance with previous

studies, which indicates that the profile of supplemental health care patients is pretty much similar to those from international registries[10] and that it differs from Brazilian data when HFmrEF reaches the absolute majority.[18] The predominance in our study of older individuals with ischemic etiology is also compatible with data from developed countries.[19-21] In-hospital death, which occurred in 14% of the population studied, is in accordance with data from the Brazilian registry of acute HF patients admitted to public and private hospitals.[18]

Twenty-six percent of the population presented HFmrEF, which corroborates the estimated range, from 10-20%, in recent studies.[22,23] These patients were aged over 65 years (80%), with a higher proportion of females, similarly to the HFpEF profile. As for ischemic etiology, HFmrEF had a prevalence of 56 % and was closer in value to the HFrEF group. Hypertensive etiology showed intermediate values in relation to the other two groups.

DHF associated with ACS was more prevalent among HFmrEF patients (46%) compared to those from the other two groups. In Brazil, recent data have shown that the main cause of DHF is poor medication adherence;[18] other studies presented different results.[23] Data from OPTIMIZE-HF,[24] a comprehensive European registry, were consistent with those reported in this study, which can be justified by differences between the profile and data of the population seen at supplemental health system and in the public health system.

HFmrEF presented with high comorbidity rates, such as diabetes mellitus, hypertension, IC and MI, and showed intermediate values for valve disease, kidney disease and alcoholism. It is also interesting to stress that left ventricular end-diastolic diameter values were intermediate, which indicates a possible transition stage between the other two HF groups. The similarities between HFmrEF and HFpEF suggest that HFmrEF may represent recovered or early stages of HFrEF,[25,26] but other long-term echocardiographic follow-up studies in these patients are needed.

Mortality and Prognostic Factors

In-hospital mortality in HFmrEF was similar in absolute values to HFpEF but lower than HFrEF, although the study has no sufficient statistical power to prove this difference. The same pattern was observed in hospital readmission rates. The "benignity" of HFpEF has been documented in the literature.[27] Data from the OPTIMIZE registry have shown lower in-hospital mortality rates in HFpEF patients. Nevertheless, the criterion adopted in this study was HFpEF (EF ≥ 40%),[28] and thus included those patients currently classified as HFmrEF, which poses limitations to comparisons. A meta-analysis involving over 60,000 patients reported lower mortality in HFpEF (EF ≥ 50%) compared to HFrEF. However, the evaluation itself does not make a distinction between outpatients or patients with DHF, which may influence the outcomes.[29] Only a handful of published studies have focused on patients with HFmrEF which, comparable to the sample of this study, have shown an intermediate group with mortality rates similar to those in the other HF groups.[30] Consequently, the population data shown is this report are consistent with recently published studies that used data from hospitalized patients.[30] When the outcomes were analyzed, after the one-year follow-up evaluation, including death by any cause and admission due to HF, there were similarities between HFmrEF and HFpEF, with HFrEF patients presenting the worst prognosis.[31] It was not possible to establish comparisons with national data due to the scarcity of publications.

In general, heart failure mortality prediction scores have limited accuracy.[10] The BIOSTAT–CHF[32] emerged as a comprehensive European program designed to develop and validate risk prediction models, in an attempt to minimize this problem. The authors highlighted the small percentage of models validated in a separate cohort and the fact these models performed only moderately (c-statistic values 0.71 and 0.63 for mortality and HF hospitalization, respectively). Using a multivariable model (249), they found that the strongest predictors of mortality were urea and serum sodium. It is interesting to highlight that there was no significant difference between patients with acute or chronic HF. An LVEF cut-off of 45% was used to distinguish HFrEF from HFpEF, and no similarities were found between the risk factors of the population studied and the validation cohort, which has also included a small percentage of patients with an LVEF greater than 45%. The LVEF cut-off adopted may be a limiting factor for extrapolation of any findings to the HFmrEF group.[32]

A recent Swedish HF registry has reported that chronic kidney disease is a strong predictor of mortality in both HFmrEF and HFrEF patients.[33] However, in the population assessed here, renal involvement, whether due to previous kidney disease or to increased urea at admission, was the only mortality predictor that revealed similarities between the 3 HF

groups. Similarly, urea has been strongly associated to in-hospital death risk in traditional scores, such as BIOSTAT[32] and ADHERE.[10] The persistence of urea in all these models indicates its prognostic strength. Thus it should be the object of more attention by those who monitor patients with HF, due to the higher death risk among HFmrEF individuals (6 times more), for instance. It is possible to suggest that the presence of valve disease as a factor of worse prognosis in HF patients with LVEF greater than 40% indicates that it could be the etiology of heart failure. At the same time, it involves clinical characteristics and challenges, especially among the elderly population, due to the small number of randomized clinical trials. Consequently, treatment is also less well established.

It is necessary to highlight the efficacy of medication, since recent international publications, as observed by this study, originally in Brazil, have demonstrated significant benefits of beta-blockers both in HFrEF[32] and HFmrEF,[34] thus suggesting benefits in all HF patients with an ejection fraction less than or equal to 49%. This fact has not been registered in randomized clinical trials which have included exclusively patients with systolic HF.[17,35] A recent meta-analysis involving 11 randomized studies and over 14,000 patients on the use of beta-blockers has confirmed their benefits in patients with EF < 50% and sinus rhythm.[36] As for ACEI/ARB, it is important to point out that the results only remained among HFmrEF patients, with a 5 times increased mortality among those who did not receive the medication. In the OPTIMIZE-HF registry, although the use of ACEI/ARB has been associated with less mortality and hospital readmission within 30- and 90-days in HFrEF patients, such benefit has not been observed among the HFmrEF and HFpEF groups.[28] In a subanalysis of CHARM, the benefit of candesartan was also seen in patients with HFmrEF.[37] Furthermore, in spite of the results of the TOPCAT trial, studies have found benefits of spironolactone in patients with EF between 45-49%,[38] which was not observed in this study's population. Therefore, HFmrEF signals a transition behavior or a "gray area" in which a better characterization of this group may soon bring prognostic and therapeutic benefits.

Limitations

The study is based on patients with a clinical picture of decompensated heart failure, and their physical and laboratory variables were collected at admission on a database. Thus information was collected retrospectively. Other potentially relevant variables, such as natriuretic peptide levels, were not selected in the multivariate model because data was not available in all patients.

Conclusion

The demographic/clinical profiles of HFmrEF are intermediate, between those of HFpEF and HFrEF. Kidney disease was the only risk factor for death in HFrEF and HFpEF, whereas valve disease and increased urea levels were associated with HFmrEF. The use of ACEI/ARB and beta-blockers, already established as mortality reducing drugs in HFrEF, has been independently related to better evolution in this HF group. The benefits of the beta-blockers in HFmrEF have also been reported, which indicates this conduct in the intermediate scenario, since there have been no recommendations based on guidelines.

Author contributions

Conception and design of the research: Cavalcanti GP, Sarteschi C, Gomes GES, Medeiros CA, Pimentel JHM, Lafayette AR, Almeida MC, Oliveira PSR, Martins SM. Acquisition of data: Cavalcanti GP, Sarteschi C, Gomes GES, Medeiros CA, Pimentel JHM, Lafayette AR, Almeida MC, Oliveira PSR, Martins SM. Analysis and interpretation of the data: Cavalcanti GP, Sarteschi C, Gomes GES, Medeiros CA, Pimentel JHM, Lafayette AR, Almeida MC, Oliveira PSR, Martins SM. Statistical analysis: Cavalcanti GP, Sarteschi C, Gomes GES, Medeiros CA, Pimentel JHM, Lafayette AR, Almeida MC, Oliveira PSR, Martins SM. Writing of the manuscript: Cavalcanti GP, Sarteschi C, Gomes GES, Medeiros CA, Pimentel JHM, Lafayette AR, Almeida MC, Oliveira PSR, Martins SM. Critical revision of the manuscript for intellectual content: Cavalcanti GP, Sarteschi C, Gomes GES, Medeiros CA, Pimentel JHM, Lafayette AR, Almeida MC, Oliveira PSR, Martins SM.

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 monograph of the work of conclusion of the residency in cardiology submitted by Gabriela Paiva Cavalcanti, from *Real Hospital Português de Beneficência de Recife*.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Centro de Pesquisa da Universidade Católica de Pernambuco* under the protocol number 70897517.8.0000.5206. 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. Kapoor JR, Kapoor R, Ju C, Heidenreich PA, Eapen ZJ, Hernandez AF, et al. Precipitating clinical factors, heart failure characterization, and outcomes in patients hospitalized with heart failure with reduced, borderline, and preserved ejection fraction. JACC Heart Fail. 2016;4(6):464-72.
2. Banerjee P. Heart failure with preserved ejection fraction: a clinical crisis. Int J Cardiol. 2016 Feb 1;204:198-9.
3. Rickenbacher P, Kaufmann BA, Maeder MT, Bernheim A, Goetschalckx K, Pfister O, et al. Heart failure with mid-range ejection fraction: a distinct clinical entity ? Insights from the trial of intensified versus standard medical therapy in elderly patients with congestive Heart Failure (TIME-CHF). Eur J Heart Fail. 2017;19(12):1586-96.
4. Pascual-Figal DA, Ferrero-Gregori A, Gomez-Otero I, Vazquez R, Delgado-Jimenez J, Alvarez-Garcia J, et al. Mid-range left ventricular ejection fraction: clinical profile and cause of death in ambulatory patients with chronic heart failure. Int J Cardiol. 2017 Aug 1;240:265-70.
5. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62(16):e147-239.
6. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129–2200.
7. Hunt SA. American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). ACC/AHA 2005 Guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the american college of cardiology/american heart association task force on practice guidelines (writing committee to update the 2001 guidelines for the evaluation and management of heart failure). J Am Coll Cardiol. 2005;46(6):e1-82.
8. Colafranceschi AS, Freitas Jr AF, Ferraz AS, Biolo A, Barretto ACP, Ribeiro ALP, et al. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arq Bras Cardiol. 2018;111(3):436-539.
9. Lang RM, Badano LP, Mor-Avi V, Afilalo 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.
10. Fonarow GC, Heywood JT, Heidenreich PA, Lopatin M, Yancy CW, ADHERE Scientific Advisory Committee and Investigators. Temporal trends in clinical characteristics, treatments, and outcomes for heart failure hospitalizations, 2002 to 2004: findings from Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2007;153(6):1021-8.
11. Organização Mundial da Saúde. Série de relatórios técnicos no182. Geneva: WHO; 1959.
12. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham study. J Am Coll Cardiol. 1993;22(4 Suppl A):6A-13A.
13. Katsi V, Georgiopoulos G, Laina A, Koutli E, Parissis J, Tsioufis C, et al. Left ventricular ejection fraction as therapeutic target: is it the ideal marker? Heart Fail Rev. 2017;22(6):641-55.
14. Kinno M, Nagpal P, Horgan S, Waller AH. Comparison of echocardiography, cardiac magnetic resonance, and computed tomographic imaging for the evaluation of left ventricular myocardial function: part 1 (Global Assessment). Curr Cardiol Rep. 2017;19(1):9.
15. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB Jr, Cohn JN. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med. 1992;327(10):685-91.
16. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med. 1999;341(10):709-17.
17. Dargie HJ, Lechat P. The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomised trial. Lancet. 1999;353(9146):9-13.
18. Albuquerque DC, Souza Neto JD, Bacal F, Rohde LEP, Bernardez-Pereira S, Berwanger O, et al. I Brazilian registry of heart failure - clinical aspects, care quality and hospitalization outcomes. Arq Bras Cardiol. 2015;104(6):433-42.
19. Rohde LE, Clausell N, Ribeiro JP, Goldraich L, Netto R, Dec GW, et al. Health outcomes in decompensated congestive heart failure: a comparison of tertiary hospitals in Brazil and United States. Int J Cardiol. 2005;102(1):71-7.
20. Abraham WT, Fonarow GC, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Predictors of in-hospital mortality in patients hospitalized for heart failure: insights from the Organized Program To Initiate Lifesaving Treatment In Hospitalized Patients With Heart Failure (OPTIMIZE-HF). J Am Coll Cardiol. 2008;52(5):347-56.
21. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJ, Swedberg KB, et al. Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J. 2006;27(1):65-75.
22. Lam CSP, Solomon SD. The middle child in heart failure: heart failure with mid-range ejection fraction (40-50%). Eur J Heart Fail. 2014;16(10):1049-55.
23. Andronic AA, Mihaila S, Cinteza M. Heart failure with mid-Range ejection fraction – a new category of heart failure or still a gray zone. Maedica (Buchar). 2016;11(4):320-4.

24. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes. Arch Intern Med. 2008;168(8):847-54.

25. Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. Circulation. 2011;123(18):2006-13.

26. Kalogeropoulos AP, Fonarow GC, Georgiopoulou V, Burkman G, Siwamogsatham S, Patel A, et al. Characteristics and outcomes of adult outpatients with heart failure and improved or recovered ejection fraction. JAMA Cardiol. 2016;1(5):510-8.

27. Kelly JP, Mentz RJ, Mebazaa A, Voors AA, Butler J, Roessig L, et al. Patient selection in heart failure with preserved ejection fraction clinical trials. J Am Coll Cardiol. 2015;65(16):1668-82.

28. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF registry. J Am Coll Cardiol. 2007;50(8):768-77.

29. Martínez-Sellés M, Doughty RN, Poppe K, Whalley GA, Earle N, Tribouilloy C, et al. Gender and survival in patients with heart failure: interactions with diabetes and aetiology. Results from the MAGGIC individual patient meta-analysis. Eur J Heart Fail. 2012;14(5):473-9.

30. Gómez-Otero I, Ferrero-Gregori A, Varela Román A, Seijas Amigo J, Pascual-Figal DA, Delgado Jiménez J, et al. Mid-range ejection fraction does not permit risk stratification among patients hospitalized for heart failure. Rev Esp Cardiol (Engl Ed). 2017;70(5):338-46.

31. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail. 2017;19(12):1574-85.

32. Voors AA, Ouwerkerk W, Zannad F, van Veldhuisen DJ, Samani NJ, Ponikowski P, et al. Development and validation of multivariable models to predict mortality and hospitalization in patients with heart failure. Eur J Heart Fail. 2017;19(5):627-34.

33. Löfman I, Szummer K, Dahlström U, Jernberg T, Lund LH. Associations with and prognostic impact of chronic kidney disease in heart failure with preserved, mid-range, and reduced ejection fraction. Eur J Heart Fail. 2017;19(12):1606-14.

34. Tsuji K, Sakata Y, Nochioka K, Miura M, Yamauchi T, Onose T, et al. Characterization of heart failure patients with mid-range left ventricular ejection fraction-a report from the CHART-2 Study. Eur J Heart Fail. 2017;19(10):1258-69.

35. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). Lancet. 1999;353(9169):2001-7.

36. Cleland JGF, Bunting K V, Flather MD, Altman DG, Holmes J, Coats AJS, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. Eur Heart J. 2018;39(1):26-35.

37. Lund L. European Society of Cardiology. Candesartan provides similar benefit for patients with mid- range ejection fraction as those with reduced ejection fraction [Internet]. 2017 [citado fev. 2019]. Disponível em: https://www.escardio.org/Congresses-&-Events/Heart-Failure/Congress-resources/News/candesartan-provides-similar-benefit-for-patients-with-mid-range-ejection-fracti.

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

EDITORIAL

Obesity: A Risk Marker or an Independent Risk Factor for Coronary Artery Disease?

Tufi Dippe Jr. and Rodrigo Julio Cerci

Quanta Diagnóstico por Imagem, Curitiba, PR – Brazil

We congratulate Pereira et al. for their study investigating the role of obesity as a risk factor for coronary artery disease (CAD) using coronary computed tomography angiography. The study included 1,383 patients, none with a history of CAD.[1]

Obesity is a multifactorial chronic disease, characterized by accumulation of subcutaneous and visceral fat, that predisposes individuals to metabolic disorders. Several mechanisms are involved in the association between obesity and atherosclerosis, including lipid abnormalities, insulin resistance, chronic inflammation, endothelial dysfunction, reduction of fibrinolysis and hypercoagulability. In addition, the production of proinflammatory cytokines, such as IL-6, TNF-alpha, MCP-1 and leptin contributes to chronic subclinical inflammation. More recent data have indicated that impaired autophagy and altered gut microbiome homeostasis are contributing factors for the development of atherosclerosis in obese individuals.[2]

In the study by Pereira et al.,[1] the authors demonstrated, using coronary computed tomography angiography, that the prevalence of obstructive CAD was similar between obese and non-obese individuals, with a similar prevalence of cardiovascular risk factors. However, mean calcium score was significantly higher in obese than non-obese subjects. Another important finding was that, after multivariate analysis, the clinical variables age, male sex and diabetes mellitus were associated with the presence of obstructive CAD. In this study, obesity was not correlated with CAD.

In a recent publication by our group, we studied a large population of obese individuals without known CAD using myocardial perfusion scintigraphy. We found that age, diabetes mellitus, typical chest pain, poor exercise capacity during stress test, need for pharmacological protocol and low left ventricular ejection fraction were associated with abnormal perfusion. In our study, we did not detect a higher percentage of perfusional abnormalities with increasing degree of obesity.[3]

It is unquestionable the association between obesity, atherosclerosis, and increased total and cardiovascular mortality; however, medical research on the theme has led to controversial results. The first controversy is whether obesity is an independent risk factor for CAD or merely a risk marker, as it is associated with many pathophysiological mechanisms involved in the development of atherosclerosis. Prospective, cohort observational studies, such as the Framingham Study, the Nurses' Health Study and the Health Professionals Follow-Up Study have demonstrated an almost linear relationship between a body mass index (BMI) ≥ 25 kg/m² and risk of CAD. Besides, the Framingham cohort study pointed towards obesity as an independent risk factor for atherosclerosis, although these findings were not confirmed by the Seven Countries Study.[4] Another evidence for obesity as an independent risk factor for atherosclerosis emerged from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study. In this study, the researchers, through pathological examination, analyzed coronary arteries and aorta of young people aged 15 to 30, who had accidental deaths or committed suicide.The authors found that atherosclerosis starts early in life, and that obesity is associated with higher prevalence of coronary atherosclerotic lesions, such as fatty streaks, atheroma, and complex coronary lesions, especially in men.[4]

Another controversial point in the association between obesity and atherosclerosis is the "metabolically healthy obesity" phenotype, or MHO. The controversy starts with the MHO's definition, since the diagnostic criteria varied among the studies, resulting in variations in the

Keywords

Obesity; Risk Factors; Atherosclerosis; Coronary Artery Disease/physiopathology; Metabolic Syndrome; Angiography, Coronary.

Mailing address: Tufi Dippe Jr.
Rua Rocha Pombo, 920 apto. 501. Postal Code: 80530-290, Juvevê, Curitiba, PR – Brazil.
E-mail: tufidippejr@gmail.com

DOI: https://doi.org/10.36660/ijcs.20190210

prevalence of obesity, ranging from 8% to 40%.[5] Ortega et al.[5] proposed a universal classification of MHO, which should be diagnosed by the absence of all diagnostic elements of the metabolic syndrome (MS) proposed by the International Diabetes Federation, except for abdominal circumference, as follows – blood pressure ≥ 130/85 mmHg (or antihypertensive drug treatment), HDL-cholesterol < 40 mg/dL (or drug treatment for this condition), triglycerides > 150 mg/dl (dL (or drug treatment for this) and fasting glucose ≥ 100 mg/dl (or treatment for this condition).[5]

The most correct study in terms of methodology, that evaluated the relationship between MHO and atherosclerosis by coronary computed tomography angiography, was the study by Chang et al.[6] The authors concluded that MHO individuals had a higher prevalence of coronary calcification than normal weight individuals. However, such association was no longer statistically significant after adjustment of the values for the metabolic risk factors. This fact suggests that, in MHO subjects, this association occurred at higher (but still normal) levels. One limitation of this study is that it was conducted with a relatively young (mean age of 39.8 years), homogenous population of Asian patients, making the extrapolation of results to other populations difficult.[6]

Previous studies that did not show an association between MHO, CAD and cardiovascular risk had methodological limitations, such as the presence of one of the MS diagnostic criteria (in addition of abdominal circumference); the authors did not detect new-onset metabolic changes in MHO individuals after inclusion in the study; and control groups were composed of overweight subjects rather than metabolically healthy or normal weight individuals.[6]

Another important consideration is that MHO is not a stable condition, and hence should not be considered as a reliable clinical parameter for predicting cardiovascular risk. Mongraw-Chaffin et al.[7] followed 6,809 participants of the MESA (Multi-Ethnic Study of Atherosclerosis) for approximately 12 years. The authors concluded that although MHO individuals had a low risk of developing cardiovascular diseases in the beginning of the study, at least 50% of them developed the metabolically unhealthy obesity (MUO). The presence and duration of MUO was strongly associated with the development of cardiovascular disease and increased mortality.[7] A large cohort study,[8] evaluating individuals with MHO, concluded that weight lost, particularly greater than 5% of body weight was associated with lower incidence of atherosclerosis, assessed using carotid artery ultrasonography.[8]

The prevalence of obesity has increased in the last three decades, reaching epidemic proportions in the world. In Brazil, recent data from VIGITEL, a surveillance system for risk factors for chronic diseases by telephone survey, showed that 56% of Brazilians were overweight and 20% were obese in 2018.[9]

Although it has not been precisely defined whether obesity is an independent risk factor or simply a risk marker, its association with atherosclerosis, and total and cardiovascular mortality is unquestionable. MHO should not be considered a benign or stable condition, since it frequently progresses to MS, which has been proven to increase cardiovascular risk. In conclusion, obesity must be prevented and treated since childhood.

References

1. Pereira LLS, Moraes GM, Castro Carneiro AC, Moreira V, Bello JH, Prazeres CE, et al. Relationship between Obesity and Coronary Artery Disease Defined by Coronary Computed Tomography Angiography. Int J Cardiovasc Sci. 2020;33(1):57-64.
2. Lovren F, Teoh H, Subodh V. Obesity and Atherosclerosis: Mechanistic Insights. Can J Cardiol. 2015; 31(2):177-83.
3. Dippe Jr. T, Cunha CLP, Cerci RJ, Stier Jr AL, Vitola JV, et al. Study of Myocardial Perfusion in Obese Individuals without Known Ischemic Heart Disease. Arq Bras Cardiol. 2019; 11S, et al.2(2)a:121-8.
4. Mandviwala T, Khalid U, Deswal A. Obesity and Cardiovascular Disease: a Risk Factor or a Risk Marker.Curr Atheroscler Rep. 2016;18(5):21.
5. Ortega FB, Lavie CJ, Blair S N. Obesity and Cardiovascular Disease. Circulation Research. 2016;118(11):1752–70.
6. Chang Y, Kim BK, Yun KE, Cho J, Zhang Y, Rampal S, et al. Metabolically healthy obesity and coronary artery calcification. J Am Coll Cardiol. 2014; 63(24):2679-86.
7. Mongraw-Chaffin M, Foster MC, Anderson CAM, Burke GL, Haq N, Kalyani R. et al. Metabolically Healthy Obesity, Transition to Metabolic Syndrome and Cardiocascular Risk. J Am Coll Cardiol. 2018;71(17):1857-65.
8. Sinn DH, Kang D, Cho SJ,Chang Y, Ryu S, Song YB. et al. Weight Change and Development of Subclinical Carotid Atherosclerosis Among Metabolically Healthy Adults: A Cohort Study. J Clin Endocrinol Metab. 2019;104(11):145-63.
9. Brasil.Ministério da Saúde.Vigitel Brasil 2018. Vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico. .[Internet] [Citado em 2019 jul 30]. Disponível em: portalarquivos2.saude.gov.br/images/pdf/2019/julho/25/vigitel-brasil-2018.pdf

Agora você já pode acessar todas as **Publicações da SBC** em um só aplicativo

BAIXE GRÁTIS

- Arquivos Brasileiros de Cardiologia
- International Journal of Cardiovascular Sciences
- Jornal SBC
- Diretrizes da SBC
- Pocket Book
- ABC Imagem Cardiovascular
- Outras Publicações

Baixar na App Store

DISPONÍVEL NO Google Play

SOCIEDADE BRASILEIRA DE CARDIOLOGIA SBC 1943

MOVIDOS PELO CORAÇÃO

International Journal of Cardiovascular Sciences. 2020;33(1):57-64

ORIGINAL ARTICLE

Relationship between Obesity and Coronary Artery Disease Defined by Coronary Computed Tomography Angiography

Lara Luiza Silvello Pereira,[1] Gisele Marochi de Moraes,[1] Adriano Camargo de Castro Carneiro,[2] Valéria de Melo Moreira,[2] Juliana Hiromi Silva Matsumoto Bello,[2] Carlos Eduardo Elias dos Prazeres,[2] Carlos Eduardo Rochitte,[2] Tiago Magalhaes[2]

Pontifícia Universidade Católica do Paraná (PUCPR),[1] Paraná, PR - Brazil
HCOR,[2] São Paulo, SP - Brazil

Abstract

Background: Although associated with traditional cardiovascular risk factors, it is unclear whether obesity alone is associated with coronary artery disease (CAD).

Objective: To investigate the role of obesity as a risk factor for CAD, defined by coronary computed tomography angiography (CCTA).

Methods: This study retrospectively included 1,814 patients referred for CCTA in a hospital in São Paulo, from August 2010 to July 2012. CAD was identified by coronary calcium score and presence of coronary stenosis > 50%. Images were analyzed by two specialists, and the coronary findings were compared between obese and non-obese groups. A multivariate analysis model was used to assess obesity as an independent variable for the occurrence of obstructive CAD.

Results: Among the study population, mean age was 58.5 +/- 11.5 years, 22.8% were obese (BMI = 30 kg/m^2) and 66.3% were male. The prevalence of obstructive CAD was 18.4% in both groups. Obese patients had higher median calcium score compared to non-obese subjects (14.7 vs. 1.4, respectively, p = 0.019). In the multivariate analysis, obesity was not an independent factor for obstructive CAD (coefficient = -0.035, p = 0.102).

Conclusion: Although no differences were observed in the prevalence of obstructive CAD between obese and non-obese individuals, coronary calcium scores were significantly in lower the latter group. (Int J Cardiovasc Sci. 2020;33(1):57-64)

Keywords: Coronary Artery Disease; Obesity; Body Mass Index; Dyslipidemias; Risk Factors; Prevalence; Tomography/métodos; Coronary Angiography/methods.

Introduction

Cardiovascular diseases are the main causes of morbidity and mortality in the world population. Due to aging of the global population, cardiovascular diseases, mainly represented by coronary artery disease (CAD), play an incremental role on global mortality.[1]

In this context, changes in lifestyle have contributed to increased incidence of cardiovascular risk factors and ultimately of coronary disease. Due to its increasing incidence on a global scale (39% of adults aged 18 years and older are obese), obesity has become one of the factors with the greatest impact on the risk of CAD.[2]

Obesity is recognized as one of the most important underlying risk factors for a wide variety of metabolic diseases, such as hypertension, dyslipidemia, and diabetes, which are strongly associated with the development of cardiovascular diseases.[3] Nevertheless, whether obesity alone is a risk factor for CAD has not been well established.[4-6] In this regard, the phenotype

Mailing Address: Tiago Magalhaes
Rua Moysés Marcondes, 181, ap 501. Postal Code: 80030-410, Juveve, Curitiba, PR - Brazil.
E-mail: tiaugusto@gmail.com, taugusto@cardiol.br

DOI: 10.5935/2359-4802.20190029

Manuscript received March 22, 2018; revised manuscript August 27, 2018; accepted September 03, 2018.

of metabolically healthy but obese (MHO) individuals, with hormonal and insulin resistance profile not compatible with increased adiposity has become a matter of discussion.[7,8]

Previous studies have investigated the incidence of cardiovascular disease in MHO, with controversial results.[9,10] Also, although data derived from intermediate markers of disease (e.g. the carotid intima media thickness) can evaluate the association of these parameters with the presence of CAD in MHO individuals, there are few data available about the association between body mass index (BMI) and coronary artery calcium score as determinant of subclinical atherosclerosis. Coronary artery calcium score was shown to be superior than other methods for the evaluation of subclinical atherosclerosis in cardiovascular event prediction.[11]

Therefore, the aim of the present study was to evaluate whether obesity alone is correlated with the presence of CAD, evaluated by coronary computed tomography angiography (CCTA).

Methods

Patients and study design

We reviewed the database and patients medical records in a tertiary hospital in Sao Paulo (Brazil). The sample was composed of 1,814 patients consecutively referred for cardiac/coronary computed tomography angiography between August 2010 and July 2012.

The study was approved by the ethics committee of the Pontifical Catholic University of Paraná (approval number 1524216) and was in accordance with the Helsinki Declaration. The study was registered in Plataforma Brasil (registration number 55363016.6.0000.0020) and informed consent to participate in this study was waived. All data were collected and registered in specific spreadsheets by trained investigators, and then manually transferred to a database of the CCTA division.

Epidemiological and clinical data

Data contained in the patient admission questionnaire were collected by direct interview and/or from medical records. Variables included demographic and anthropometric data, indication for CCTA, risk factors for CAD – hypertension, diabetes, dyslipidemia, smoking, family history of CAD – parameters of CCTA acquisition and results of the test.

Computed tomography angiography, a contrast computed tomography, is clinically used for evaluation of coronary stenosis/obstruction. The test allows the calculation of the coronary artery calcium, which consists in a non-invasive imaging method to identify atherosclerosis in asymptomatic individuals.

Definitions of obese and metabolically healthy but obese patients

Patients with a BMI greater than 30 kg/m^2 were considered obese, and MHO patients were identified based on the absence of the following criteria – 1) hypertriglyceridemia (triglycerides > 150 mg/dL) or pharmacological treatment for this condition; 2) low HDL-cholesterol (HDL < 40 mg/dL) or pharmacological treatment for this condition; 3) hypertension, defined as blood pressure ≥ 130/85 mmHg or pharmacological treatment for this condition; 4) altered fasting glucose (glucose ≥ 100 mg/dL) or diagnosis of diabetes, or pharmacological treatment for this condition.

Coronary computed tomography angiography

1. Acquisition parameters and protocol

Two computed tomography scanners were used for the tests - Siemens Somatom Sensation 64 and Siemens Somaton Definition Flash (Siemens Healthcare, Forchheim, Germany), following respective protocols. Patients with blood pressure higher than 100 mmHg received 5 mg sublingual nitrates prior to the test, whereas a beta-blocker (metoprolol 150 mg in patients with BMI ≥ 30 kg/m^2, and 75 mg in those with BMI ≤ 30 kg/m^2) was orally administered to patients with a heart rate higher than 80 bpm on the test day. In addition, if necessary, intravenous metoprolol (maximum 20 mg) was used during CCTA to achieve target heart rate (≤ 65 bpm).

Patients with no history of angioplasty or surgical revascularization underwent computed tomography scanning synchronized with electrocardiography before contrast injection for quantification of coronary artery calcium (Agatston units). Subsequently, contrast was injected at high flow rates (maximum of 6 mL/s - Henetix 350 mg/mL, Guerbet, Rio de Janeiro, Brazil), with concomitant acquisition of CCTA. The following parameters were obtained for analysis: 1) tube voltage of 100-140 kV; 2) adjusted tube current (estimated by the tomography device according to chest attenuation of each patient); 3) collimation 2 x 128 x 0.6 mm or 64 x 0.6 mm, according to the scanner specifications. The tests on both

scanners were performed in helical acquisition mode, or in prospective axial and high-pitch spiral mode by the dual-source (two x-ray sources) scanner.

2. Image reconstruction

For coronary artery calcium score calculation, images were reconstructed with a section thickness of 3 mm and 3 mm- interval. Coronary calcifications with attenuation ≥ 130 HU in an area ≥ 3 mm^2 were quantified, according to the algorithm proposed by Agatston et al.[12]

CCTA images were reconstructed with a section thickness of 0.6 mm and increment of 0.3 mm in systole and/or automatically or manually determined (in case of spiral or prospective acquisition), to minimize cardiac motion artifacts. For better image quality, iterative reconstruction algorithms were performed.

3. Image interpretation

All images (calcium score and CCTA) were analyzed on a dedicated workstation (Leonardo Definition, Siemens Healthcare, Erlanger, Germany). All CCTA images were analyzed by two observers; discrepancies were resolved by consensus.

Coronary artery calcium was quantitively determined by visual identification of coronary calcifications. Lesions in different coronary territories were automatically summed to determine the total calcium score.

Per-segment analysis of CCTA images was performed following the Society of Cardiovascular Computed Tomography guidelines.[13]

CAD was established at two levels: 1) calcium score > 0 (Agatston); 2) presence of atherosclerotic plaque (CCTA). Obstructive coronary disease was defined by the presence of any coronary stenosis ≥ 50%.

Statistical analysis

Binary data were described in absolute numbers and percentages. Continuous variables with normal distribution were presented as mean and standard deviation, whereas those without a normal distribution were presented as median and interquartile range. Data normality was tested by the Shapiro-Wilk test; coronary artery calcium score was the only variable that was not normally distributed. Categorical variables were compared using the chi-square test. Continuous variables were compared using the unpaired Student's t-test. Calcium score between obese and non-obese patients was compared by the Mann-Whitney test.

A multiple linear regression model was used to assess the relationship between cardiovascular risk factors and the presence of obstructive CAD. For continuous variables of the model, β coefficients were used to indicate changes in the dependent variable (presence of obstructive CAD) for a unit change in each independent variable after controlling for confounding variables. For categorical variables (e.g. sex, smoking), β coefficient represents the difference in the dependent variable (presence of obstructive CAD) according to the status (e.g. male vs. female; smokers vs. non-smokers) after controlling of confounding variables of the model.

Statistical analysis was performed using the STATA software (version 11, STATACorp, College Station, Texas, USA). The level of significance was set as 5%.

Results

A total of 1,814 consecutive patients with a medical indication for cardiac/coronary computed tomography angiography, were referred to a tertiary hospital in São Paulo between August 2010 and July 2012. We excluded from analysis patients whose indication for the test was not screening for CAD (e.g. patients with congenital heart disease, patients referred for evaluation of valve disease or pulmonary veins). In addition, we also excluded patients with history of CAD (myocardial infarction, angioplasty and /or surgical myocardial revascularization). A total of 1,383 patients were evaluated (Figure 1). Table 1 describes main epidemiological characteristics of the patients. Mean age was 58.5 +/- 11.5 years, and 66.3% (n = 917) of patients were men.

In general, the prevalence of cardiovascular risk factors was not different between obese and non-obese subjects (Table 1), and the same was observed for the prevalence of obstructive CAD. Obstructive CAD was present in a similar percentage (18.4% in both groups) in obese patients (n = 58) and in those with BMI < 30 kg/m^2 (n = 197) (Figure 2). The presence of CAD, defined by the presence of coronary calcifications, was significantly different between the groups. Median calcium score was 1.4 and 14.7 Agatston units in the groups of non-obese and obese patients, respectively (Figure 2). In our sample, mean calcium score percentile, by age, sex and ethnicity was 61.

In order to establish the role of each risk factor on the development of obstructive CAD, we used a multiple

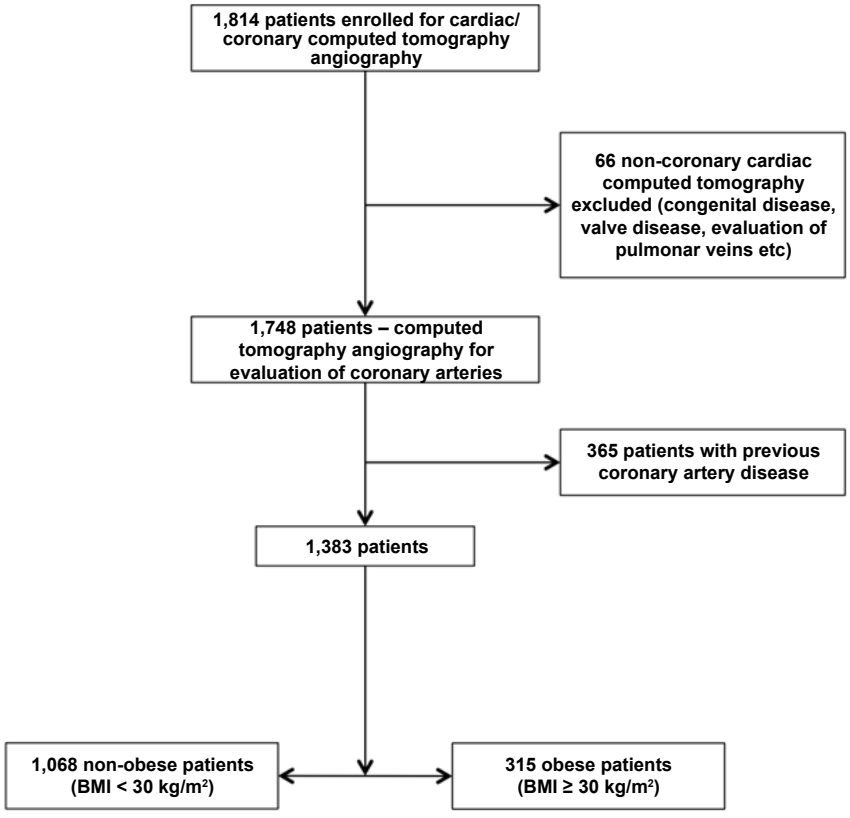

Figure 1 - Flowchart of patients' selection.

Table 1 - Characteristics of the study population

Variable	Non-obese (n = 1,068)	Obese (n = 315)	p
Age (years)	58.1 ± 11.2	59.8 ± 11.3	0.02†
Male sex	694 (65.0%)	223 (70.8%)	0.06††
Weight (kg)	75.8 ± 14.0	99.9 ± 15.9	< 0.001†
Body mass index (kg/m²)	26.2 ± 3.4	34.0 ± 4.0	< 0.001†
Diabetes (n, %)	227 (21.3%)	61 (19.4%)	0.47††
Hypertension (n, %)	586 (54.9%)	184 (58.4%)	0.27††
Dyslipidemia (n, %)	413 (38.7%)	108 (34.3%)	0.16††
Current and previous smoking (n, %)	718 (67.2%)	215 (68.3%)	0.71††
Family history of CAD (n, %)	169 (15.8%)	53 (16.8%)	0.67††
Calcium score (median)*	1.4	14.7	0.019§
Prevalence of obstructive CAD (n, %)	197 (18.4%)	58 (18.4%)	-

*CAD: coronary artery disease; *Agatston units; † Unpaired Student's t-test. †† Chi-squared test (χ^2); § Mann-Whitney test.*

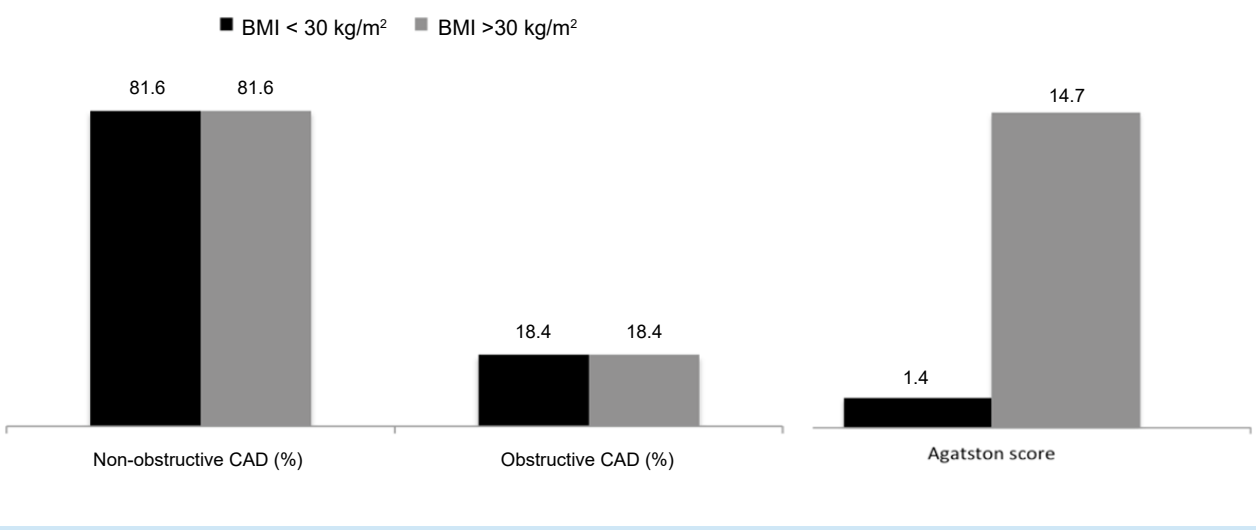

Figure 2 - Prevalence of obstructive coronary artery disease (CAD) and coronary artery calcium score by body mass index (BMI).

linear regression model including all cardiovascular risk factors (Table 2). Variables significantly associated with obstructive CAD, defined by CCTA, included age, male sex, and diabetes; hypertension was of marginal significance for outcome definition (p = 0.08). Obesity was not correlated with obstructive CAD (p = 0.10) when the other variables were maintained constant.

Discussion

The present study showed that, although the prevalence of obstructive CAD was not different between obese and non-obese patients, coronary artery calcium scores were significantly lower in non-obese than obese patients.

Obesity is believed to have a direct effect on metabolic health, since proinflammatory cytokines released by the adipose tissue can lead to subclinical inflammation at long-term, even if counterbalanced by anti-inflammatory cytokines. This condition is characterized by a gradual increase in inflammatory markers, such as C-reactive protein, TNF-alpha and interleukin-6, which have a direct relationship with insulin resistance, hepatic steatosis and endothelial dysfunction, leading to atherosclerosis.[14]

Table 2 - Obesity and risk factors as predictors of obstructive coronary arterial disease according to coronary computed tomography angiography

Obstructive coronary artery disease	Coef.	Standard error	95%CI	p*
Obesity	-0.035	0.021	-0.077 – 0.007	0.102
Age	0.005	0.0008	0.003 – 0.0065	< 0.001
Sex	0.046	0.01	0.027 – 0.066	< 0.001
Diabetes	0.065	0.024	0.019 – 0.11	0.006
Hypertension	0.034	0.020	-0.004 – 0.073	0.08
Dyslipidemia	0.012	0.020	-0.027 – 0.05	0.548
Smoking	0.015	0.015	-0.014 – 0.04	0.308
Family history of CAD	-0.022	0.013	-0.048 – 0.004	0.105

** p-values by multiple linear regression model.*

Despite the great potential of the method, the use of CCTA for the establishment of a correlation between CAD and obesity is still little explored. Compared with catheterization, computed tomography angiography is a highly accurate, non-invasive method, with acceptable levels of patient radiation and contrast, that can be useful in the identification of coronary arterial narrowing by atherosclerotic plaques.

Although the association of obesity with CAD is well documented,[15,16] there is evidence supporting that cardiovascular risk factors are not more common in MHO individuals compared with non-obese subjects.[17-19] In other words, obesity alone would not be determinant for increased incidence of CAD. This is corroborated by our findings on the prevalence of obstructive coronary disease, which was not different between obese and non-obese subjects.

On the other hand, the higher values of coronary artery calcium score among obese individuals suggest a correlation between this condition with the development of subclinical atherosclerosis. Chang et al.,[20] demonstrated that MHO patients have higher calcium score values than non-obese patients. However, after adjusting for metabolic risk factors, this association was attenuated and no longer statistically significant. The authors concluded that obesity is an additional risk for coronary atherosclerosis, including the subclinical form, mediated by metabolic changes whose thresholds are lower than those considered abnormal.

In this context, one important factor is the influence of BMI on tomography imaging analysis. Obese individuals show a reduced signal-to-noise ratio in chest images, due to increased adipose tissue compared with non-obese individuals. The higher chest wall thickness in obese subjects attenuates the X-rays emitted from the tubes, allowing that a lower amount of photons reaches the detector for image construction, resulting in a more "grained" image. Such loss could be compensated by modulations in the tube voltage and in the X-ray tube current, improving the signal-to-noise ratio of these tests. However, the methods used for image acquisition for coronary artery calcium scoring do not allow adjustments in tube voltage of the tomography scanner, fixing it at 120 kilovolts. In practical terms, that implicates that images with lower signal-to-noise ratio are obtained from CCTA in obese patients. In parallel with the potential effect of obesity on coronary calcification, we believe that this change in the signal-to-noise ratio in obese patients image may have contributed to changes in the threshold for coronary artery calcium detection, artificially increasing calcium score levels in this population. In this regard, mean calcium score percentile in our patients was 61 according to the Multi-Ethnic Study of Atherosclerosis (MESA),[21] indicating a higher-than-average coronary calcification. However, these results are not comparable with those reported in the MESA study, which evaluated asymptomatic individuals, with not history of CAD, due to selection bias of our study population (patients referred for coronary tomography for investigation of CAD and hence more likely to have the disease).

Limitations

Our study has limitations inherent to its retrospective design. Since this was a cross-sectional study evaluating the association of obesity with CAD based on medical records, the results do not take into account some variables, such as the time of exposure to triggering factors of the disease.

The definition of metabolically healthy obesity was based on the identification and exclusion of obesity-related metabolic abnormalities (hypertension, dyslipidemia, diabetes). Nevertheless, laboratory markers of insulin resistance, including the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) were not used in patients recruitment in our study.

Our study population was selected based on BMI, which, although is the most widely used anthropometric variable to characterize obesity, it does not provide information regarding body composition. Therefore, assuming that the percentage of body fat has a direct effect on insulin resistance, BMI alone does not give us any insight into this condition. In addition, other anthropometric measures known to provide a more accurate estimation of visceral fat (e.g. waist circumference and waist-to-hip ratio measurements) were not registered in the medical records, and hence could not be used in the analysis.

Finally, the definition of CAD by CCTA may be controversial; although CCTA is a very robust method to define non-obstructive atherosclerosis by coronary artery calcium scoring, the method considered the gold-standard method to detect obstructive coronary disease is invasive coronary angiography combined or not with intracoronary ultrasound.

Conclusion

Obese patients without other associated risk factors did not show a higher prevalence of obstructive CAD, according to CCTA, compared with non-obese patients. However, coronary artery calcium score was higher in obese than in non-obese individuals, indicating a higher prevalence of subclinical atherosclerosis mediated by obesity.

Author contributions

Conception and design of the research: Pereira LLS, Moraes GM, Carneiro ACC, Moreira VM, Bello JHSM, Prazeres CEE, Rochitte CE, Magalhaes T. Acquisition of data: Pereira LLS, Moraes GM, Carneiro ACC, Moreira VM, Bello JHSM, Prazeres CEE, Rochitte CE, Magalhaes T. Analysis and interpretation of the data: Pereira LLS, Moraes GM, Rochitte CE, Magalhaes T. Statistical analysis: Pereira LLS, Moraes GM, Magalhaes T. Writing of the manuscript: Pereira LLS, Moraes GM, Magalhaes T. Critical revision of the manuscript for intellectual content: Pereira LLS, Moraes GM, Carneiro ACC, Moreira VM, Bello JHSM, Prazeres CEE, Rochitte CE, Magalhaes T.

Potential Conflict of Interest

The authors have declared that no competing interests exist.

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of academic works submitted by Lara Luiza Silvello Pereira and Gisele Marochi de Moraes in partial fulfillment of the requirements for the Bachelor's degree in Medicine, from *Pontifícia Universidade Católica do Paraná*.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Pontifícia Universidade Católica do Paraná* under the protocol number 1.524.216. 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. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1151-210.
2. World Health Organization.(WHO). Global status of noncommunicable diseases. Geneva; 2014.
3. Arnlov J, Ingelsson E, Sundstrom J, Lind L. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. Circulation.2010;121(2):230-6.
4. Karelis AD. To be obese–does it matter if you are metabolically healthy? Nat Rev Endocrinol. 2011;7(12):699–700.
5. BlüherM. Are there still healthy obese patients? Curr Opin Endocrinol Diabetes Obes. 2012;19(5):341–6.
6. Després JP. What is "metabolically healthy obesity?": from epidemiology to pathophysiological insights. J Clin Endocrinol Metab. 2012;97(7):2283–5.
7. Primeau V, L. Coderre, A.D. Karelis, Brochu M, Lavoie ME, Messler V, et al. Characterizing the profile of obese patients who are metabolically healthy, Int J Obes (Lond).2011;35(7):971-81.
8. Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004), Arch Intern Med. 2008;168(15):1617-24.
9. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions?: A systematic review and meta-analysis, Ann Intern Med.2013;159(11):758-69.
10. Meigs JB, Wilson PW, Fox CS, Vassan RS, Nathan DM, Sullivan LM, et al. Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. J Clin Endocrinol Metab. 2006;91(8):2906-12.
11. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA. 2012;308(8):788-95.
12. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990;15(4):827-32.
13. Raff GL, Abidov A, Achenbach S, Berman DS, Boxt LM, Budoff MJ, et al. SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. J Cardiovasc Comput Tomogr. 2009;3(2):122-36.
14. Alkhawam H, Nguyen J, Sayanlar J, Sogomonian R, Desai R, Jolly J, et al. Coronary artery disease in patients with body mass index J 30 kg/m 2 : a retrospective chart analysis. J Community Hosp Intern Med Perspect. 2016;6(3):31483.
15. McGill HC, McMahan CA, Herderick EE, Zieske AW, Malcom GT; Tracy RE, et al. Pathobiological determinants of atherosclerosis in youth (PDAY) Research Group. Obesity accelerates the progression of coronary aterosclerosis in young men. Circulation. 2002;105(23):2712-8.

16. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health. 2009 Mar 25;9:88.

17. St-Pierre AC, Cantin B, Mauriège P, Bergeron J, Dagenais GR, Després JP, et al.et al. Insulin resistance syndrome, body mass index and the risk of ischemic heart disease. CMAJ. 2005;172(10):1301–5.

18. Meigs JB, Wilson PW, Fox CS, Vasan RS, Nathan DM, Sullivan LM, et al. Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. J Clin Endocrinol Metab. 2006;91(8):2906–12.

19. Hamer M, Stamatakis E. Metabolically healthy obesity and risk of all-cause and cardiovascular disease mortality. J Clin Endocrinol Metab. 2012;97(7):2482–8.

20. Chang Y, Kim BK, Yun KE, Cho J, Zhang Y, Rampal S, et al. Metabolically-healthy obesity and coronary artery calcification. J Am Coll Cardiol. 2014; 63(24):2679-86.

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

International Journal of Cardiovascular Sciences. 2020;33(1):65-67

EDITORIAL

Challenges for Anticoagulation in Atrial Fibrillation

Ana Inês da Costa Bronchtein

Hospital Copa D'or – Rio de Janeiro, RJ – Brazil

Atrial fibrillation (AF) is the most prevalent arrhythmia in the world.[1] It is considered a current epidemic and one of the main causes of ischemic stroke, usually with severe and debilitating conditions, and is responsible for systemic cardioembolic phenomena, increased number of cases of congestive heart failure (CHF), cognitive impairment related to silent embolic phenomena, and increased overall mortality in affected patients.

Vitamin K antagonists (VKA) represented in the vast majority of studies with warfarin have been widely used for many years; however, they have complex adherence due to several factors, including the need for frequent INR monitoring, regular dose adjustments for maintaining a suitable time in therapeutic range (TTR) (>= 70%) and interactions with a number of drugs and foods, which contributed to its ever decreasing use.[2] Direct-acting anticoagulants (DACs), represented by dabigatran, rivaroxaban, apixaban and, more recently, edoxaban, offer an alternative to VKA, without the disadvantages presented by the latter.

DACs have been increasingly used for the prevention of ischemic stroke and systemic embolic phenomena in non-valvular AF, with efficacy and safety confirmed in randomized multicenter non-inferiority studies with an overwhelming number of patients included.[3] Besides, in real-life studies, the results of phase III studies have been confirmed, demonstrating advantages of using DACs even in older populations, with confirmed reduction in intracranial hemorrhage and some DACs demonstrating superiority in mortality compared to warfarin.

Nevertheless, although the introduction of DACs has promoted the use of anticoagulation in patients with non-valvular AF (absence of moderate to severe mitral stenosis and/or presence of mechanical valve), and despite the availability of national and international guidelines on the subject,[4-6] the application of these guidelines in clinical practice is still far from desired worldwide, either due to the use of incorrect doses (usually below the recommended ones) or to inadequate use due to lack of knowledge of related drug interactions and fear of bleeding in the older population.

In this retrospective observational study, which collected data from an electronic medical record, conducted at a single center of a private tertiary hospital in Salvador (BA), Geraldes et al.[7] evaluated the predictors of oral anticoagulation in patients with non-valvular AF and atrial flutter from 2011 to 2016 and how DACs are being incorporated in this context. A well-written original article where the authors evaluated 377 patients, mostly with paroxysmal AF, with a high rate of comorbidities such as: SAH, DM, history of HF, AMI and stroke were separated into two groups: with and without anticoagulants. The anticoagulated group was divided into use of DACs and warfarin, and the following variables were listed: previous paroxysmal AF, presence of CHF, serum creatinine, EF, LA diameter, presence of biological prosthesis, moderate valvular disease and history of previous electrical or chemical cardioversion.

The authors demonstrated that, during these 5 years of follow-up, there was a significant increase in the number of patients anticoagulated with DACs (from 29% to 70% — a relative increase of 144.8% and an annual incorporation of 10.4%) and a progressive decrease in warfarin use (36% to 17%) in the population evaluated, with a drop in antiplatelet use alone (21% to 6%), confirming the initial impression that the increase in DAC prescriptions has accelerated the decline in warfarin prescriptions. It is worth noting that the use of antiplatelets alone in AF does not protect from ischemic stroke/thromboembolism (ET) in

Keywords

Atrial Fibrillation; Anticoagulants; Brain Ischemia; Vitamin K; Thromboembolism/ prevention and control.

Mailing Address: Ana Inês da Costa Bronchtein
Rua Rainha Guilhermina, 23/401. Postal Code: 22441120, Leblon Rio de Janeiro – RJ – Brazil.
E-mail: a.bronchtein@gmail.com

DOI: https://doi.org/10.36660/ijcs.20190003

patients with high CHA2DS2VASc and high HAS-BLED (prevalent study population), and increases the risk of bleeding in this population.

In the study by Geraldes et al.,[7] the variables previous AF episode ($p < 0.001$), hypertension ($p < 0.001$) and low HAS-BLED score were predictors of anticoagulation, while increased serum creatinine ($p < 0.002$), increased LA ($p = 0.003$) and presence of biological prosthesis ($p = 0.007$) were predictors inversely associated with the prescription of DACs, i.e., they were predictors of warfarin prescription. Each 1 mg/ml increase in serum creatinine led to 82% less chance of patients using DACs, reflecting the rejection of anticoagulating patients with impaired renal function despite the safety demonstrated in patients with clearance of up to 30 mg/ml with all DACs. They also demonstrated a high correlation between HAS-BLED and CHA2DS2VASc in the study population, which reflects the reality of AF patients with a high rate of associated comorbidities and a high risk of both thromboembolic events and major bleeding.

Of the total population evaluated in the study, 75% were discharged on oral anticoagulation (20% VKA and 55% DACs) and the vast majority had a history of AF ($p = 0.001$) and TIA/stroke ($p = 0.008$), were elderly ($p = 0.005$) and had smaller HAS-BLEDs with higher weights. Surprisingly, 93 patients referred for anticoagulation were discharged without using such drugs and, in this group, 54% (50 patients) had no reason for not using them or the reasons were inconsistent with the medical literature.

The authors also point out, which seems extremely relevant, that some physicians did not apply the CHA2DS2VASc risk score to assess patients' thromboembolic risk. Instead, they used only their clinical impression, which is often inaccurate, although the population's average CHA2DS2VASc was as high as 3.4 +-2. Of the 208 patients on DACs, 63 (30%) had inadequate prescriptions for severe interactions and 58 patients were prescribed inadequate doses for the patient profile. Doses below effective levels were the most common error found.

Marzec et al.,[8] in an article published in the JACC in 2017 (7), studied 655,000 patients with risk score CHA2DS2VASc>1 in the PINNACLE registry, where they analyzed the use of warfarin and DACs in non-valvular AF. The authors also concluded that the introduction of DACs in clinical practice was associated with improved rates of anticoagulation for AF but many gaps were still to be filled and variations in clinical practice were quite inconsistent regarding anticoagulation with DACs. These authors reported that DACs were preferably used in patients with few comorbidities, low risk of ischemic stroke and in those previously anticoagulated with warfarin. The authors suggested that further studies would be needed to better define the factors associated with variations and underuse of DACs in patients with high risk of ischemic stroke, emphasizing the importance of applying specific strategies to reduce the risk of ischemic stroke in patients with AF.

Monelli et al.,[9] in a single-center prospective observational real-life Italian study assessed records of patients using DACs (the REGINA study — registry of patients on non-vitamin K oral anticoagulants), which included 227 patients with mean age of 81.6 years (about 80% > 80 years of age) and mean CHA2DS2vasc of 5 and HAS-BLED of 4, with mean clearance of 59.2 and concluded that in a population of elderly and clinically complex patients, especially octogenarians, a population that is similar to the study discussed here, DACs were safe and effective and the careful follow-up of these elderly people with a high treatment adherence rate contributed to better prognosis in this population (8).

Another study evaluating anticoagulation in AF, the ORBIT-AF study (outcomes registry for better quality of care in the treatment of AF) showed a higher prevalence of DAC use among AF patients seen by electrophysiologists compared with clinical cardiologists and primary care physicians or generalists. This is probably due to the fact that electrophysiologists receive the referral of a larger number of patients without contraindication for anticoagulation, because after an ablative procedure, full anticoagulation is recommended, i.e., they deal with a previously selected population.[10]

In conclusion, the study by Geraldes et al.,[7] realistically portrays the current situation of AF anticoagulation in our community, highlighting an important advance in the use of anticoagulation, especially DACs, but also drawing attention to improvements in this practice, which requires significant and urgent changes in order to use oral anticoagulation at discharge in this population with higher thromboembolic risk as a quality factor in AF care and an important indicator of primary prevention in public health.

References

1. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis A, Kenneth A, et al. ACC/AHA/ESC 2006 guidelines 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 European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Arial Fibrillation). J Am Coll Cardiol 2007;50(6):562

2. Birman-Deych E, Radford MJ, Nilasena DS, Gage BF. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. Stroke 2006;37(4):1070-4.

3. Heidbuchel H, Verhamme P, Alings M, Camm AJ. Updated European Heart Rhythm Association practical guide on the use of non-vitamin-K antagonist anticoagulants in patients with non-valvular atrial fibrillation: Executive summary. ESC Scientific Document Group. Eur Heart J. 2017 Jul 14; 38(27): 2137–49.

4. Magalhães LP, Figueiredo MJ, Cintra FD. Executive Summary of the II Brazilan Guidelines for Atrial Fibrillation.II Brazilian Guidelines for Atrial Fibrillation. Arq Bras Cardiol.2016;107(6):501-8.

5. Kirchhof P, Benussi S, Kotecha D, (Task force members). 2016 Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016; 37(38): 2893–962.

6. January CT, Wann S, Calkins H, Chen LY, Cigarroa JE, Cleveland Jr JC, et al. 2019 Focused Update on Atrial Fibrillation. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. Circulation. 2019; 140(2):e125-e151.

7. Geraldes MFA, Darze ES, Rocha PN. Trends and predictors of oral anticoagulation in patients with atrial fibrillation: a serial cross-sectional study from 2011 to 2016. Int J Cardiovasc Sci. 2020;33(1):68-78.

8. Marzec LN, Wang J, Shah, Chan PS, Ting HH, Gosch KL, et al. Influence of direct oral anticoagulants on rates of oral anticoagulation for atrial fibrillation. J Am Coll Cardiol. 2017;69(20):2475-83.

9. Monelli M, Molteni M, Cassetti G, Bagnara L, Del Grazia V, Zingale L, et al. Non- Vitamin K oral anticoagulante use in the elderly: a prospective real-world study – data from the REGIstry of patients on Non-vitamin K oral anticoagulants (REGINA). Vasc Health Manag. 2019;15:19-25.

10. Fosbol L, Holmes DN, Piccin JP, Hplmes DN, Piccini JP, Thomas L, Reiffel JA, Mills RN, et al. Provider specialty and atrial fibrillation treatment strategies in United States Community practice: findings from the ORBIT-AF registry. J Am Heart Assoc. 2013;2(4):e000110.

ORIGINAL ARTICLE

Trends and Predictors of Oral Anticoagulation in Patients with Atrial Fibrillation: A Serial Cross-Sectional Study from 2011 to 2016

Maria de Fátima de Araújo Geraldes,[1,2] Eduardo Sahade Darze,[1,2] Paulo Novis Rocha[1]

Universidade Federal da Bahia,[1] Salvador, BA – Brazil
Hospital Cárdio Pulmonar,[2] Salvador, BA - Brazil

Abstract

Background: Despite the efficacy of vitamin K antagonists against stroke in patients with atrial fibrillation (AF), the underuse of this therapy is well documented.

Objectives: To evaluate trends and predictors of oral anticoagulants utilization in patients with AF.

Methods: Observational, retrospective, serial cross-sectional study between 2011-2016. Comparisons between groups were performed using the Student t, Mann-Whitney and Chi-square tests. Logistic regression was used to identify independent predictors of anticoagulation. A p value < 0.05 was considered significant.

Results: A total of 377 patients were analyzed. The mean age was 70 ± 15 years; 52% were male and 75% were anticoagulated (20% with VKA and 55% with DOAC). Over 5 years, the overall frequency of anticoagulation increased by 22.4%. The use of DOACs increased from 29% to 70%, whereas the use of VKA decreased from 36% to 17%. The use of antiplatelet agents alone also fell from 21% to 6%. The predictors of anticoagulation were previous episodes of AF (OR 3.1, p < 0.001), hypertension (OR 3.0, p < 0.001) and HASBLED score (OR 0.5, p < 0.001). The predictors of DOAC use were serum creatinine (OR 0.2, p = 0.002), left atrial size (OR 0.9, p = 0.003) and biological valve prosthesis (OR 0.1, p = 0.007). Of the 208 patients using DOACs, 63 (30%) received inadequate prescriptions: 5 with severe drug interactions and 58 with incorrect dosing.

Conclusions: Between 2011 and 2016, DOACs were rapidly incorporated into clinical practice, replacing AVKs and antiplatelets, and contributing to greater use of anticoagulation in patients with AF. (Int J Cardiovasc Sci. 2020;33(1):68-78)

Keywords: Atrial Fibrillation; Anticoagulants; Brain Ischemia; Vitamin K/antagonists & inhibitors; Thromboembolism/ prevention & control.

Introduction

Atrial fibrillation (AF) affects about 1–2% of the world's population and is associated with a five-fold increased risk of stroke. The use of vitamin K antagonists (VKA) as anticoagulants reduces the risk of stroke or systemic embolism by 64% and all-cause death by 26%.[1-7] However, observational studies have shown that only 50–60% of patients with AF eligible for the use of anticoagulants are anticoagulated. Reasons for underutilization of VKAs include numerous drug and food interactions and the inconvenience of laboratory monitoring process, which make it difficult to maintain the International Normalized Ratio (INR) in the narrow therapeutic range, placing patients at risk for ischemic and hemorrhagic events.[8-10]

Over the past 10 years, several randomized trials, involving more than 70,000 patients with AF, compared the use of AVK with direct-acting oral anticoagulants (DOACs). In these studies, DOACs were at least as effective as VKAs in preventing thromboembolic events and promoted a significant reduction in the frequency of intracranial hemorrhage.[11] In addition, DOACs

Mailing Address: Maria de Fátima de Araújo Geraldes
Universidade Federal da Bahia - Rua Augusto Viana, s/n. Postal Code: 40110-060, Salvador, Salvador, BA - Brazil.
E-mail: mfageraldes@gmail.com

DOI: 10.5935/2359-4802.20190083

Manuscript received on March 03, 2019, revised manuscript on April 15, 2019, accepted on May 22, 2019.

do not require laboratory monitoring to determine effective therapeutic level and have few significant drug interactions.

The purpose of this study is to determine the pattern and predictors of the use of anticoagulants in eligible patients with AF and how fast DOACs are incorporated in this context.

Methods

Reference population

Data were collected from an electronic medical record of all hospitalized patients diagnosed with AF and/or atrial flutter at a private tertiary institution in Salvador, Bahia, from May 23, 2011 (date of approval of dabigatran in Brazil) to June 30, 2016. Patients were screened from ICDs I48 and R00, and only those with documented AF or atrial flutter were recruited.

Study design

Retrospective observational study based on electronic chart review, with annual cross-sections for five consecutive years (trends study).

Inclusion and exclusion criteria

Inclusion criteria were: age ≥ 18 years, AF diagnosis and/or atrial flutter confirmed by ECG and/or Holter. Patients without electronic prescription of discharge were excluded, as this was the source of the data regarding the use of anticoagulant. On readmissions, the most recent admission was chosen for analysis.

Data collected and definitions

Demographic and anthropometric data were collected, in addition to the cardiovascular risk factors traditionally related to AF (systemic arterial hypertension [SAH], diabetes, valve disease, myocardial infarction, heart failure, history of bleeding, medications). The risk scores for stroke and bleeding were CHA_2DS_2VASc and HASBLED, validated in international studies.[12-14] AF was classified according to the II Brazilian Guidelines for Atrial Fibrillation of the Brazilian Society of Cardiology.[15] When there was insufficient information for classification, AF was considered of indefinite duration. Prior AF was defined as the identification of episodes of this arrhythmia prior to the reference admission during review of medical records.

Echocardiographic data were collected from the most recent test, respecting the period of up to 1 year before admission. Valvular heart disease was defined as the presence of any moderate or severe mitral or aortic lesion. The presence of a valve prosthesis was defined by echocardiogram or clinical history.

Electronic prescription of discharge was used to collect information on anticoagulants, antiplatelets and their doses, and other drugs with potential for drug interaction.

All information regarding hemorrhagic events was collected, but only major bleeding — intracranial hemorrhage, need for blood products or corrective surgical treatment — were considered for analysis.

The following were considered absolute contraindications for oral anticoagulants: active bleeding, severe hemorrhagic diathesis, thrombocytopenia < 50,000, invasive surgery or procedure to be done, major trauma, hemorrhagic stroke, intracranial or spinal tumor, spinal anesthesia, uncontrolled SAH. Relative contraindications included: end-stage neoplasia, active peptic ulcer, advanced dementia (without a caregiver), alcoholism and frequent falls (more than three per year). Patients with zero CHA_2DS_2-VASc were not considered candidates for anticoagulation.

Inappropriate use of DOAC[16] was defined as follows: prescriptions containing drugs with strong drug interaction potential; dose inconsistent with the dosage recommended by the manufacturer, considering patient's age, weight and renal function; presence of absolute contraindications (mechanical cardiac valve prosthesis or moderate to severe mitral stenosis).

Statistical analysis

Continuous variables were summarized by mean and standard deviation or median and interquartile distance, as indicated by the frequency distribution. Comparisons of quantitative variables between 2 groups were done using Student's t test for independent samples and Mann-Whitney. Categorical variables were summarized using simple and relative frequencies, compared between groups using the chi-square test. For analysis of correlation between the HASBLED and CHA_2DS_2-VASc scores, the Spearman's technique was used.

To identify predictors of anticoagulation and anticoagulant type, we used binary logistic regression. Firstly, we made a selection of variables using univariate logistic regression. The variables associated with anticoagulation and use of DOAC with p value < 0.05 in

the univariate analyses were later included in multivariate logistic regression models using the backward stepwise method. The variables that reached $p < 0.05$ in the final analyses were considered statistically significant.

All analyses were conducted in the Statistical Package for the Social Sciences (SPSS) version 23.

Ethical issues of research

This study was approved in a plenary session at the Ethics Research Committee Prof. Celso Figuerôa, Hospital Santa Izabel on 11-24-2014, according to Resolutions 466/12 and 251/97, protocol number 917.116.

Results

From 2011 to 2016, there were 464 admissions with diagnosis of AF discharge. Of these, 87 patients were excluded: 28 for not presenting AF (coding error); 26 hospital readmissions; 20 deaths during admission; 13 for not having electronic prescription of discharge. The final population analyzed consisted of 377 patients.

Demographic and clinical data

Patients were separated into two groups: patients with and without anticoagulants. The group on anticoagulants was subsequently divided into patients using VKA or DOAC (Table 1). The mean age of the patients was 70 ± 15 years, and 52% were male with mean body mass index (BMI) of 27 ± 6. Regarding the type of AF, 42% had paroxysmal AF, 12% had persistent AF, 27% had permanent AF, 19% with indefinite duration; 10% of the patients had atrial flutter. There was a high prevalence of comorbidities, with 71% of hypertensive patients, 23% of diabetics, 26% with a history of heart failure, 7.4% with a history of myocardial infarction and 18% had ischemic stroke. Of the study population, 25% had moderate or severe valvulopathy, 3.9% had biological valve prosthesis and 1.8% had mechanical valve prosthesis (Table 1).

Mean CHA_2DS_2-VASc risk score was 3.4 ± 2.0 and the HASBLED score was 1.2 ± 1.0, with 11.2% of these having HASBLED 3 and 79.8% having CHA_2DS_2-VASc ≥ 2 (Chart 1).

Use of anticoagulant therapy

Considering the total population over a 5-year period, 75% of the patients were discharged on anticoagulants (20% received VKA and 55% received DOACs), 15% were on antiplatelets alone and 10% were not on antithrombotic therapy.

Table 1 - Demographic and clinical characteristics of 377 adult patients admitted with atrial fibrillation at a tertiary hospital in Salvador, Bahia, Brazil

Variable	Without anticoagulant (n = 93)	With anticoagulant (n = 284)	p*	VKA (n = 76)	DOACs (n = 208)	p†
Age (years)	73 ± 18	69 ± 13	0.059	70 ± 13	69 ± 14	0.493
Male	42 (45.2)	155 (54.6)	0.115	41 (53.9)	114 (54.8)	0.897
Weight (kg), n = 370	71.8 ± 15.5	78.4 ± 20.6	0.002	75.8 ± 21.4	79.3 ± 20.3	0.207
Height (meters), n = 370	1.64 ± 0.11	1.66 ± 0.10	0.036	1.65 ± 0.10	1.67 ± 0.10	0.114
SAH	59 (63.4)	210 (73.4)	0.052	59 (77.6)	151 (72.6)	0.392
DM	27 (29)	61 (21.5)	0.135	18 (23.7)	43 (20.7)	0.584
CHF	23 (24.7)	77 (72)	0.652	30 (39.5)	47 (22.6)	0.005
AMI in the past year	10 (10.8)	18 (6.3)	0.159	5 (6.6)	13 (6.3)	0.920
TCA in the past year	4 (4.3)	4 (1.4)	0.093	1 (1.3)	3 (1.4)	0.936
History of TIA/ischemic stroke	25 (26.9)	42 (14.8)	0.008	10 (13.2)	32 (15.4)	0.640
History of hemorrhagic stroke	0 (0)	2 (0.7)	0.417	1 (1.3)	1 (0.5)	0.456
History of AF n=357	42 (50)	191 (70)	0.001	49 (70)	142 (69.9)	0.994

Cont. Table 1 - Demographic and clinical characteristics of 377 adult patients admitted with atrial fibrillation at a tertiary hospital in Salvador, Bahia, Brazil

Variable	Without anticoagulant (n = 93)	With anticoagulant (n = 284)	p*	VKA (n = 76)	DOACs (n = 208)	p†
AF classification n = 339						
Paroxysmal	35 (41.7)	106 (41.6)		20 (27.8)	86 (47)	
Persistent	5 (6)	35 (13.7)	0.185	13 (18.1)	22 (12)	0.002
Permanent	28 (33.3)	64 (25.1)		28 (38.9)	36 (19.7)	
Undetermined	16 (19)	50 (19.6)		11 (15.3)	39 (21.3)	
CHA_2DS_2-VASc	4 (0 to 8)	3 (0 to 9)	0.010	3 (0 to 8)	3 (0 to 9)	0.199
HASBLED	2 (0 to 4)	1 (0 to 4)	< 0.001	1 (0 to 4)	1 (0 to 4)	0.089
Recent ischemic stroke/TIA	4 (4.3)	21 (7.4)	0.298	6 (7.9)	15 (7.2)	0.846
Recent hemorrhagic stroke	2 (2.2)	0 (0)	0.013	0	0	
Biological prosthesis	2 (2.2)	13 (4.6)	0.299	9 (11.8)	4 (1.9)	< 0.001
Metallic prosthesis	0 (0)	7 (2.5)	0.126	7 (9.2)	0 (0)	< 0.001
Valvular heart disease	23 (24.7)	70 (24.6)	0.987	28 (36.8)	42 (20.2)	0.004
Hemorrhage	9 (9.7)	12 (4.2)	0.047	5 (6.6)	7 (3.4)	0.233
Major bleeding	4 (4.3)	5 (1.8)	0.164	2 (2.6)	3 (1.4)	0.500
Interaction with DOAC	60 (64.5)	225 (79.2)	0.004	67 (88.2)	158 (76)	0.025
Creat. (mg/dl), n = 350	1.1 ± 0.9	1.1 ± 0.7	0.986	1.3 ± 1.3	1 ± 0.3	0.031
LA (mm), n = 349	42.6 ± 7.4	43.5 ± 6.6	0.283	47.3 ± 6.14	42.2 ± 6.3	< 0.001
LVEF (%), n = 349	62.1 ± 12.9	59.8 ± 15	0.176	55.1 ± 16	61.5 ± 14.5	0.002
Arrhythmia reversal						
Electric	10 (10.8)	82 (28.9)		19 (25)	63 (30.3)	
Not Executed	41 (44.1)	100 (35.2)		40 (52.6)	60 (28.8)	
Chemical	30 (32.3)	41 (14.4)	< 0.001	6 (7.9)	35 (16.8)	0.005
Spontaneous	10 (10.8)	41 (14.4)		7 (9.2)	34 (16.3)	
Ablation	02 (2.2)	20 (7)		4 (5.3)	16 (7.7)	
Antiplatelet agents	56 (60.2)	3 (15)	< 0.001	13 (17.1)	30 (14.4)	0.577

For continuous variables n (± standard deviation) and for continuous variables n (%); in case of missing data, total n was placed next to the variable; p refers to comparison between groups with and without anticoagulants; p† refers to comparison between the groups with VKA and DOAC; TCA: transcutaneous coronary angioplasty; TIA: transient ischemic attack; Creat.: serum creatinine; LA: left atrium; LVEF: left ventricular ejection fraction.*

From 2011 to 2015, there was a progressive increase in the use of anticoagulants from 64% to 87%, largely at the expense of an increase in the use of DOACs, which rose from 29% to 70% (a relative increase of 144.8%), and reduced use of VKA and antiplatelets alone in the same period. Average annual incorporation of DOACs was 10.4% (Chart 2). About 25% of the patients were on antiplatelets alone or combined with anticoagulants.

The prevalence of prescription of oral anticoagulants, antiplatelets and no antithrombotic drugs stratified by risk category according to the CHA_2DS_2-VASc and HASBLED scores are shown in charts 3 and 4. There

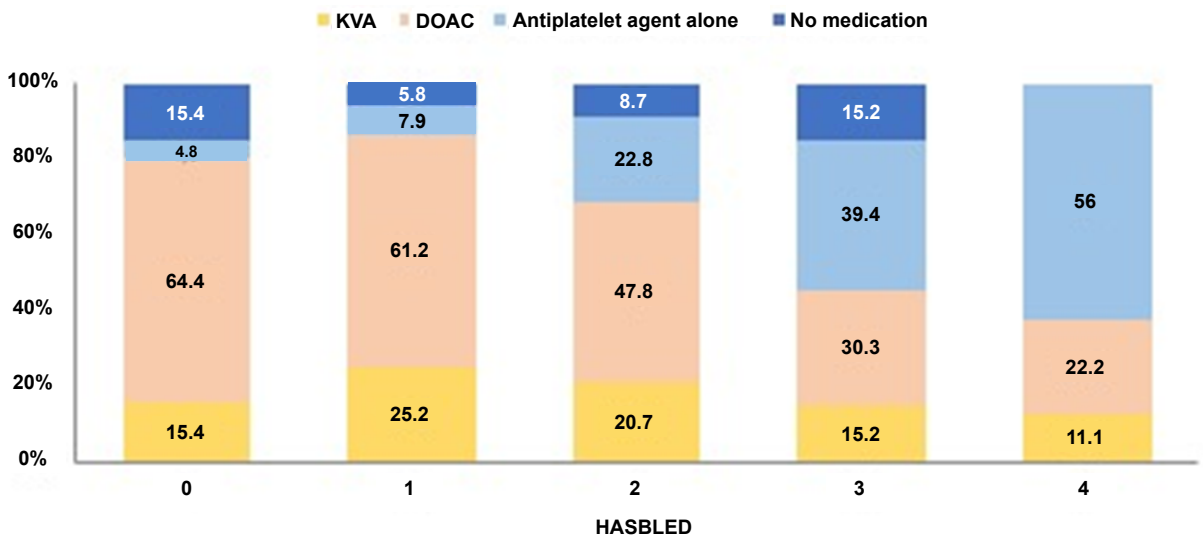

Chart 1 - Frequency of risk scores, CHA_2DS_2VASc and HASBLED in 377 patients admitted with atrial fibrillation at a tertiary hospital in Salvador, Bahia, Brazil.

was a strong correlation between the HASBLED and CHA_2DS_2-VASc scores (Spearman's r 0.706).

Predictors of use and type of anticoagulants

Most patients who had anticoagulants prescribed on hospital discharge had a history of previous episodes of AF (p = 0.001) and TIA/stroke (p = 0.008), were older (p = 0.056), had lower mean HASBLED (p < 0.001), higher mean weight (p = 0.002) and higher prevalence of SAH (p = 0.052) than non-anticoagulated patients. In the multivariate logistic regression analysis, the following remained as independent predictors of anticoagulation: previous episodes of AF, SAH and HASBLED (p < 0.001) (Table 2).

To identify variables associated with the prescription of a given class of anticoagulants, we built a multiple logistic regression model using DOAC as a dependent variable and paroxysmal AF, CHF, serum creatinine, left ventricular ejection fraction, LA diameter, biological valve prosthesis, moderate valvular heart disease and electrical or chemical CV as independent variables. The variables serum creatinine (p < 0.002), LA diameter (p = 0.003) and biological valve prosthesis (p = 0.007) were inversely associated with the prescription of a DOAC, that is, were predictors of VKA prescription (Table 3).

Appropriateness of the use of anticoagulants

Of the 93 patients with AF whose discharge prescriptions did not contain anticoagulants, 43 had legitimate reasons for doing so: 14 with zero CHA_2DS_2VASc, 16 with absolute contraindications and 13 with relative contraindications. In the other 50 patients (54%), no reasons were found for the non-prescription of anticoagulants (45 patients) or the reasons on record were inconsistent with the literature (5 patients) — "requested by the attending physician"; "already had an indication of using anticoagulants and the attending physician did not prescribe"; "has bronchiectasis and history of bleeding"; "due to the risks of anticoagulation"; "will have pacemaker implanted" (Table 4).

Discussion

This is the first Brazilian study to demonstrate an increase in the use of oral anticoagulants in patients with AF as a result of progressive incorporation of DOACs into clinical practice. Despite the high thromboembolic risk of the study population, one-quarter of patients with AF were discharged without anticoagulant prescription, confirming findings from contemporary international registries. However, over the study period

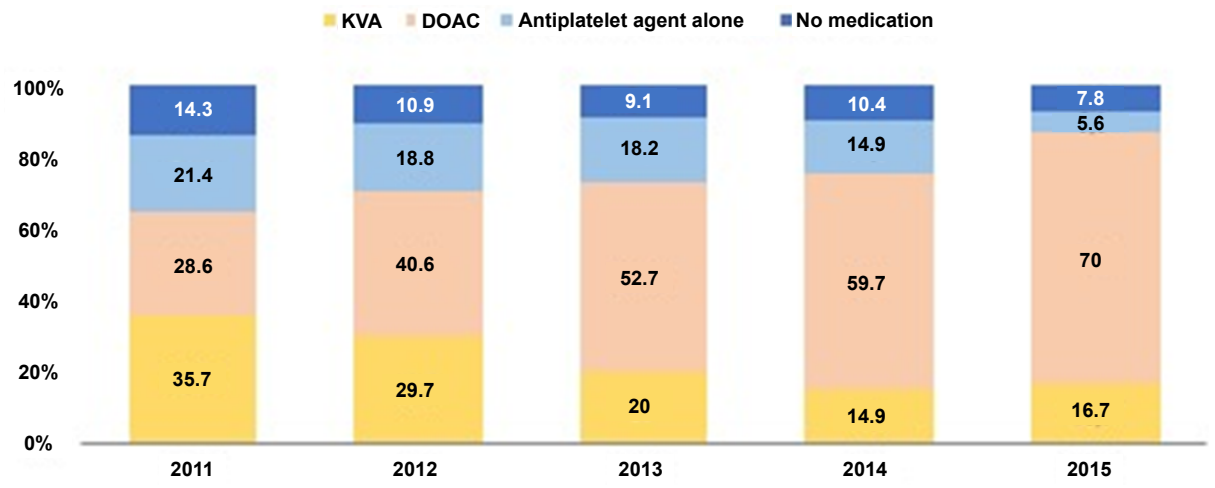

Chart 2 - Temporal evolution of the use of anticoagulants in 318 admitted adults with atrial fibrillation at a tertiary hospital in Salvador, Bahia, Brazil.
**Patients from the year 2016 were excluded from this analysis, as only data from admissions taking place in the 6 first months of that year were collected.*

(2011–2016), there was a significant increase in the rate of anticoagulant use, which is largely due to the rapid incorporation of DOACs into clinical practice, which progressively replaced VKAs and antiplatelet agents. We did not find any other Brazilian study showing the evolution of anticoagulation rates in patients with AF after the introduction of DOACs on the market. A cross-sectional study involving 407 patients with AF treated at the emergence service of a tertiary center in Porto Alegre evaluated the rate of anticoagulant use. Only 34% of these patients received anticoagulation, and even in patients with CHA_2DS_2-VASc ≥ 2, only 40% had anticoagulants prescribed.[17]

ANVISA approved the first DOAC in Brazil — dabigatran in 2011 — then two new direct inhibitors of factor Xa: rivaroxaban and apixaban. This study documented a rapid incorporation of these new anticoagulants (annual average of 10.4%), rising from 28% in 2011 to 70% in 2016. This was the determining factor in the 34.8% increase in the overall use of anticoagulants in our population of patients with AF.

Most contemporary international registries show the same trend. The GARFIELD AF registry (The Global Anticoagulant Registry in the FIELD-Atrial Fibrillation), which started in 2011, with completed recruitment in follow-up phase, also showed a significant increase in the use of DOACs (4.2% to 37%) associated with to an absolute increase of 13.7% (57.4% to 71.1%) in the frequency of anticoagulant use. Likewise, the GLORIA-AF registry documented a marked increase in the overall rate of anticoagulant use (64% to 80%) between phase 1 and 2 of the study, concomitantly with the introduction and incorporation of DOACs into clinical practice, now used by 48% of patients, compared to 32% of VKA users. Both GLORIA AF and GARFIELD AF registries observed a marked decrease in the use of antiplatelet agents.[18,19]

These changes in the pattern of anticoagulant use seem to be occurring in almost all regions of the world, according to GLORIA AF data, except for Asia, where more than 40% of patients with AF do not receive anticoagulants yet. Also in this registry, Latin America presented high rates of oral anticoagulants and DOACs, of 85% and 56%, respectively. It seems clear that the greatest factor for the improvement in the global anticoagulation rates in AF observed in international registries and in this study over the past 5 years was the emergence of DOACs. These drugs overcame many difficulties and limitations associated with the practical use of traditional anticoagulants, which strongly impacted the decision on its use.

In addition to the DOACs, the latest therapeutic guidelines for AF may have contributed to an increase in

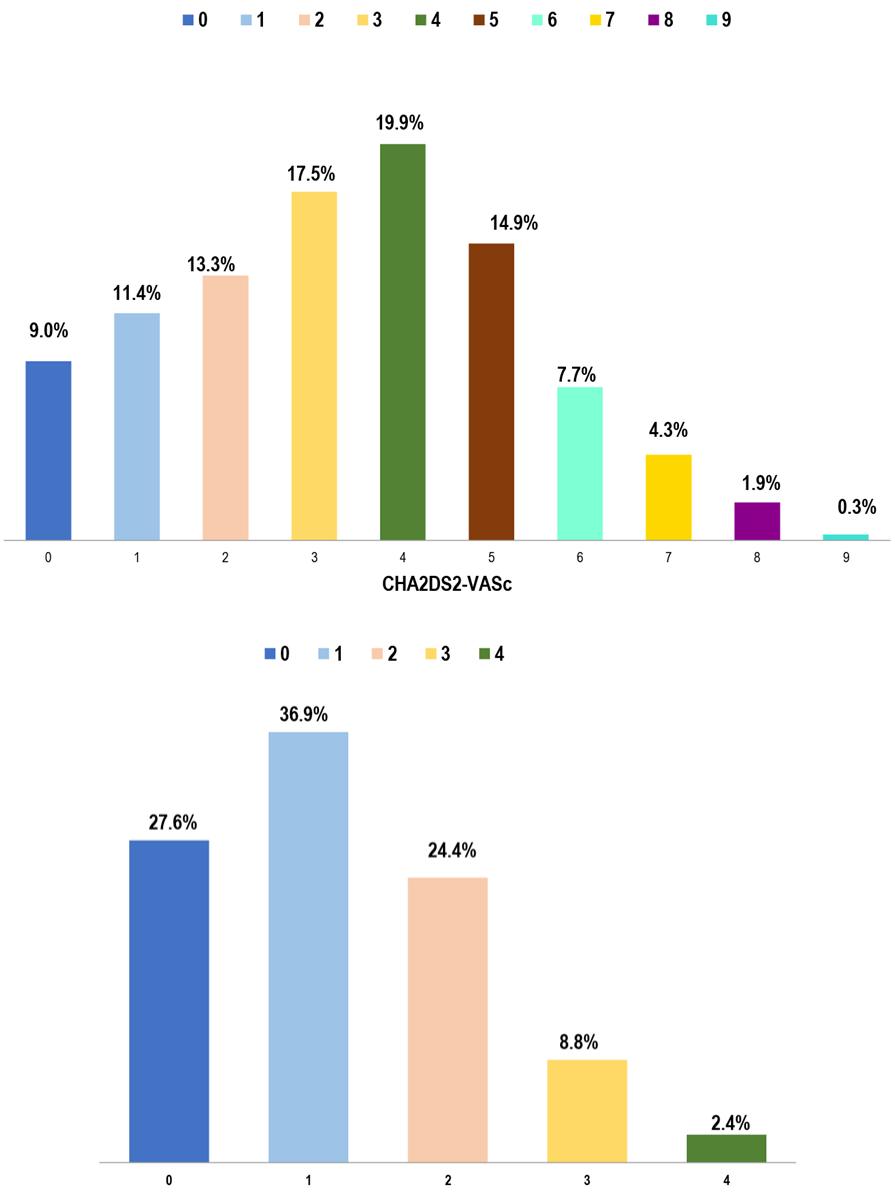

Chart 3 - Frequency of use of anticoagulants regarding the HASBLED score in adult patients admitted with atrial fibrillation at a tertiary hospital in Salvador, Bahia, Brazil.

the number of AF patients receiving oral anticoagulants, since they no longer consider antiplatelet agents as acceptable alternatives to anticoagulants in patients with lower thromboembolic risk.[16,20]

Another important finding of our study was the lack of linearity between thromboembolic risk and the percentage of anticoagulant use. The frequency of anticoagulant prescription increased with the thromboembolic risk score up to CHA_2DS_2-VASc 3. However, in scores > 3, there was a progressive decrease in the use of anticoagulants. Similar findings were observed in other cohort studies, where anticoagulation rates peaked at CHA_2DS_2-VASc 3-4 scores, followed, unlike our study, with a plateau without an observable decline.[18,19] Thus, despite the known increase in the annual risk of stroke at each point of the CHA_2DS_2-VASc

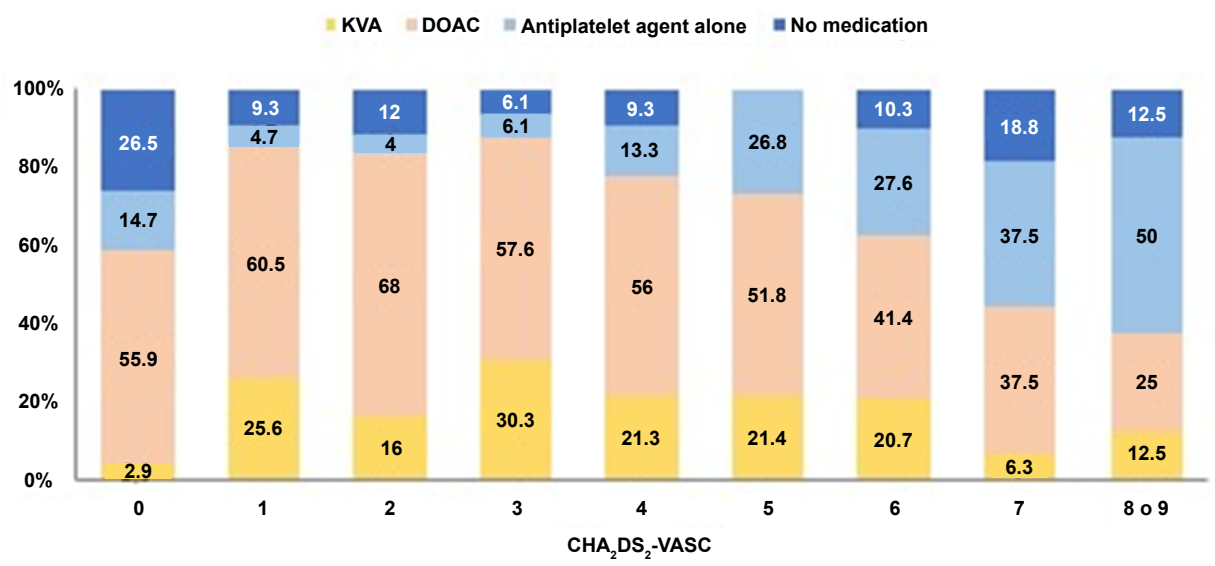

Chart 4 - Frequency of use of anticoagulants regarding the CHA_2DS_2-VASC score in adult patients admitted with atrial fibrillation at a tertiary hospital in Salvador, Bahia, Brazil.

Table 2 - Multivariate logistic regression model for predictors of anticoagulant use in patients admitted with atrial fibrillation at a tertiary hospital in Salvador, Bahia, Brazil

Variable	OR (95% CI)	p
History of AF	3.13 (1.80 to 5.44)	< 0.001
SAH	3.05 (1.66 to 5.62)	< 0.001
HASBLED	0.50 (0.38 to 0.66)	< 0.001

Table 3 - Multivariate logistic regression model for predictors of DOAC use in adult patients admitted with atrial fibrillation at a tertiary hospital

Variable	OR (95% CI)	p
Serum creatinine (mg/dL)	0.18 (0.06 to 0.52)	0.002
LA diameter (mm)	0.92 (0.87 to 0.97)	0.003
Biological valve prosthesis	0.12 (0.03 to 0.57)	0.007
CV (electrical or chemical)	2.02 (0.97 to 4.22)	0.060

Electrical or chemical CV; CV: electrical cardioversion; LA: left atrium.

Table 4 - Frequency of inappropriate use of DOACs in 208 patients with atrial fibrillation, with indication for use of anticoagulants at a private tertiary hospital in Salvador, Bahia, Brazil

DOAC used	DOAC misuse frequency n (%)	Contraindication for drug interaction n (%)	Improper dose reduction n (%)	Improper full dose n (%)
Dabigatran (n = 60)	33 (55)	2 (3.3)	29 (67)	2/17 (11.8)
Rivaroxaban (n = 119)	22 (18.5)	1 (0.8)	18 (48.6)	3/82 (3.6)
Apixaban (n = 29)	8 (27.6)	2 (6.9)	6 (46.1)	0/16 (0)

score, 20–50% of high-risk patients remain unprotected without anticoagulants. Several reasons may have contributed to these findings. Many physicians may not use any tools as structured as CHA_2DS_2-VASc for evaluation of thromboembolic risk in AF, using only their imprecise clinical impression[12] and failing to capture the actual risk of some patients. Besides, patients with higher CHA_2DS_2-VASc have a higher prevalence of comorbidities associated with both higher risk of stroke and bleeding risk. Exploring this assumption, we demonstrated a strong correlation between the CHA_2DS_2-VASc and HASBLED scores (Spearman's r 0.706). Physicians may be fearful of prescribing anticoagulants for patients with higher CHA_2DS_2-VASc if they also present higher risk of bleeding, translated by higher HASBLED. Additionally, since many of these patients are also older and have higher prevalence of atherosclerotic disease, a significant percentage already use antiplatelet agents, which adds to the risk of bleeding and reluctance to prescribe anticoagulants.

Predictors of use of anticoagulants and DOACs

In our study, history of AF episodes and the presence of SAH individually increased by three-fold the chances of patients receiving anticoagulant prescription at discharge. On the other hand, at every 1 point where HASBLED increased, the chance of anticoagulation was reduced by 50%. These are logical and intuitive predictors of anticoagulation, since the first two increase the perception of thromboembolic risk and the last one increases the risk of bleeding. In the NCDR PINNACLE registry, there were more hypertensives among patients taking anticoagulants than among those who did not use anticoagulants (80% versus 74%; $p < 0.001$).[21]

In an analysis of participants from the 2nd and 5th cohorts of the GARFIELD-AF study in the UK, the two main reasons for the physician to avoid using anticoagulant in patients with CHA_2DS_2-VASc ≥ 2 were risk of fall and hemorrhagic event, respectively.[22]

Regarding the predictors of use of DOACs, we observed that for each 1.0 mg/dl increase in serum creatinine, there was 82% less chance of the patient being discharged on DOAC. For 1 year, Luger et al. analyzed AF patients who had stroke or TIA and concluded that the decision on the use of VKA or DOAC was mainly determined by the patient's renal function and absence of previous anticoagulant therapy, both reducing the chance of using DOAC.[23]

In addition to renal function, the presence of a biological valve prosthesis also significantly reduced the chance of DOAC prescription. Although not all studies comparing DOACs with VKA excluded patients with biological prostheses, which do not represent contraindication for the use of DOACs, the unfavorable experience of dabigatran in patients with mechanical prostheses[24] may cause some fear of using these anticoagulants in the context of any valve prosthesis.

Appropriateness of DOAC prescription

Our study demonstrated that in 28% of DOAC prescriptions, the doses were inadequate for the patients' clinical profile. However, as opposed to the findings of the cited studies, the most frequent dosing error was improper reduction of DOAC dose, rather than lack of adjustment. Both the lack of adjustment and improper dose reduction may compromise the efficacy and safety of anticoagulant therapy with DOACs. The randomized cluster study IMPACT-AF showed that multifaceted educational interventions were able to improve the frequency of anticoagulation and reduce the incidence of stroke.[25]

Limitations

Limitations of this paper include its retrospective design based on electronic medical records, making it subject to registration bias due to lack of information in medical records. In some cases, for example, it was not possible to assess the suitability of the DOAC dose because we did not have serum creatinine, weight or height information. Some patients were excluded because they did not have electronic prescription for discharge. However, these events were infrequent and did not compromise the results found.

Regarding the possibility of generalizing our findings to other populations, although it was conducted in a single center, the characteristics of the study population are similar to those of major international registries of AF. However, because it was conducted in a private medical center, our data cannot be extrapolated to patients with AF from the public healthcare system.

Conclusions

This study demonstrated that, following the approval of DOACs for clinical use in Brazil in 2011, these anticoagulants were rapidly incorporated into clinical

practice, becoming the therapy of choice for patients with AF and contributing decisively to the increase of anticoagulation rates in this group of patients. Despite this important achievement, 13% of eligible patients remained without anticoagulation. Additionally, besides the long-standing historical difficulty of keeping patients on VKA in the narrow therapeutic range, at least 25% of patients using DOACs are exposed to inappropriate doses, compromising its efficacy and safety.

The data and reflections described in this study should serve to guide the leaders of our healthcare system and medical societies towards building educational and awareness-raising strategies for health professionals and patients regarding the importance of correct prescription and adherence to anticoagulant therapy in AF.

Author contributions

Conception and design of the research: Geraldes MFA, Darze ES, Rocha PN. Acquisition of data: Geraldes MFA. Analysis and interpretation of the data: Geraldes MFA, Darze ES, Rocha PN. Statistical analysis: Geraldes MFA, Darze ES, Rocha PN. Writing of the manuscript: Geraldes MFA, Darze ES, Rocha PN. Critical revision of the manuscript for intellectual content: Geraldes MFA, Darze ES, Rocha PN.

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 Maria de Fátima de Araújo Geraldes, from *Universidade Federal da Bahia*.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Prof. Celso Figuerôa, *Hospital Santa Izabel* under the protocol number 917.116. 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. Benjamin EJ, Wolf PA, Agostino RBD, Silbershatz H, Kannel WB, Levy D. Clinical Investigation and Reports Impact of Atrial Fibrillation on the Risk of Death The Framingham Heart Study. Circulation. 1998;98(10):946–53.
2. Krahn AD, Manfreda J, Tate RB, Mathewson FAL, Cuddy TE. The natural history of atrial fibrillation: Incidence, risk factors, and prognosis in the manitoba follow-up study. Am J Med.1995;98(5):476–84.
3. 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.
4. Vidaillet H, Granada JF, Chyou P o-H, Maassen K, Ortiz M, Pulido JN, et al. A population-based study of mortality among patients with atrial fibrillation or flutter. Am J Med [Internet]. 2002;113(5):365–70.
5. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med. 2002;113(5):359–64.
6. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby J V., et al. Prevalence of Diagnosed Atrial Fibrillation in Adults. JAMA. 2001;285(18):2370-75.
7. 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.
8. Fornari LS, Calderaro D, Nassar IB, Lauretti C, Nakamura L, Bagnatori R, et al. Misuse of antithrombotic therapy in atrial fibrillation patients: Frequent, pervasive and persistent. J Thromb Thrombolysis. 2007 Feb;8:65-71.
9. Dewilde S, Carey IM, Emmas C, Richards N. Trends in the prevalence of diagnosed atrial fibrillation, its treatment with anticoagulation and predictors of such treatment in UK primary care. Heart. 2006;92(8):1064–70.
10. Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: A systematic review. Circ Cardiovasc Qual Outcomes. 2008;1(2):84–91.
11. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. n engl j medJLH); R Perth Hospi-tal N Engl J Med 2011;36510365(10):883–91.
12. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. 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.
13. Lip GYH, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: The HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drug. J Am Coll Cardiol. 2011;57(2):173–80.
14. Yao X, Gersh BJ, Sangaralingham LR, Kent DM, Shah ND, Abraham NS, et al. Comparison of the CHA2DS2-VASc, CHADS2, HAS-BLED, ORBIT, and ATRIA Risk Scores in Predicting Non–Vitamin K Antagonist Oral Anticoagulants-Associated Bleeding in Patients With Atrial Fibrillation. Am J Cardiol 2017;120(9):1549–56.

15. Magalhães LP, Figueiredo MJO, Cintra FD, Saad EB, Kuniyoshi RR, Teixeira RA, et al. II Diretrizes Brasileiras de Fibrilação Atrial. Arq Bras Cardiol. 2016;106(4):1-22.

16. Steffel J, Verhamme P, Potpara T, Albaladejo P, Antz M, Desteghe et al. ESC Scientific Document Group; The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. European Heart Journal.2018; 39(16):1330–1393.

17. Almeida ED, Guimarães RB, Stephan LS, Medeiros AK, Foltz K, Santanna RT, et al. Clinical Differences between Subtypes of Atrial Fibrillation and Flutter: Cross-Sectional Registry of 407 Patients. Arq Bras Cardiol. 2015;105(1) 3–10.

18. Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, et al. The Changing Landscape for Stroke? Prevention in AF: Findings From the GLORIA-AF Registry Phase 2. J Am Coll Cardiol. 2017;69(7):777–85.

19. Ten Cate V, ten Cate H, Verheugt FWA. The global anticoagulant registry in the FIELD-atrial fibrillation (GARFIELD-AF): Exploring the changes in anticoagulant practice in patients with non-valvular atrial fibrillation in the Netherlands. Netherlands Hear J. 2016;24(10):574–80.

20. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease. J Am Coll Cardiol. 2017; 70(2):252-289.

21. Hsu JC, Maddox TM, Kennedy KF, Katz DF, Marzec LN, Lubitz SA, Gehi AK, Turakhia MP, Marcus GM. Oral Anticoagulant Therapy Prescription in Patients With Atrial Fibrillation Across the Spectrum of Stroke RiskInsights From the NCDR PINNACLE Registry. JAMA Cardiol. 2016;1(1):55–62.

22. Apenteng PN, Gao H, Hobbs FR, Fitzmaurice DA, UK GARFIELD-AF Investigators and GARFIELD-AF Steering Committee. Temporal trends in antithrombotic treatment of real-world UK patients with newly diagnosed atrial fibrillation: findings from the GARFIELD-AF registry. BMJ Open 2018;8(1):e 018905.

23. Luger S, Hohmann C, Kraft P, Halmer R, Gunreben I, Neumann-Haefelin T, et al. Prescription Frequency and Predictors for the Use of Novel Direct Oral Anticoagulants for Secondary Stroke Prevention in the First Year after Their Marketing in Europe – A Multicentric Evaluation. Int J Stroke. 2014;9(5):569–75.

24. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, et al. Dabigatran versus Warfarin in Patients with Mechanical Heart Valves. N Engl J Med. 2013;369(13):1206–14.

25. Rao MP, Ciobanu AO, Lopes RD, Fox KA, Xian Y, Pokorney SD, et al. A clustered randomized trial to IMProve treatment with AntiCoagulanTs in patients with Atrial Fibrillation (IMPACT-AF): Design and rationale. Am Heart J. 2016 Jun;176:107–13.

International Journal of Cardiovascular Sciences. 2020;33(1):79-86

ORIGINAL ARTICLE

Cardiac Autonomic Modulation of Healthy Individuals and Patients with Chronic Obstructive Pulmonary Disease During Spontaneous and Controlled Breathing

Mario Augusto Paschoal,[1] Livea Gianfrancesco,[1] Luisa Torres Camargo,[1] Náira Bueno Seixas,[1] Ana Beatriz Paschoal[2]

Pontifícia Universidade Católica de Campinas,[1] São Paulo, SP - Brazil
Faculdade de Ciências Médicas da Santa Casa de São Paulo,[2] SP - Brazil

Abstract

Background: Lung diseases and different forms of breathing may interfere with cardiac autonomic modulation (CAM).

Objective: To compare CAM in individuals with chronic obstructive pulmonary disease (COPD) with healthy individuals during spontaneous breathing (SB) and controlled breathing (CB).

Methods: Cross-sectional study involving 30 individuals selected by convenience, divided into COPD group (n = 19) and control group (CG; n = 12). All participants were submitted to heart beat recordings during five minutes at rest (SB) and another five minutes during CB performed at six cycles/min. CAM was made by assessment of the heart rate variability (HRV) through time domain (TD) and frequency domain (FD). Comparisons between groups were performed by Mann Whitney test, and significance level was set at $p < 0.05$.

Results: During SB, HRV TD and FD indices were higher in the controls than in the COPD group, respectively – RR intervals (53.2 ms versus 36.6 ms), RMSSD (42.1 ms versus 26.6 ms) ($p < 0.05$), total power (28322.8 ms²/Hz versus 2011.6 ms²/Hz), and high-frequency band (800.5 ms² versus 330.7 ms²). During CB, the CG also showed higher values for the TD parameters pNN50 (11.7% versus 5.1%), RMSSD (48.3 ms versus 26.7 ms), and SD of RRi (64.9 ms versus 44.7 ms), as well as for the low-frequency component of FD analysis (2848.6 ms² versus 1197.9 ms²).

Conclusion: COPD patients have different CAM when compared with healthy individuals during spontaneous (SB) and controlled breathing (CB). (Int J Cardiovasc Sci. 2020;33(1):79-86)

Keywords: Autonomic Nervous System; Heart Rate; Respiratory Rate.

Introduction

Cardiac autonomic modulation (CAM) is essential for the preservation of heart function according to metabolic needs, contributing to the maintenance of internal stable conditions.[1,2] Time variation between heart beats is considered normal and is related to greater or lesser activation of sympathetic and parasympathetic systems in response to central and peripheral stimuli.[3-5]

Among the events that may interfere with the physiological oscillations of the heart rate (HR), the most prominent are those originating from respiration.[6,7] Therefore, any disease that may impair breathing in some way, such as chronic obstructive pulmonary disease (COPD), tend to interfere with cardiovascular mechanisms[8-10] by affecting the RR intervals (RRi) of the cardiac cycle and, consequently, the CAM.[5,8,11,12]

Changes in the CAM can be detected and quantified by analysis of the heart rate variability (HRV). In studies on spontaneous breathing in patients with COPD, however, HRV analysis has yielded conflicting results.[11-13] Part of this controversy may be due to the use of certain

Mailing Address: Mario Paschoal
Av. John Boyd Dunlop, s/n. Postal Code: 13060-904, Campus II, Campinas, São Paulo, SP - Brazil.
E-mail: mapascka@gmail.com

DOI: 10.5935/2359-4802.20190072

Manuscript received on August 21, 2018; reviewed on January 29,2019; accepted on March 08,2019.

drugs that cannot be withdrawn from patients during data collection, and the inclusion of patients with different disease severity and, consequently, different cardiovascular conditions.

Other methods to assess the CAM consist of standardized autonomic functional tests, including controlled breathing (CB) techniques, which promote the increase of respiratory sinus arrhythmia frequently employed as an index of cardiac parasympathetic control. During CB, the oscillatory components present in the high frequency band (0.15 to 0.4 Hz) of HRV, related to cardiac parasympathetic activity, are generally potentiated[1,14-16] and sensitive changes in the RRi are documented.

Considering these assumptions, the objective of the present study was to evaluate and compare the CAM in COPD patients with CAM in healthy people, subjected to spontaneous breathing (SB) and CB trials, to identify the presence of cardiac dysautonomia in COPD and how much the CB may interfere with cardiac modulation of these patients.

Method

Cross-sectional observational study approved by the Ethics Committee in Research Involving Human Beings of the Pontifical Catholic University of Campinas (PUC Campinas – approval number 393.938), São Paulo state, Brazil.

Selection of Volunteers

From a total of 40 COPD patients preselected from the outpatient physiotherapy clinic, 18 met the inclusion criteria. The sample calculation (20% error margin and 90% confidence level) indicated a minimum of 13 COPD patients. All of them were clinically stable and had mild or moderate COPD, with clinical diagnosis confirmed by specialists. Also, they were ex-smokers (who had quit smoking at least 6 months before intervention), non-alcoholic, did not participate in any physical activity program, and had a body mass index (BMI) between 20 and 35 kg/m².

In addition, a further 12 healthy individuals (control group - CG) were selected, who met the following inclusion criteria: age group similar to that of the COPD, BMI between 20 and 35 kg/m², had not performed any regular physical activity in the last six months and did not use any medication.

The study was conducted at the outpatient physiotherapy clinic of PUC Campinas and all participants signed the consent form developed in accordance with Resolution 466/12 of the National Health Council.

Anthropometric and Clinical Assessment

The clinical assessment consisted of clinical history, measurement of heart rate (HR) and blood pressure (BP), cardiac and pulmonary auscultation, and measurement of peripheral oxygen saturation (SpO_2) by a pulse oximeter (Nonin®, USA). Anthropometric evaluation consisted of the measurement of weight and height using the Filizola® scale (São Paulo, Brazil), for BMI calculation.

Heart Rate Measurement in SB and CB

Before heart rate measurement in SB or CB conditions, we confirmed that each volunteer had followed the protocol instructions to refrain from tea, soda, coffee or chocolate on the day of registration and that they had had a good night's sleep before the test.

Heart rate recording was performed using a Polar RS800CX® heart rate monitor (Kempele, Finland), in a room at 23°C of temperature. The volunteers were instructed to relax, and not to move or talk during the recordings.

First, participants were asked to stand on a bench, where they remained for 5min before the beginning of the recordings. During the first five minutes of heartbeat recording, the volunteers were asked to breath spontaneously, followed by another five minutes of CB.

CB was performed by 5 seconds (s) for inspiration and 5 s for expiration, at six respiratory cycles per minute, as proposed by Andresen et al.,[17] Instructions on breathing were given orally by the investigator who performed the test and used a timer to control the process. Participants were asked to perform diaphragmatic breathing, i.e., by contracting the diaphragm.

Subsequently, the RRi recordings were sent to a computer via an interface (Polar IR® interface - Kempele, Finland), and HRV was analyzed using the Polar Precision Performance® software (Kempele, Finland).

Data Analysis

Since HRV analysis was based on RRi recordings obtained under controlled conditions, there was a great concern about possible artifacts, and thus a very narrow filter (of the own software) was applied.

Therefore, it was possible to obtain HR recordings under stationary conditions, which visually confirmed by the HR tachogram analysis. The data obtained during SB and CB was analyzed in the time domain (TD) and frequency domain (FD) of HRV.

In the TD the following parameters were assessment, according to the European Society of Cardiology and the North American Society of Pacing and Electrophysiology Task Force.[18]

a) mean RRi; b) standard deviation of the mean RRi (SD RRi) - that depends on cardiac sympathetic and parasympathetic tones; c) square root of the mean of the sum of the squares of differences between adjacent normal to normal (NN) intervals (RMSSD), which expresses cardiac parasympathetic tone; d) mean HR (bpm); e) number of pairs of adjacent NN intervals differing by more than 50ms in the entire recording divided by the total number of all NN intervals (pNN50), which expresses cardiac parasympathetic tone. The results of RRi, SD RRi and RMSSD were expressed in milliseconds (ms), while pNN50 values were expressed as percentage.

In the FD, the following indexes were calculated based on the fast Fourier transform (FFT) algorithm:

a) Total power (TP) – obtained in the range of 0.0 to 0.4Hz; it is composed of the sum of the following indices: ultra-low frequency (ULF 0.0 to 0.003Hz), very low frequency (VLF – 0.003 to 0.04Hz), low frequency (LF - 0.04 to 0.15Hz) and high frequency (HF - 0.15 to 0.4Hz) power.[18] The TP expresses the total variability resulting from the fundamental oscillatory components present during recording; b) density of oscillatory components present in the LF band reflecting both sympathetic and cardiac parasympathetic activities;[1,19] c) density of oscillatory components present in the HF band, reflecting the cardiac parasympathetic activity.[1,19]

LF and HF were also calculated in normalized units (n.u.) as proposed by Pagani et al.,[20] and the European Society of Cardiology and the North American Society of Pacing and Electrophysiology Task Force,[18] and expressed as the percentage of contribution of each branch of the ANS to the autonomic modulation of the heart. Finally, the LF/HF ratio was also calculated.

Statistical Analysis

Values of the TD and FD indexes of the HRV were inserted in tables and analyzed by the GraphPad Prism 4.0® statistical program (San Diego, California, USA). The Shapiro-Wilk test was used to test normality of data distribution and showed a non-normal distribution of HRV values, which were then compared by the Mann-Whitney test was then used to compare these the clinical and anthropometric data. Also, this same test was applied to compare the HRV parameters obtained during SB and CB within group and between the groups. Due to their normal distribution, anthropometric and clinical data were compared by the paired Student's t test to analyze the differences between the means. The level of significance was set at $p < 0.05$.

Results

There was no significant difference in anthropometric data between the CG and the COPD group (Table 1). The COPD group showed significantly higher BP values and lower SpO_2 compared with controls.

During SB, in the TD parameters, statistical differences were found in SD RRi and RMSSD index, which were reduced in individuals with COPD (Table 2). In the FD, TP and HF were statistically lower in the COPD group, confirming the reduction of both parasympathetic and sympathetic cardiac tones in COPD.

During CB, the COPD group showed significantly lower values of SD RRi, RMSSD and pNN50 (Table 3). For the HRV indexes in FD, significant differences were found in PT, LF (ms^2) and HF (ms^2), which were reduced in the COPD group.

Figure 1 depicts the values of median TP during SB and CB, showing a great difference ($p < 0.0001$) between the groups, with higher values for the CG.

Table 4 shows the medications used by the patients during data collection. It is noteworthy that, at the request of the ethics committee, the researchers did not interfere with patients' usual medications during data collection.

Discussion

The main finding of the present study was that COPD patients showed changes in CAM, characterized by lower sympathetic and parasympathetic modulation during SB and CB. In addition to this, other relevant results are discussed below.

First, it is worth pointing out that all factors that could be sources of bias in the analyses were controlled during patients' selection and before and during data collection. These factors included age, body weight, functional

Table 1 - Clinical and anthropometric characteristics of the study groups

	COPD (n = 18)	Control group (n = 12)	p-values
Age (years)	62.1 ± 8.7	47.9 ± 19.0	0.34
Weight (kg)	69.4 ± 16.5	63.7 ± 10.3	0.89
Height (cm)	159.8 ± 8.9	159.9 ± 8.0	0.98
BMI (kg/m²)	26.9 ± 5.4	25.1 ± 4.0	0.77
Rest systolic BP (mmHg)	125.5 ± 17.8	110.0 ± 12.0	p = 0.007*
Rest diastolic BP (mmHg)	78,8 ± 10.2	69.1 ± 7.9	p = 0.01*
Rest HR (bpm)	72.6 ± 12.2	73.9 ± 12.1	0.87
Rest resp. freq. (rpm)	18.0 ± 2.8	15.5 ± 2,8	0.34
SpO_2	95.3 ± 1.5	97.1 ± 1.8	p = 0.006*

*COPD: chronic obstructive pulmonary disease; BMI: body mass index; HR: heart rate; bpm: beats per minute; rpm: respiration per minute; BP: blood pressure; SpO_2: peripheral oxygen saturation; * p ≤ 0.05 paired Student's t test; data in mean ± standard deviation.*

Table 2 - Parameters of time and frequency domains of the heart rate variability during spontaneous breathing (SB)

		COPD (n = 18)	CG (n = 12)	p-values
TD	RRi (ms)	889.0	902.5	0.32
	Sd RRi (ms)	36.6	53.2	0.04*
	RMSSD (ms)	26.6	42.1	0.03*
	pNN50 (%)	5.4	8.5	0.47
FD	TP (ms²/Hz)	2,011.6	28,322.8	p < 0.0001*
	LF(ms²)	472.8	1,186.3	0.81
	LF (un)	63.9	53.4	0.54
	HF (ms²)	330.7	800.5	p = 0.04*
	HF (un)	36.0	46.2	0.54
	LF/HF	2.25	2.1	0.62

*CG: control group; COPD: chronic obstructive pulmonary disease; TD: time domain; FD: frequency domain; SD: standard deviation; RRi: RR interval; RMSSD: root mean square of the standard deviation of RRi; pNN50: percentage of RRi adjacent with equal or superior values of 50ms; TP: total power; LF: low frequency; HF: high frequency; ms: milliseconds; Hz: Hertz; u.n.: normalized units. Test U of Mann-Whitney; * p ≤ 0.05.*

capacity acquired through physical training, caffeine intake, sleep hours, room temperature and circadian rhythm of HR.[19,21]

In addition, medications used by the patients may have influenced the results. However, one of the objectives of this investigation was to know how patients with COPD would react when they were submitted to SB and CB trials at the same conditions of their daily lives, which included their usual medications. Also, despite our concern about the influence of medications on HRV measurements, it is worth mentioning that there are studies that have concluded that anticholinergic or β-agonist drugs do not interfere with these measures.

The only variable related to anthropometric data that may draw attention would be age, particularly due to the high standard deviation in the CG. However, no significant difference between the groups was found according to the p-value (Table 1).

Table 3 - Parameters of time and frequency domains of the heart rate variability during controlled breathing (CB)

		COPD (n = 18)	CG (n = 12)	p-value
TD	RRi (ms)	912.2	907.6	0.72
	SD iRR (ms)	44.7	64.9	0.02*
	RMSSD (ms)	26.7	48.3	0.004*
	pNN50 (%)	5.1	11.7	0.01*
FD	TP (ms²/Hz)	2,555.3	18,447.1	p < 0.0001*
	LF (ms²)	1,197.9	2,848.6	0.05*
	LF (un)	84.1	71.9	0.31
	HF (ms²)	232.8	780.0	0.004*
	HF (un)	15.8	28.0	0.31
	LF/HF	7.4	5.9	0.27

*CG: control group; COPD: chronic obstructive pulmonary disease; TD: time domain; DF: frequency domain; SD: standard deviation; RRi: RR intervals; RMSSD: root mean square standard deviation of RRi; pNN50: percentage of adjacent RRi that are equal or superior to 50ms; TP: total power; LF: low frequency; HF: high frequency; ms: milliseconds; Hz: Hertz; u.n.= normalized units. * p ≤ 0.05, Mann–Whitney U test; data expressed in median.*

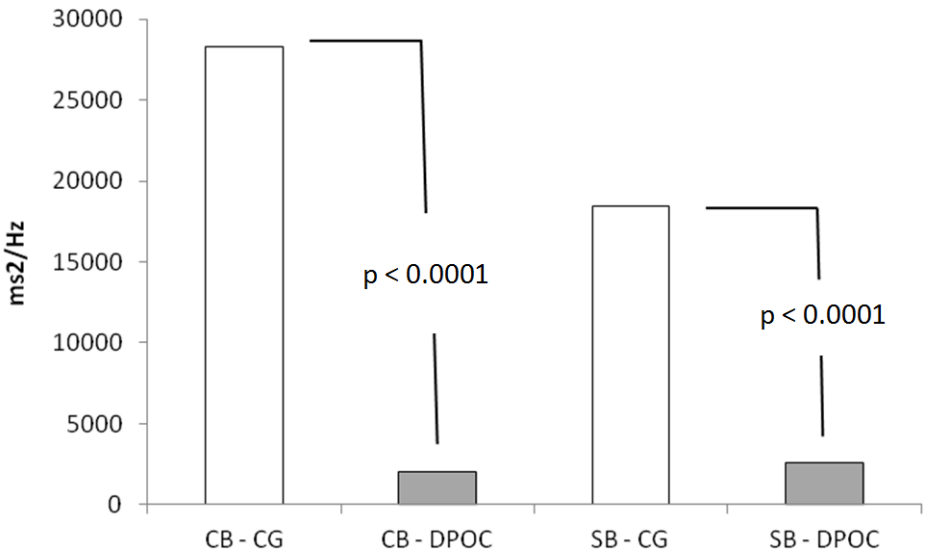

Figure 1 - Median values of total power (TP) in the Control Group (CG) and in Chronic Obstructive Pulmonary Disease (COPD) group during spontaneous breathing (SB) and controlled breathing (CB); Mann–Whitney U test.

With respect to clinical data, although COPD patients showed higher BP values than controls, these values were within normal range and probably had no effect on autonomic modulation.[21,22] Similarly, despite lower in COPD than controls, SpO_2 values were also within normal standards. According to Schettino et al.,[23] and Dourado et al.,[24] significant falls in SpO_2 may occur even in the resting state; however, these changes are documented only in advanced stages of the disease.

In a previous study by our group published in 2002,[11] which included analysis of HRV in COPD, we already showed that patients with COPD had lower values of

Table 4 - Medications used by chronic obstructive pulmonary disease (COPD) patients during data collection

COPD Group	Medications
1	Losartan, Haloperidol, acetylsalicylic acid (ASA)
2	Alenia
3	ASA, Sinvastatin
4	Formoterol
5	Alenia spray
6	Without medications during data collection
7	Alenia, ASA, Budesonide
8	Aerogold, Sinvastatina, Losartan, AAS, Alenia, Budesonide
9	Aerolin spray, Salbutamol, Simvastatin
10	Captopril, Alenia
11	Simvastatin
12	Simvastatin, Aerolin, AAS
13	Simvastatin, Enalapril
14	Ferrous sulfate, Alenia, azathioprine, folic acid
15	Carvedilol, Furosemide, Alenia
16	Alenia, Enalapril
17	Enalapril, hydrochlorizide, Alenia, Aerolin
18	Without medications during data collection

SD RRi than healthy individuals, corroborating other works.[20,25,26] A reduction in SD RRi can be associated with the time a disease affects the cardiovascular system, disease severity and the use of some drugs. The SD RRi is also influenced by respiratory, vasomotor and thermoregulatory stimuli, among others.[27]

Another result obtained by us in 2002[11] and confirmed in the present study was that COPD patients had lower TP values during SB. In the present study, besides the fact that TP values in COPD were decreased during SB, they were also lower than CG group during CB. These results lead us to suggest that the investigation of the TP index is fundamental when the aim is to evaluate the presence of cardiac dysautonomia in COPD patients (Figure 1).

Therefore, we have one index of TD (SD RRi) and one index of FD (TP) that confirm the reduction in HRV in the COPD group. Maybe the most important problem that causes changes in the indexes of total variability is related to characteristics of the respiratory system in COPD. The less compliant thoracic-pulmonary system does not allow great changes in tidal volume, regardless of the form of breathing interfering with the venous return to the heart.

This lower complacency decreases the volume of blood directed to the right atrium during the inspiratory phase and the lower venous return tends to decrease HRV at rest, and thereby is one of the important factors involved in the reduction of the autonomic modulation of the heart of these patients.

The impaired blood flow from the right ventricle to the lungs may also contribute to these HRV changes. Patients with COPD have greater resistance to blood circulation in the heart-lung circuit, which requires more force from the heart. This may result in increased sympathetic tone and decreased vagal tone.[11,21]

Other aspects to be considered in HRV reduction, according to Van Gestel and Steier,[28] are recurrent hypoxemia, hypercapnia, increased intrathoracic pressure due to airway obstruction, increased respiratory effort, and asystemic inflammation.

Our results suggest that the tendency of increase in sympathetic tone to overcome altered pressure in the heart-lung circuit of COPD, has interfered with the absolute and relative index values of the LF component - LF (ms^2) and LF (un) - during the SB, so that they did not differ from the values presented by the CG. Also, during SB, TP values in COPD patients were only 7.1% of those shown by the CG. However, in CB, TP increased by 27.0% in the COPD group compared to that obtained during SB and was 13.8% of that presented by the CG.

These findings reveal that in COPD, even with its limitations related to complacency of the thoracic-pulmonary system, the TP is increased by almost 100% during deeper, oriented breathing. Despite this, COPD patients still showed significantly lower values of TP ($p < 0.0001$) than the CG. Therefore, we suggest that, during diaphragmatic breathing, COPD patients experience positive changes in CAM,[14] despite significantly lower values of PT compared with controls.

Considering the analysis of HRV through TD variables, it is known that the lower the frequencies of the ventilatory cycles, as performed during the CB trial, the higher the values of TD indexes in HRV.[14] However, the COPD group showed similar pNN50 and RMSSD values during both CB and SB, differently from what

was observed with the CG, which showed elevation of the two parameters during CB.

Similar results were reported by Gunduz et al.,[26] in COPD patients during SB, with lower RMSSD (25.0 ± 10.0 ms vs 60.0 ± 35.0 ms) and pNN50 values (11.8 ± 9.4 vs 15.7 ± 8.1%) compared with healthy individuals. Reis et al.,[12] reported RMSSD values of 17.7 ± 6.1 ms and 18.3 ± 15.6 ms during CB and SB, respectively in COPD patients. These values were lower than those observed in controls, and lower than those presented by our volunteers with COPD. The authors, however, did not evaluate pNN50 in these patients.

Although many clinicians believe that patients with COPD tend to have elevated cardiac sympathetic tone, the present study and other studies have shown that both the LF index (considered mainly as a sympathetic component) and the LF/HF ratio (considered mainly as a sympathetic component when greater than 1) in these patients are not different from those in healthy subjects (Tables 2 and 3).[12,28,29]

In the present study, the absolute values found in the LF band (LFms^2) were lower in the COPD group than in CG. However, when these data were analyzed in standardized units (LFun), the percentage of sympathetic contribution to the autonomic modulation of the heart was not different between COPD patients and the CG. In other words, when ULF and VLF values were excluded from the analysis, the percentage of the LF band in COPD was similar to that presented by the CG.

Our results are similar to those of Antonelli Incalzi et al.,[29] who also reported that sympathetic modulation decreases according to the severity of COPD. They also confirm the statement by Carvalho et al.[5] who reported reductions in HRV indexes that reflect not only parasympathetic modulation alone but also sympathetic and parasympathetic modulation together in COPD patients.

In relation to the absolute index of HF, COPD patients showed lower values as compared with the CG. This is in accordance with that observed by Pantoni et al.,[9] who found lower values of the HF components in absolute units in these patients. This suggests that this parameter of the HRV analysis is decreased in COPD patients, and hence should be carefully observed when dealing with this group of patients.

The lower values of HF in COPD were more significant during CB than SB, which agrees with the data reported by Reis et al.,[12] According to these authors, during CB, there is an increase in tidal volume and in respiratory rate in healthy individuals. Therefore, the respiratory pattern performed during the CB protocol could affect lung compliance and pulmonary stretch receptors, and consequently increase the values of LF, HF and TP indexes of HRV. On the other hand, in COPD patients, changes in chest expansion and pulmonary volume are less evident. The elevated and unchanged intrapulmonary pressure reduces venous return, resulting in lower RRi oscillations and changes in cardiocirculatory adjustments promoted by the autonomic nervous system.

As a study limitation, we could not determine the exact volume of air mobilized during the breaths, which would allow the establishment of the relationship between the volume of air during breathing and respective changes in HRV measurements.

Conclusion

The study showed a reduction in cardiac sympathetic and parasympathetic modulation in patients with COPD during both SB and CB. These changes, together with the findings on TP, were the main contributions to the literature. These changes reinforce the need for the analysis of CAM as part of the evaluation of these patients aiming at early detection and treatment of possible cardiac dysautonomia.

Author contributions

Conception and design of the research: Paschoal MA. Acquisition of data: Gianfrancesco L, Camargo LT, Seixas NB. Analysis and interpretation of the data: Paschoal MA, Gianfrancesco L, Camargo LT, Seixas NB, Paschoal AB. Statistical analysis: Paschoal MA, Gianfrancesco L, Paschoal AB. Writing of the manuscript: Paschoal MA, Gianfrancesco L, Seixas NB. Critical revision of the manuscript for intellectual content: Paschoal MA.

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 PUC-Campinas under the protocol number 393.938. 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. Vanderlei LC, Pastre CM, Hoshi RA, Carvalho TD, Godoy MF. Noções básicas da variabilidade da frequência cardíaca e sua aplicabilidade clínica. Rev Bras Cir Cardiovasc. 2009; 24(2):205-17.
2. Kawaguchi LY, Nascimento AC, Lima MS, Frigo L, Paula Jr AR, Tierra-Criollo CJ , et al. Caracterização da variabilidade de frequência cardíaca e sensibilidade do barorreflexo em indivíduos sedentários e atletas do sexo masculino. Rev Bras Med Esporte. 2007,13(4):231-6.
3. Ribeiro JP, Moraes Filho RS. Variabilidade da frequência cardíaca como instrumento de investigação do sistema nervoso autônomo. Rev Bras Hipertens. 2005;12(1):14-20.
4. Akselrod S, Gordon D, Madwed JB, Snidman NC, Shannon DC, Cohen RJ. Hemodynamic regulation: investigation by spectral analysis. Am J Physiol. 1985;249(4 Pt 2):H867-75.
5. Carvalho Td, Pastre CM, Rossi CR, Abreu LC, Valenti VE, Vanderlei LC. Índices geométricos de variabilidade da frequência cardíaca na doença pulmonar obstrutiva crônica. Rev Port Pneumol. 2011;17(6):260-5
6. Sin DD, Wong E, Mayers I, Lien DC, Feeny D, Cheung H, Gan WQ, et al. Effects of nocturnal noninvasive mechanical ventilation on heart rate variability of patients with advanced COPD. Chest. 2007 ;131(1):156-63.
7. Mendes FAR, Moreno IL, Durand MT, Pastre CM, Ramos E, Vanderlei LC. Análise das respostas do sistema cardiovascular ao teste de capacidade vital forçada na DPOC. Rev Bras Fisioter. 2011; 15(2):102-8.
8. Roque AL, Valenti VE, Massetti T, Silva TD, Monteiro CB, Oliveira FR, et al. Chronic obstructive pulmonary disease and heart rate variability: a literature update. Int Arch Med. 2014 Oct;7:43.
9. Pantoni CB, Reis MS, Martins LE, Catai AM, Costa D, Borghi-Silva A. Study on autonomic heart rate modulation at rest among elderly patients with chronic obstructive pulmonary disease. Rev Bras Fisioter. 2007;11(1):35-41.
10. Camillo CA, Pitta F, Possani HV, Barbosa MV, Marques DS, Cavalheri V, et al. Heart rate variability and disease characteristics in patients with COPD. Lung. 2008;186(6):393-401
11. Paschoal MA, Petrelluzzi KF, Gonçalves NV. Estudo da variabilidade da frequência cardíaca em pacientes com doença pulmonar obstrutiva crônica. Rev Ciênc Méd. 2002; 11(1):27-37.
12. Reis MS, Deus AP, Simões RP, Aniceto IA, Catai AM, Borghi-Silva A. Autonomic control of heart rate in patients with chronic cardiorespiratory disease and in healthy participants at rest and during a respiratory sinus arrhythmia maneuver. Rev Bras Fisioter. 2010;14(2)106-13.
13. Chen WL, Chen Gy, Kuoa CD. Hypoxemia and autonomic nervous dysfunction in patients with chronic obstructive pulmonary disease. Respir Med. 2006;100(9):1547-53.
14. Barth J, Del Vecchio FB. Efeitos da frequência ventilatória sobre os índices da variabilidade da frequência cardíaca. Revista Iberoamericana de Arritmología. 2014 5(1):185-93.
15. Acharya UR, Joseph KP, Kannathal N, Lim CM, Suri JS. Heart rate variability: a review. Med Bio Eng Comput. 2006;44(12):1031-51.
16. Smilde TD, van Veldhuisen DJ, van den Berg MP. Prognostic value of heart rate variability and ventricular arrhythmias during 13-year follow-up in patients with mild to moderate heart failure. Clin Res Cardiol. 2009;98(4):233-9.
17. Andresen D, Bruggemann T, Behrens S, Ehlers C. Heart rate response to provocative maneuvers. In: Malik M, Camm AJ (eds) Heart rate variability. Hoboken (NJ): Wiley-Blackwell; 1995. p.267-74.
18. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart Rate Variability – Standards of measurement, physiological interpretation, and clinical use. Circulation. 1996;93(5):1043-65.
19. Paschoal MA, Volanti VM, Pires CS, Fernandes FC. Variabilidade da frequência cardíaca em diferentes faixas etárias. Rev Bras Fisioter. 2006;10(4):413-9.
20. Pagani M, Lucini D, Pizzinelli P, Sergi M, Bosisio E, Mela GS, et al. Effects of aging and of chronic obstructive pulmonary disease on RR interval variability. J Aut Nerv Syst. 1996;59(3):125-32.
21. Chethan HA, Murthy N, Basavaraju K. Comparative study of heart rate variability in normal and obese young adult males. Int J Biol Med Res. 2012;3(2):1621-3.
22. Sociedade Brasileira de Cardiologia. Sociedade Brasileira de Hipertensão; Sociedade Brasileira de Nefrologia. VI Diretrizes Brasileiras de Hipertensão. Arq Bras Cardiol. 2010;95(1 Suppl 1):1-51.
23. Schettino CD, Deus FC, Gonçalves AA, Wallace E. Relação entre DPOC e doença Cardiovascular. Pulmão (RJ). 2013;22(2):19-23.
24. Dourado VZ, Tanni SE, Vale AS, Faganello MM, Sanchez FF, Godoy I. Manifestações sistêmicas na doença pulmonar obstrutiva crônica. J Bras Pneumol. 2006;32(2):161-71.
25. Volterrani M, Scalvini S, Mazzuero G, Lanfranchi P, Colombo R, Clark AL, et al. Decreased heart rate variability in patients with chronic obstructive pulmonary disease. Chest. 1994;106(5):1432-7.
26. Gunduz H, Talay F, Arinc H, Ozyildirim S, Akdemir R, Yolcu M, et al. Heart rate variability and heart rate turbulence in patients with chronic obstructive pulmonary disease. Cardiol J. 2009;16(6):553-9.
27. Heathers JA. Everything Hertz: methodological issues in short-term frequency-domain HRV. Front Physiol. 2014 May;5:177.
28. Van Gestel AJ, Steier J. Autonomic dysfunction in patients with chronic obstructive pulmonary disease (COPD). J Thorac Dis. 2010;2(4):215–22.
29. Antonelli Incalzi R, Corsonello A, Trojano L, Pedone C, Acanfora D, Spada A, et al. Heart rate vascubility and drawing impairment in hypoxemic COPD. Brain and Cognition. 2009;70(1):163-70.

International Journal of Cardiovascular Sciences. 2020;33(1):87-93

REVIEW ARTICLE

Molecular Imaging in the Diagnosis of Infectious Endocarditis – the Role of PET and SPECT

Domenico Albano, Francesco Bertagna, Raffaele Giubbini

ASST Spedali Civili di Brescia, Brescia, Lombardia – Italy

Abstract

18-fluorine-fluorodeoxyglucose positron emission computed tomography (18F-FDG PET/CT) and single-photon emission computed tomography (SPECT) using radiolabeled white blood cells (WBC) are non-invasive techniques widely used in the diagnosis of infections, like endocarditis. The aim of our paper was to provide a systematic review of the published data on the use of 18F-FDG PET/CT and SPECT in infective endocarditis (IE). A comprehensive literature search of the PubMed/MEDLINE, Scopus, Embase and Cochrane library databases was conducted to find relevant published articles about the diagnostic performance of SPECT using WBC and 18F-FDG PET/CT in the diagnosis of infectious endocarditis. Twenty papers were included, with a total of 1,154 patients (166 studies with WBC SPECT and 988 with 18F-FDG PET/CT). From the analyses of the studies, the following results were obtained: both SPECT and PET/CT had good diagnostic accuracy in the study of endocarditis. 18F-FDG PET/CT had good specificity (85.8%) and lower sensitivity (68%), with high heterogeneity among the studies; WBC SPECT/CT had an overall sensitivity of 80% and specificity of 98%. Specific preparations for PET/CT can affect the diagnostic accuracy of the test. Both 18F-FDG PET/CT and WBC SPECT are useful for the diagnosis of IE, and WBC SPECT appears to be slightly more specific than 18F-FDG PET/CT. A specific diet could influence the diagnostic performance of PET/CT.

Keywords

Endocarditis,Infectious/ diagnostic imaging; Positron Emission Tomography Computed/methods; Positron Emission Tomography Computed Tomography/methods; Radiommunodetect/ methods; Leukocytes.

Introduction

Infectious endocarditis (IE) is a serious, potentially life-threatening condition, and a challenge for clinicians due to difficulties in its diagnosis.[1,2] The current diagnostic approach often revolves around the modified Duke criteria, which are composed of a composite of clinical criteria, blood cultures and echocardiographic findings,[3] but cases of uncertain diagnosis are still significant.

Cardiac infections include a group of conditions involving the heart muscle, the pericardium or the endocardial surface of the heart. Infections can extend to the prosthetic material or the leads in case of device implantation. The heterogeneity of clinical presentations requires, besides the diagnostic criteria, a discussion by a multidisciplinary team.

IE is a representative example where the use of nuclear medicine has evolved as an important diagnostic tool.[4,5]

Single photon emission computed tomography (SPECT) using radiolabelled white blood cell (WBC) and fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) have been widely used in the diagnosis of infections and in IE, with controversial findings.

The aim of this review is to provide a systematic review of published data about the role of WBC SPECT and 18F-FDG PET/CT in the diagnostic work-up of patients with IE.

Materials and Methods

The present meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (see supplementary material for PRISMA Checklist).[6]

Mailing Address: Domenico Albano
ASST Spedali Civili di Brescia - Nuclear Medicine - Piazzale Spedali Civili, 1. Postal Code: 25125 Brescia, Lombardia – Italy
E-mail: doalba87@libero.it

DOI: https://doi.org/10.36660/ijcs.20190207

Manuscript received on November 06, 2019; reviewed on November 06, 2019; accepted on December 09, 2019.

Search strategy

A comprehensive literature search of the PubMed/MEDLINE, Scopus, Embase and Cochrane library databases was conducted to find relevant published articles about the diagnostic accuracy of WBC SPECT and 18F-FDG PET/CT in patients affected by IE. We used a search algorithm based on a combination of the terms: a) ''SPECT" OR "Single-photon emission computed tomography" OR "WBC" OR "radiolabeled leukocytes" OR "PET" OR "positron emission tomography" AND b) "endocarditis" OR "heart infection". No beginning date limit was used; the search was updated until August 31, 2019. Only articles in the English language were selected; pre-clinical or not *in vivo* studies, review, letters, editorials and conference proceedings were excluded. To expand our search, references of the retrieved articles were also screened for additional studies. Studies considering cardiovascular implantable electronic device infections were excluded by this review. All literature studies collected were managed using EndNote Web 3.3.

Study selection

All articles reporting patients with IE evaluated by WBC SPECT and 18F-FDG PET/CT in clinical setting were eligible for inclusion. Two researchers (DA and FB) independently reviewed the titles and abstracts of the retrieved articles. The same two researchers then independently reviewed the full-text version of the remaining articles to determine their eligibility for inclusion. Disagreements were resolved by a third opinion (RG). Moreover, in case of studies that included the same population, the report with the highest number of enrolled patients was considered for the analysis.

Data abstraction

For each included study, the following data were extracted – authors' names, year of publication, type of study, number of patients, diagnostic test, diagnostic criteria, reference standard, diagnostic performance. The main findings of the articles included in the review are reported in the Results section.

Results

Literature search

The comprehensive computer literature search revealed 665 articles (Figure 1). On reviewing the titles and abstracts, 645 articles were excluded because the data reported data were not within the field of interest of this review. Twenty articles were selected and retrieved in full-text version[7-25]; no additional study was found when screening the references of these articles. In total, 20 articles were included in the systematic review, four about WBC SPECT[7-10] and 16 about 18F-FDG PET/CT[11-25]

Qualitative analysis

Characteristics of the studies are detailed in Tables 1 and 2. The IE group included 16 [18F] FDG PET/CT (overall 988 patients) and four SPECT/CT studies (overall 166 patients). Among the PET/CT studies, seven analyzed only prosthetic valve endocarditis (PVE),[9,13,15,16,19-21] two only native valve endocarditis (NVE),[11,23] and the remaining seven analyzed a mixed population or the type of endocarditis was not reported.[12,14,17,18,22,24,25] Among SPECT studies, two included only PVE,[8,9] and the remaining two papers included both NVE and PVE.[7,10] In only one paper,[9] both SPECT and PET/CT techniques were used to study IE.

The pooled sensitivity of 18F-FDG PET/CT was 68% (95% CI 55–87), with a high heterogeneity (I2 = 94%, $p < 0.001$), whereas pooled sensitivity of WBC SPECT was 80% (95% CI 67–94) with a lower heterogeneity (I2 = 75%, p = 0.017). The pooled specificity of 18F-FDG PET/CT was 86.8% (95% CI 82–95) with a high heterogeneity (I2 = 86%, $p < 0.001$), whereas WBC SPECT showed a pooled specificity of 98% (95% CI 94–100) with no heterogeneity (I2 = 0%, p = 0.625). In a sub-analysis, pooled sensitivity of 18F-FDG PET/CT and WBC SPECT for NVE was 71% (95% CI 49–93) with a high heterogeneity (I2 = 95%, $p < 0.001$), while pooled sensitivity for PVE was 81% (95% CI 78–93) with a significant heterogeneity (I2 = 67%, $p < 0.001$). Pooled specificity of 18F-FDG PET/CT and WBC SPECT for NVE was 96% (95% CI 93-100) with a low heterogeneity (I2 = 52%, p = 0.016), while pooled specificity for PVE was 92% (95% CI 86-96) with a significant heterogeneity (I2 = 79%, $p < 0.001$).

Of 17 manuscripts considering the diagnostic performance of 18F-FDG PET/CT, 11 showed specific preparation before PET/CT scan [9,13,15-18,21-25] and five did not.[11,12,14,19,20] In six studies,[9,13,21-24] participants underwent dietary preparation to promote myocardial suppression (high-fat, low-carbohydrate diet), without heparin injection; in two studied only heparin injection was suggested;[16,18] in the remaining three works,[15,17,25] both myocardial suppression and heparin injection were done. Despite this, there was strong heterogeneity in

Figure 1 - Flow-chart of the search strategy.

Table 1 - Characteristics of the studies on single photon emission computed tomography using radiolabelled white blood cell and infectious endocarditis

Author	Year	Design study	N pts	Clinical setting	Sensitivity	Specificity	Accuracy	Diagnostic criteria	Reference standard
Erba et al.	2012	Retrospective	51	16 NVE, 35 PVE	90%	nr	90%	Visual analysis	Microbiological analysis or clinical follow-up
Hyafil et al.	2013	Retrospective	42	42 PVE	nr	100%	nr	Visual analysis	Pre-operative macroscopic analysis and bacteriological analysis + clinical follow-up
Rouzet et al.	2014	Retrospective	39	39 PVE	65%	100%	86%	Visual and semiquantitative analysis	Combination of modified Duke criteria and clinical follow-up
Caobelli et al.	2017	Retrospective	34	12 NVE, 22 PVE	86%	95%	91%	Visual analysis	Microbiological analysis + combination of modified Duke criteria and clinical follow-up

NVE: native valve endocarditis; PVE: prosthetic valve endocarditis; nr: not reported.

Table 2 - Characteristics of the studies on fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) and infectious endocarditis

Author	Year	Design study	N pts	Clinical setting	Sensitivity	Specificity	Accuracy	Diagnostic criteria	Reference standard
Van Riet et al.	2010	Prospective	25	25 NVE	12%	100%	18%	Visual analysis	Clinical follow-up
Ozcan et al.	2013	Retrospective	72	12 PVE, 52 NVE	18%	nr	18%	Visual analysis	Clinical follow-up
Saby et al.	2013	Prospective	72	72 PVE	73%	80%	76%	Visual analysis (AC and NAC)	Modified Duke criteria and clinical follow-up
Kouijzer et al.	2013	Prospective	72	nr	39%	93%	nr	Visual analysis	Modified Duke criteria
Rouzet et al.	2014	Retrospective	39	39 PVE	93%	71%	80%	Visual (AC and NAC) and semiquantitative analysis	Modified Duke criteria and clinical follow-up
Ricciardi et al.	2014	Retrospective	27	27 PVE	55%	100%	nr	Visual (AC and NAC) and semiquantitative analysis	Modified Duke criteria and clinical/ microbiological follow-up
Pizzi et al.	2015	Prospective	92	92 PVE	87%	92%	nr	Visual (AC and NAC) and semiquantitative analysis	Modified Duke criteria and clinical follow-up
Jimenez-Ballvè et al.	2016	Prospective	41	39 PVE, 2 NVE	88%	79%	85%	Visual (AC and NAC)	Modified Duke criteria and clinical/ microbiological follow-up
Granados et al.	2016	Prospective	51	29 PVE, 21 NVE	82%	96%	nr	Visual (AC and NAC) analysis	Clinical, imaging and microbiological follow-up
Fagman et al.	2016	Retrospective	30	30 PVE	75%	86%	83%	Visual (AC and NAC) and semiquantitative analysis	Modified Duke criteria and clinical/ microbiological follow-up
Guenther et al.	2017	Retrospective	26	26 PVE	94%	29%	76%	Visual and semiquantitative analysis	Modified Duke criteria and clinical follow-up
Salomaki et al.	2017	Prospective	23	16 PVE, 7 NVE	100%	71%	91%	Visual (AC and NAC) and semiquantitative analysis	Modified Duke criteria and clinical/ microbiological follow-up
Kouijzer et al.	2018	Retrospective	88	88 NVE	45%	100%	87.5%	Visual (AC and NAC) analysis	Modified Duke criteria and clinical/ microbiological follow-up
de Camargo et al.	2019	Prospective	303	188 PVE, 115 NVE	93% PVE 70% NVE	90% PVE 93% NVE	91% PVE 69% NVE	Visual (AC and NAC) and semiquantitative analysis	Modified Duke criteria
El-Dalati et al.	2019	Retrospective	14	8 PVE, 6 NVE	nr	100%	nr	Visual (AC and NAC) and semiquantitative analysis	Histological diagnosis

Table 3 - Preparations for fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography described in the studies included in the review

Author	N pts	Diet	Heparin	Specific preparation
Van Riet et al.	25	no	no	4-hour fasting
Ozcan et al.	72	no	no	6-hour fasting (4-hour for diabetic patients)
Saby et al.	72	yes	no	HFLW (only one meal) diet, 12-hour fasting
Kouijzer et al.	72	no	no	6-hour fasting
Rouzet et al.	39	yes	no	HFLW (only one meal) diet, 12-hour fasting
Ricciardi et al.	27	yes	yes	HFLW diet, 6-hour fasting
Pizzi et al.	92	no	yes	12-hour fasting, 50 IU/Kg heparin bolus 15 min before FDG
Jimenez-Ballvè et al.	41	yes	yes	48-hours HFLC diet, 12-hour fasting, 50 IU/Kg heparin bolus 15 min before FDG
Granados et al.	51	no	yes	12-hour fasting, 50 IU/Kg heparin bolus 15 min before FDG
Fagman et al.	30	no	no	18-hour fasting
Kokalova et al.	13	no	no	6-hour fasting
Guenther et al.	26	yes	no	HFLW diet, 12-hour fasting
Salomaki et al.	23	yes	no	24-hour HFLW diet, 10-hour fasting
Kouijzer et al.	88	yes	no	24-hour HFLW diet, 6-hour fasting
de Camargo et al.	303	yes	no	24-hour HFLW diet, 8-hour fasting
El-Dalati et al.	14	yes	yes	36-hour HFLC diet, 30 IU/kg of heparin administered in three boluses (10 IU/kg) at 10 min before FDG and 5 and 20 min after FDG

MS: myocardial suppression; HFLW: High-fat low-carbohydrate; NR: not reported.

preparation for PET/CT, with different time of fasting or diet for myocardial suppression (Table 3). Pooled sensitivity of PET/CT was 47% (95% CI 18-81) in patients without specific protocol and 78% (95% CI 45-99) in patients who performed specific preparation (myocardial suppression diet and/or heparin injection).

Pooled sensitivity of PET/CT was 76% (95% CI 64–88) and 72% (95% CI 46–99) in patients with and without specific preparation, indicating a high heterogeneity. Also, a pooled specificity of 93% (95% CI 70-100) was observed in the first group and 91% (95% CI 85-94) in the second group.

Discussion

An accurate diagnosis of IE is critical for clinical decision making and represents a challenge for clinicians; in the latest update of the European Society of Cardiology Guideline,[26] nuclear medicine imaging was integrated in the diagnostic flow-chart of IE. Although blood cultures and echocardiography continue to play a crucial role in the diagnosis and the subsequent clinical management of IE, they have limitations, with a significant number of doubtful reports. Also, ultrasound may have difficulties to study prosthetic valves and inconclusive results have been reported in up to 30% of cases.[27]

In this context, WBC SPECT and 18F-FDG PET/CT studies have demonstrated a significant impact on the study of both PVE and NVE. In particular, in case of suspected PVE, abnormal 18F-FDG PET/CT and WBC SPECT/CT uptake should be considered as a pathological finding. In this systematic review we included 19 studies, with a total of 1,115 patients. Overall, 18F-FDG PET/CT had good specificity (86%) and low sensitivity (68%), with high heterogeneity among papers, while WBC SPECT had high specificity (98%) and good sensitivity (80%) but a small number of patients evaluated.

Our results are similar to those reported in previous reviews and meta-analysis.[4,5]

The 18F-FDG PET/CT has the advantage to be a whole-body study that allows the assessment of extracardiac sites of the disease, including clinically unsuspected distant foci, and more appropriate and timely intervention, including antibiotic therapy. In fact, whole-body 18F-FDG PET/CT leads to treatment modification in up to 35% of patients with IE.[28] Several factors, such as antimicrobial therapy, small vegetation size and elevated blood glucose level may impact the accuracy of PET/CT and increase the number of false negative findings. The difficulty to detect small vegetations is directly related to the resolution power of the PET/CT device (about 4-5 mm), which is aggravated in case of high FDG uptake in the surrounding myocardium.

Physiological uptake of FDG is a common problem in the evaluation of heart infection; for this reason, preparation protocols before and/or after FDG injection were suggested, like dietary preparation for MS and heparin injection. However, different diets have been proposed in the literature, without consensus (Table 3). These MS protocols include patient preparation with the use of a low-carbohydrate and high-fat diet plus fasting for at least 6 hours, and use of heparin prior to imaging. Prolonged fasting and low-carbohydrate, high-fat diets lead to decreased insulin and blood glucose levels, and increased free fatty acid levels, reducing physiological FDG uptake. Heparin induces lipolysis and leads to an increase in free fatty acid levels.

Another possible limitation affecting FDG evaluation of IE is the time between valve surgical procedure and PET/CT scan; PET/CT studies performed shortly after cardiac procedures can also be affected by the presence of inflammation foci near to the prostheses.

Although 18F-FDG PET/CT is generally considered a method with higher accuracy than SPECT due to higher spatial resolution and detection efficiency, this was not observed in our results. In fact, in our analysis, both sensitivity and specificity of WBC SPECT were better than PET/CT. 18F-FDG PET/CT has several clear advantages over SPECT imaging such as the lack of blood handling, a shorter study time and high target-to-background ratio; however, a high specificity of 18F-FDG PET/CT requires specific protocols to increase diagnostic accuracy.[29,30]

Limitation of the studies

Several limitations affect the quality of our review on the role of SPECT and PET in IE such as the lack of multicenter studies, the low number of patients evaluated (also due to the rarity of this disease), and the heterogeneity of included papers. This heterogeneity arises from the diversity of patients' characteristics, methodological aspects, reference standards and global quality of the studies.

Conclusion

Our findings support the utility of both WBC SPECT and 18F-FDGPET/CT as diagnostic tools in the study of IE, particularly in patients with prosthetic valve. Specific protocols including diet and/or heparin injection may improve the diagnostic performance of PET/CT.

Author contributions

Conception and design of the research: Bertagna F, Giubbini R. Acquisition of data: Albano D. Analysis and interpretation of the data: Albano D, Bertagna F, Giubbini R. Statistical analysis: Albano D. Writing of the manuscript: Albano D. Critical revision of the manuscript for intellectual content: Albano D, Bertagna F, Giubbini R.

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. Thuny F, Grisoli D, Cautela J, Riberi A, Raoult D, Habib G. Infective endocarditis: prevention, diagnosis, and management. Can J Cardiol. 2014;30(9):1046-57.

2. Thuny F, Grisoli D, Collart F, Habib G, Raoult D. Management of infective endocarditis: challenges and perspectives. Lancet. 2012;379(9819):965-75.

3. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30(4):633-8.

4. Cantoni V, Sollini M, Green R, Berchiolli R, Lazzeri E, Mannarino T, et al. Comprehensive meta-analysis on [18F] FDG PET/CT and radiolabelled leukocyte SPECT–SPECT/CT imaging in infectious endocarditis and cardiovascular implantable electronic device infections. Clin Transl Imaging. 2018;6(1):3-18.

5. Juneau D, Golfam M, Hazra S, Erthal F, Zuckier LS, Bernick J, et al. Molecular imaging for the diagnosis of infective endocarditis: a systematic literature review and meta-analysis. Int J Cardiol. 2018 Feb 15;253:183-8.

6. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009;62(10):e1-34.

7. Erba PA, Conti U, Lazzeri E, Sollini M, Doria R, De Tommasi SM, et al. Added value of 99mTc-HMPAOlabeled leukocyte SPECT/CT in the characterization and management of patients with infectious endocarditis. J Nucl Med. 2012;53(8):1235-43.

8. Hyafil F, Rouzet F, Lepage L, Benali K, Raffoul R, Duval X, et al. Role of radiolabelled leucocyte scintigraphy in patients with a suspicion of prosthetic valve endocarditis and inconclusive echocardiography. Eur Heart J Cardiovasc Imaging. 2013;14(6):586-94.

9. Rouzet F, Chequer R, Benali K, Lepage L, Ghodbane W, Duval X, et al. Respective performance of 18F-FDG PET and radiolabelled leukocyte scintigraphy for the diagnosis of prosthetic valve endocarditis. J Nucl Med. 2014;55(12):1980-5.

10. Caobelli F, Wollenweber T, Bavendiek U, Kühn C, Schütze C, Geworski L, et al. Simultaneous dual-isotope solid-state detector SPECT for improved tracking of white blood cells in suspected endocarditis. Eur Heart J. 2017;38(6):436-43.

11. Van Riet J, Hill EE, Gheysens O, Dymarkowski S, Herregods MC, Herijgers P, et al. (18) F-FDG PET/CT for early detection of embolism and metastatic infection in patients with infective endocarditis. Eur J Nucl Med Mol Imaging. 2010;37(6):1189-97.

12. Özcan C, Asmar A, Gill S, Thomassen A, Diederichsen AC. The value of FDG-PET/CT in the diagnostic work-up of extra cardiac infectious manifestations in infectious endocarditis. Int J Cardiovasc Imaging. 2013;29(7):1629-37.

13. Saby L, Laas O, Habib G, Cammilleri S, Mancini J, Tessonnier L, et al. Positron emission tomography/computed tomography for diagnosis of prosthetic valve endocarditis: increased valvular 18F-fluorodeoxyglucose uptake as a novel major criterion. J Am Coll Cardiol. 2013;61(23):2374-82.

14. Kouijzer IJ, Vos FJ, Janssen MJ, van Dijk AP, Oyen WJ, Bleeker-Rovers CP. The value of 18FFDG PET/CT in diagnosing infectious endocarditis. Eur J Nucl Med Mol Imaging. 2013;40(7):1102-7.

15. Ricciardi A, Sordillo P, Ceccarelli L, Maffongelli G, Calisti G, Di Pietro B, et al. 18-Fluoro-2-deoxyglucose positron emission tomography-computed tomography: an additional tool in the diagnosis of prosthetic valve endocarditis. Int J Infect Dis. 2014 Nov;28:219-24.

16. Pizzi MN, Roque A, Fernández-Hidalgo N, Cuéllar-Calabria H, Ferreira-González I, Gonzàlez-Alujas MT, et al. Improving the diagnosis of infective endocarditis in prosthetic valves and intracardiac devices with 18F-fluordeoxyglucose positron emission tomography/computed tomography angiography: initial results at an infective endocarditis referral center. Circulation. 2015;132(12):1113-26.

17. Jiménez-Ballvé A, Pérez-Castejón MJ, Delgado-Bolton RC, Sánchez-Enrique C, Vilacosta I, Vivas D, et al. Assessment of the diagnostic accuracy of 18F-FDG PET/CT in prosthetic infective endocarditis and cardiac implantable electronic device infection: comparison of different interpretation criteria. Eur J Nucl Med Mol Imaging. 2016;43(13):2401-12.

18. Granados U, Fuster D, Pericas JM, Llopis JL, Ninot S, Quintana E, et al. Diagnostic accuracy of 18F-FDG PET/CT in infective endocarditis and implantable cardiac electronic device infection: a cross-sectional study. J Nucl Med. 2016;57(11):1726-32.

19. Fagman E, van Essen M, Fredén Lindqvist J, Snygg-Martin U, Bech-Hanssen O, Svensson G. 18F-FDG PET/CT in the diagnosis of prosthetic valve endocarditis. Int J Cardiovasc Imaging. 2016;32(4):679-86.

20. Kokalova A, Dell'Aquila AM, Avramovic N, Martens S, Wenning C, Sindermann JR. Supporting imaging modalities for improving diagnosis of prosthesis endocarditis: preliminary results of a single-center experience with 18F-FDG-PET/CT. Minerva Med. 2017;108(4):299-304.

21. Guenther SPW, Cyran CC, Rominger A, Saam T, Kazmierzcak PM, Bagaev E, et al. The relevance of 18F-fluorodeoxyglucose positron emission tomography/computed tomography imaging in diagnosing prosthetic graft infections post cardiac and proximal thoracic aortic surgery. Interact Cardiovasc Thorac Surg. 2015;21(4):450-8.

22. Salomäki SP, Saraste A, Kemppainen J, Bax JJ, Knuuti J, Nuutila P, et al. 18F-FDG positron emission tomography/computed tomography in infective endocarditis. J Nucl Cardiol. 2017;24(1):195-206.

23. Kouijzer IJE, Berrevoets MAH, Aarntzen EHJG, de Vries J, van Dijk APJ, Oyen WJG, et al. 18F-fluorodeoxyglucose positron-emission tomography combined with computed tomography as a diagnostic tool in native valve endocarditis. Nucl Med Comm. 2018;39(8):747-52.

24. de Camargo RA, Bitencourt MS, Meneghetti JC, Soares J, Gonçalves LFT, Buchpiguel CA, et al. The role of 18F-FDG-PET/CT in the diagnosis of left-sided endocarditis: native vs. prosthetic valves endocarditis. Clin Infect Dis. 2019 Apr 5;pii:ciz267.

25. El-Dalati S, Murthy VL, Owczarczyk AB, Fagan C, Riddell J 4th, Cinti S, et al. Correlating cardiac F-18 FDG PET/CT results with intra-operative findings in infectious endocarditis. J Nucl Cardiol. 2019 Sep 4.

26. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, 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). Eur Heart J. 2015;36(44):3075-3128.

27. Saby L, Laas O, Habib G, Cammilleri S, Mancini J, Tessonnier L, et al. Positron emission tomography/computed tomography for diagnosis of prosthetic valve endocarditis: increased valvular 18F-fluorodeoxyglucose uptake as a novel major criterion. J Am Coll Cardiol. 2013;61(23):2374-82.

28. Orvin K, Goldberg E, Bernstine H, Groshar D, Sagie A, Kornowski R, et al. The role of FDG-PET/CT imaging in early detection of extra-cardiac complications of infective endocarditis. Clin Microbiol Infect. 2015;21(1):69-76.

29. Bertagna F, Giubbini R, Treglia G. Positron emission tomography/computed tomography for diagnosis of prosthetic valve endocarditis: suggestions to increase diagnostic accuracy. J Am Coll Cardiol. 2014;63(4):378-9.

30. Treglia G, Bertagna F. Factors influencing the sensitivity of 18F-FDG PET/CT in the detection of infective endocarditis. Eur J Nucl Med Mol Imaging. 2013;40(7):1112-3.

BRIEF COMMUNICATION

Takotsubo Syndrome in the Context of Transmural Acute Myocardial Infarction: Prevalence and How to Differentiate?

João Paulo Soares Costa,[1] Luiz Eduardo Fonteles Ritt,[1,2] Rafael Modesto Fernandes,[1] Felipe Alvarenga Duarte Campos,[1] Queila Borges,[2] Eduardo Sahade Darzé[1,2]

Escola Bahiana de Medicina e Saúde Pública,[1] Salvador, BA - Brazil
Hospital Cárdio Pulmonar,[2] Salvador, BA - Brazil

Takotsubo syndrome (TTS) is characterized by acute and reversible cardiac dysfunction. Because of clinical similarities between TTS and acute coronary syndrome, their differential diagnosis is a challenge.

To describe the prevalence of TTS among patients suspected of ST-elevation myocardial infarction (STEMI) and compare the clinical profile of TTS with that of STEMI.

A retrospective analysis of medical records was performed on patients diagnosed with TTS with ST elevation (cases) and patients diagnosed with STEMI (controls) at Cárdio Pulmonar Hospital, Bahia, Brazil, between 2011 and 2017. For each case, four controls were randomly selected. Categorical data were compared using Pearson's chi-square and Mann–Whitney tests.

Six patients had a confirmed diagnosis of TTS, corresponding to 3.2% of the patients suspected of STEMI. All TTS cases were female; ejection fraction was lower in TTS than in STEMI (35.5 vs. 56.0%; p = 0.018); patients with STEMI had higher peak troponin levels (9.4 vs. 2.2 ng/mL; p = 0.033), and neuropsychiatric disorders were more common in the TTS group (50.0 vs. 12.5%; p = 0.04). The median InterTAK diagnostic score was 60.5 (interquartile range 43.0 67.0) in cases and 24 (interquartile range 18.0–39.5) in controls (p < 0.001).

TTS differed from STEMI in that it was more prevalent in females and was associated with emotional or physical stress, neuropsychiatric disorders, lower ejection fraction, and lower peak troponin levels.

Keywords

ST Elevation Myocardial Infarction; Takotsubo Cardiomyopathy; Stress, Psychological; Stress, Physiological; Ventricular Function Left; Acute Coronary Syndrome/diagnosis.

Introduction

Takotsubo syndrome (TTS) is characterized by transient left ventricular dysfunction culminating in acute cardiac dysfunction. It is frequently preceded by emotional or physical stress.[1,2]

The most common symptoms at presentation are chest pain and dyspnea. Because the presentation of TTS is similar to that of acute coronary syndrome (ACS), the differential diagnosis is difficult, especially from ST-elevation myocardial infarction (STEMI). Absence of coronary artery disease in the affected area must be confirmed to establish the diagnosis of TTS.[2] To facilitate the diagnosis of TTS, the European Society of Cardiology has recently developed the InterTAK diagnostic score, a promising tool that estimates the probability of a TTS event.[3,4]

The aim of this study was to analyze the prevalence of TTS among patients suspected of STEMI and to compare the clinical profiles of TTS and STEMI patients.

Methods

Study design and sample

This was a nested case-control study. We evaluated the medical records of patients with ST-elevation ACS admitted to *Cárdio Pulmonar Hospital*, Salvador, BA, Brazil, between 2011 and 2017, who received a final diagnosis of TTS (cases) or STEMI (controls). For each case, four controls were randomly selected.

Mailing Address: Luiz Eduardo Ritt
Centro de Estudos Clínicos - Hospital Cárdio Pulmonar - Av. Anita Garibaldi, 2199. Postal Code: 40170-130, Ondina, Salvador, BA - Brazil.
E-mail: luizritt@hotmail.com

DOI: 10.5935/2359-4802.20190080

Manuscript received on September 19, 2018, revised manuscript on December 08, 2018, accepted on January 30, 2019.

Inclusion criteria

Patients with ST-elevation and suspicion of ACS at admission, who were subsequently diagnosed with TTS according to Mayo Clinic criteria,[5] were included in the case group.

Patients with ST-elevation and suspicion of ACS at admission, who were subsequently diagnosed with STEMI according to the Universal Definition of Myocardial Infarction,[6] were included in the control group.

Exclusion criteria

Patients with a previous diagnosis of heart failure, those without coronary angiography, and patients with cardiorespiratory arrest at admission were excluded from the study.

Statistical analysis

Normally distributed continuous variables are described as mean ± standard deviation (SD), and non-normally distributed continuous variables are expressed as median and interquartile range (IQR). Categorical variables are presented as percentages. The Student's t-test (parametric) or the Mann–Whitney test (non-parametric) was used for comparison of continuous variables. Categorical variables were compared using Pearson's chi-square test and or the Fisher's exact test when appropriate. A value of $p < 0.05$ was considered to denote statistical significance.

Ethical aspects

The project was approved by the Research Ethics Committee of Santa Izabel Hospital (CAAE no. 76922117.0.0000.5520). Written informed consent was not required given the retrospective nature of the study.

Results

We evaluated 183 cases of suspected STEMI, six (3.2%) of them diagnosed with TTS. Comparison of demographic and clinical variables between cases and controls is shown in Table 1.

TTS patients had a higher frequency of previous emotional stress (50.0 vs. 12.5%; $p = 0.04$), higher prevalence of depressive disorders (50.0 vs. 12.5%; $p = 0.04$), lower peak troponin levels (2.20 vs. 9.43 ng/mL; $p = 0.033$), lower ejection fraction (35.5 vs. 56.0%; $p = 0.018$), and longer QTc intervals (516ms vs. 452 ms; $p = 0.01$) than STEMI patients. Also, TTS patients had significantly higher InterTAK scores (60.5 vs. 24.0; $p < 0.001$), figure 1.

Discussion

The data presented in this study, on a population of patients suspected of STEMI in Brazil, are in agreement with the literature and large multinational registries.[1,2] The prevalence of TTS (3.2%) was higher than that reported in other studies, probably because the study population was composed only of suspected cases of STEMI.

Most international Takotsubo registries[2,3] have collected data on patients with clinical manifestations of ACS, including STEMI and non–STEMI patients. Our study focused exclusively on patients within the spectrum of STEMI, because the need for a rapid diagnosis and rapid initiation of reperfusion therapy in STEMI cases makes the differential diagnosis from TTS a challenge. Early recognition of TTS can help avoid unnecessary procedures in these patients.

Among the variables that differed significantly between cases and controls, we highlight gender, emotional and/or physical stress, neuropsychiatric disorders, and prolonged QTc interval – all of them compose the InterTAK score, a diagnostic tool that estimates the probability of a TTS event, with good sensitivity and specificity.[3] Although each of these characteristics is not specific of TTS, when taken together, they strongly suggest TTS.[2] There was a high prevalence of coronary artery disease (50%) in the TTS group, which was not associated with left ventricular dysfunction. This prevalence was higher than that reported in international registries and may be related to the mean age of the case group (72.5 ± 7.2 years). In this age range, some degree of coronary atherosclerosis is expected.

A recent expert consensus statement on TTS[7] recommended the use of the InterTAK score only for patients suspected of TTS with non-ST elevation ACS. However, the good performance of the tool in our study suggests that it may also be used in suspected cases of STEMI, as sometimes the coronary pattern alone is not sufficient to differentiate between myocardial infarction with normal coronary arteries, myocarditis, and TTS, even in the absence of coronary obstruction.

The limitations of our study include its retrospective nature and the lack of a clinical follow-up. The small

Table 1 - Comparison of demographic and clinical variables between patients diagnosed with Takotsubo syndrome and acute myocardial infarction*

Characteristic	Takotsubo syndrome (n = 6)	Acute myocardial infarction (n = 24)	p value †
Age, years	72.5 ± 7.2	65.3 ± 13.3	0.109
Female, n (%)	6 (100%)	8 (33.3%)	0.003
Isolated chest pain, n (%)	2 (33.3%)	14 (58.3%)	0.025
Emotional and/or physical stress, n (%)	3 (50.0)	3 (12.5%)	0.040
InterTAK score	60.5 (43.0 – 67.0)	24.0 (18.0 – 39.5)	< 0.001
Heart rate, bpm	74 (68 – 84)	74 (65 – 83)	0.667
Systolic blood pressure, mmHg	128 (113 – 145)	140 (112 – 158)	0.672
Body mass index, kg/m²	22.85 (21.9 – 27.1)	28.40 (24.9 – 29.4)	0.050
QTc interval, ms	516.5 (475.0 – 550.0)	452 (429.0 – 468.5)	0.010
Peak troponin value, ng/mL	2.2 (0.69 – 3.66)	9.43 (3.19 – 30.00)	0.033
Peak CK-MB value, ng/mL	9.65 (4.40 – 24.60)	46.75 (14.35 – 80.00)	0.065
Left ventricular ejection fraction, % ‡	35.5 (30.0 – 40.0)	56.0 (45.0 – 64.0)	0.018
Coronary artery disease, n (%)	3 (50.0%)	24 (100%)	< 0.001
Systemic arterial hypertension, n (%)	3 (50.0%)	18 (75.0%)	0.232
Smoker, n (%)	0 (0%)	2 (8.3%)	0.208
Diabetes mellitus, n (%)	0 (0%)	8 (33.3%)	0.099
Dyslipidemia, n (%)	5 (83.3%)	11 (45.8%)	0.100
Neuropsychiatric disorders, n (%)	3 (50.0%)	3 (12.5%)	0.040

** Continuous data are presented as mean ± standard deviation (parametric) or as median (interquartile range) (non-parametric); † Means were compared using the Student's t-test, medians using the Mann–Whitney test, and percentages using the Pearson's chi-square test; ‡ Left ventricular ejection fraction was calculated from echocardiogram results.*

number of patients, although inherent to the low prevalence of this condition, limits the drawing of conclusions. On the other hand, our focus on patients suspected of STEMI is a strength of our study. In Brazil, future studies with clinical follow-up that include a large number of patients of this subgroup and analyze data from multicenter registries are necessary to increase the knowledge of TTS.

Conclusions

The prevalence of TTS among patients initially suspected of STEMI was 3.2%. The clinical profile of TTS differed from that of STEMI in that it was more prevalent in women and was associated with emotional and/or physical stress, neuropsychiatric disorders, lower ejection fraction, lower peak troponin levels, and higher InterTAK scores.

Author contributions

Conception and design of the research: Costa JPS, Ritt LEF, Campos FAD, Darzé ES. Acquisition of data: Costa JPS, Ritt LEF, Campos FAD, Borges Q, Darzé ES. Analysis and interpretation of the data: Costa JPS, Ritt LEF, Fernandes RM, Campos FAD, Borges Q, Darzé ES. Statistical analysis: Costa JPS, Ritt LEF, Fernandes RM, Borges Q, Darzé ES. Obtaining financing: Costa JPS, Ritt LEF, Borges Q, Darzé ES. Writing of the manuscript: Costa JPS, Ritt LEF, Fernandes RM, Borges Q, Darzé ES. Critical revision of the manuscript for intellectual content: Costa JPS, Ritt LEF, Fernandes RM, Campos FAD, Borges Q, Darzé ES.

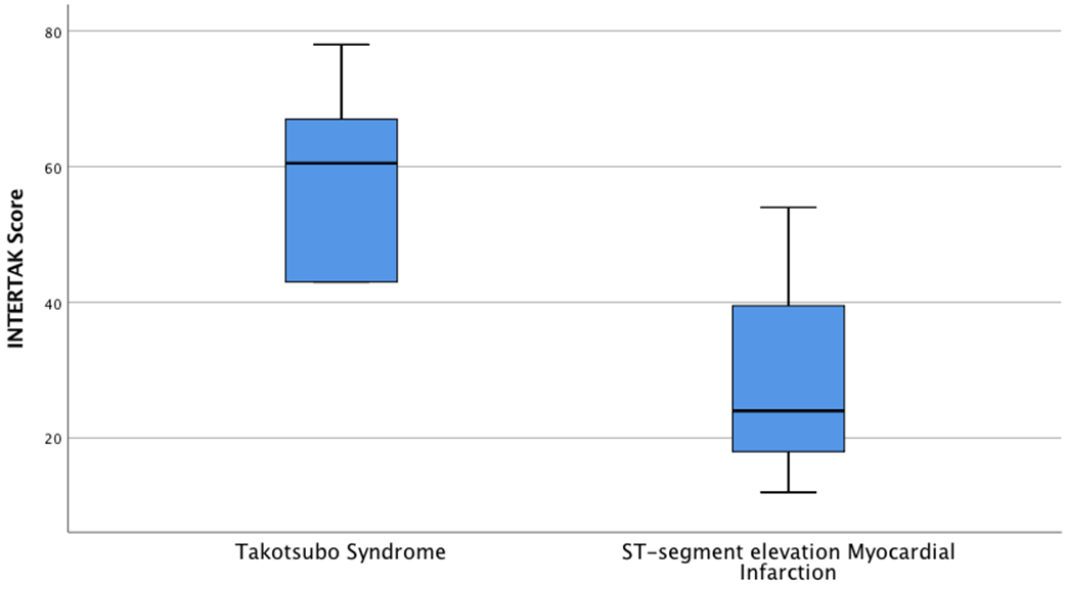

Figure 1 - Comparison of InterTAK scores between patients diagnosed with Takotsubo syndrome and patients diagnosed with ST-elevation myocardial infarction.

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. Lyon AR, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, et al. Current state of knowledge on Takotsubo syndrome: A Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2016;18(1):8–27.
2. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, et al. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. N Engl J Med. 2015;373(10):929–38.
3. Ghadri JR, Cammann VL, Jurisic S, Seifert B, Napp LC, Diekmann J, et al. A novel clinical score (InterTAK Diagnostic Score) to differentiate takotsubo syndrome from acute coronary syndrome: results from the International Takotsubo Registry. Eur J Heart Fail. 2016;1(3):335-40.
4. Rodrigues AC, Guimaraes L, Lira E, Oliveira W, Monaco C, Cordovil A, et al. Right Ventricular Abnormalities in Takotsubo Cardiomyopathy. Echocardiography. 2013;30(9):1015–21.
5. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): A mimic of acute myocardial infarction. Vol. 155, Amer Heart J. 2008;155(3):408-17.
6. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Circulation. 2012;126(16):2020–35.
7. Ghadri J, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, et al. International Expert Consensus Document on Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management. Eur Heart J.2018;39(22):2047-62.

CASE REPORT

A Rare Case of Cardiorespiratory Arrest after Metoclopramide Infusion

Cássio Alexandre Oliveira Rodrigues, Eduardo Queiroz da Cunha, Priscila Ribeiro de Paula, Rand Randall Martins

Hospital Universitário Onofre Lopes (HUOL), Universidade Federal do Rio Grande do Norte (UFRN), RN - Brazil

Introduction

Commonly used as an antiemetic and prokinetic agent, especially in critically-ill patients to reverse gastroparesis and increase in gastric emptying, metoclopramide use can result in important adverse reactions, leading the European Medicines Agency to recommend its use at minimum doses and for a short period of time, due to the risk of neurotoxicity.[1]

Although often associated to neurological events, reactions to this drug affecting the cardiovascular system are less frequent when compared to those that affect the central nervous system. There have been reports of total atrioventricular block[2] and sinus arrest,[3] but the occurrence of metoclopramide-induced cardiorespiratory arrest (CRA) is a rare and poorly described event.

Considering the scarcity of reports and its widespread use in health services, we described a case of CRA in a 21-year-old young woman immediately after the administration of metoclopramide for the treatment of diabetic gastroparesis. This report was approved by the Research Ethics Committee of HUOL (CAAE: 73091717.0.0000.5292). The free and informed consent form was signed by the patient.

Case Report

This is the case of a 21-year-old female patient with type I diabetes, using analogous insulin (lispro and glargine), allergic to dipyrone and with previous use of gabapentin and amitriptyline for the treatment of chronic pain. During anamnesis, previous cardiovascular disease was not reported or evidenced.

The patient was treated in an emergency unit due to diabetic ketoacidosis, triggered by poor diet and medication adherence when she developed lowering of consciousness level and bronchoaspiration episode, requiring orotracheal intubation and mechanical ventilation. After 24 hours, the patient was transferred to the intensive care unit (ICU) of our institution, showing increased nitrogenous waste, refractory to clinical measures and thus, renal replacement therapy with hemodialysis was indicated due to refractory acidosis and hypervolemia. There was no report of previous chronic kidney disease.

For the treatment of aspiration pneumonia, cefepime and clindamycin were used during the first three days of hospitalization, later modified for meropenem and amikacin due to the suspicion of a new infectious condition. The patient was under continuous sedation with fentanyl and midazolam, with a Richmond agitation sedation scale (RASS) target score = 0 and required hemodynamic support with norepinephrine (0.1 mcg/kg/min) for a short period of time at the beginning of hospitalization, withdrawn on the 4th day at the ICU. During this period, treatment with metoclopramide at a dose of 10 mg (iv, 8/8 hours) diluted in 100 mL of 0.9% sodium chloride (0.1 mg/mL) was started for treatment of diabetic gastroparesis. Three days later, as she required greater fluid restriction, the prescription was adjusted: the saline solution was replaced by 18 mL of bidistilled water (0.5 mg/mL). The route of administration and dose were maintained.

After initial clinical measures, there was a satisfactory evolution of the clinical condition with better glycemic control, regression of gastroparesis and discontinuation of hemodialysis due to sustained improvement of

Keywords

Metaclopramide/Adverse effects; Drug Prescriptions/standards; Heart Arrest; Pharmacokinetics; Drug Related Side Effects and Adverse Reactions.

Mailing Address: Cássio Alexandre Oliveira Rodrigues
Residência Multiprofissional em Saúde, Hospital Universitário Onofre Lopes - Avenida Nilo Peçanha, 620. Postal Code: 59.012-300, Petrópolis, Natal (RN) - Brazil.
E-mail: cassioalexandr3@live.com

DOI: 10.5935/2359-4802.20190025

Manuscript received May 22, 2018; revised manuscript September 24, 2018; accepted November 01, 2018.

renal function. She remained under sedation and mechanical ventilation until the beginning of the ninth day, being weaned without any major incidents. The prokinetic agent prescription was maintained even after gastroparesis improvement. However, by the tenth day, the administration of bolus metoclopramide was immediately followed by bradyarrhythmia and CRA (Cardiorespiratory Arrest) with Pulseless Electrical Activity (PEA). The management was performed according to the ACLS (Advanced Cardiovascular Life Support) protocol, with CPR (Cardiopulmonary Resuscitation), orotracheal intubation and administration of epinephrine (1 mg intravenously). The condition was reversed after one cycle, with no evidence of sequelae and followed by extubation one hour after the CRA.

The electrocardiogram performed later showed sinus rhythm, with an electrical axis around +60º, with no changes in the P wave or PR interval, heart rate of 83 bpm, QRS interval with normal morphology and amplitudes, no changes in the ST-segment and T wave and QTc interval of 376 msec.

The previously performed transthoracic echocardiogram, carried out on the 4th day of ICU stay, had shown only discrete mitral regurgitation, without segmental alterations, with normal-sized cardiac chambers, with an ejection fraction of 69% (Teichholz). Before the event, the patient was breathing ambient air, with stable vital signs (HR: 98 bpm; blood pressure levels: 121x71 mmHg; RR: 20 breaths per minute; SO_2: 99%; temperature: 36.3º C), conscious and oriented, with no alterations at the physical examination. The laboratory exams showed normal glycemia (112 mg/dL; and 127 mg/dL after the event) and potassium (4.6 mEq/L) levels and arterial blood gas analysis with mild respiratory alkalosis (pH: 7.469; PO_2: 114.4 mmHg; PCO_2: 31.8 mmHg; HCO_3: 23.3 mmol/L; BE: 0.5 mmol/L).

Immediately after the adverse reaction, the prescription of metoclopramide was modified to "if necessary" and withdrawn from the prescription for the next day. The patient was discharged from the ICU on the following day without further complications. Eight days later, after diabetes treatment adjustments, she was discharged from the hospital and is currently being followed in an outpatient endocrinology unit.

Discussion

Blockade of the dopaminergic pathways (D1 and D2 receptors) associated with gastrointestinal motility inhibition is characterized as the pharmacodynamic basis of metoclopramide, and in particular, blockade of central D2 receptors by the drug can cause dystonic extrapyramidal reactions and increase prolactin levels, considered the most common mechanisms of metoclopramide toxicity.[4] Moreover, this drug is a derivative of procainamide[3] and its cardiotoxic effect seems to involve the blocking of sodium channels, affecting the cardiac electrophysiology.[5]

Despite the arrhythmogenic potential, there have been few reports of CRA associated with its use. These involved patients of both genders between 28 and 66 years of age, with a variety of clinical conditions and CRA after infusion of the medication (Table 1). There have been reports of five episodes following metoclopramide infusions in one patient with subarachnoid hemorrhage, two episodes of asystole in one patient at the postoperative period of partial mastectomy, one case in a patient admitted for abdominal pain and emesis, one report of bradycardia followed by cardiac arrest in a patient at the preoperative period for gastrectomy and one case of a patient with scleroderma who had CRA five minutes after the medication infusion.[4,6-9]

All these cases have in common the intravenous administration of the same bolus dose of metoclopramide. It seems that the infusion time can have an impact on the occurrence of the event, such as extrapyramidal reactions.[10] It is noteworthy that there were no complications when the medication was administered by slow infusion in saline solution during the first days of treatment.

Other medications prescribed on the day of the event were also evaluated. In addition to metoclopramide, unfractionated heparin, glargine and regular insulin, meropenem, methylcellulose eye drops, pantoprazole, nystatin, and topical triamcinolone were prescribed. At the time of the event, the patient remained under hydration with lactated Ringer's solution in a continuous intravenous infusion at 21 mL/hour. Meropenem and methylcellulose were scheduled at the same time as metoclopramide but had not yet been administered. We emphasize the patient`s clinical stability on this day, including a scheduled ICU discharge.

According to the Naranjo algorithm, CRA as a consequence of metoclopramide administration may be characterized as a probable adverse reaction (7 points). The risk can be higher in critically-ill patients with predisposing conditions, use of multiple medications, or it may be associated with prolonged use without

Table 1 - Characterization of case reports involving CPA after metoclopramide use

Reference	Patient	Comorbid conditions	Metoclopramide
Bentsen, Stubhaug (2002)[5]	41 years, male	SAB; ICH; Pneumonia;	10 mg, iv
Tung, Sweitzer, Cutter (2002)[4]	38 years, female	Scleroderma; SAH; Gangrene;	10 mg, iv
Grenier, Drolet (2003)[6]	66 years, female	PO partial mastectomy; DM2;	10 mg, iv
Rumore et al. (2011)[8]	62 years, female	Preoperative gastrectomy; Obesity;	10 mg, iv
Al-shaer, Mustafa, Scalese (2015)[7]	28 years, male	Abdominal pain; emesis; SAH; DLP;	10 mg, iv

SAB: subarachnoid bleeding; ICH: intracranial hypertension; SAH: systemic arterial hypertension; PO: postoperative period; DM2: type 2 diabetes mellitus; DLP: dyslipidemia.

justified need. In our case, the use of metoclopramide persisted even after the gastroparesis was reversed, which may have contributed to the event. However, we emphasize the possibility of the rapid bolus infusion risk, due to its well-known neurotoxicity and, apparently, the cardiotoxic potential evidenced by the sodium channel blockade.

Author contributions

Conception and design of the research: Rodrigues CAO. Acquisition of data: Rodrigues CAO, Martins RR. Analysis and interpretation of the data: Rodrigues CAO, Cunha EQ, Paula PR, Martins RR. Writing of the manuscript: Rodrigues CAO, Cunha EQ, Martins RR. Critical revision of the manuscript for intellectual content: Rodrigues CAO, Cunha EQ, Paula PR, Martins RR. Monitoring of patient and identification of reaction: Paula PR.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Hospital Universitário Onofre Lopes* under the protocol number 37091717.0.0000.5292. 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. van der Meer YG, Venhuizen WA, Heyland DK, Van Zanten ARH. Should we stop prescribing metoclopramide as a prokinetic drug in critically ill patients? Crit Care. 2014;18(5):502.
2. Midttun M, Oberg B. Total heart block after intravenous metoclopramide. Lancet. 1994;343(8890):182-3.
3. Malkoff MD, Ponzillo JJ, Myles GL, Gomez CR, Cruz-Flores S. Sinus arrest after administration of intravenous metoclopramide. Ann Pharmacother. 1995;29(4):381-3.
4. Bentsen G, Stubhaug A. Cardiac arrest after intravenous metoclopramide – a case of five repeated injections of metoclopramide causing five episodes of cardiac arrest. Acta Anaesthesiol Scand. 2002;46(7):908-910.
5. Stoetzer C, Voelker M, Doll T, Heineke J, Wegner F, Leffler A. Cardiotoxic antiemetics metoclopramide and domperidone block cardiac voltage-gated Na+ channels. Anesth Analg. 2017;124(1):52-60.
6. Tung A, Sweitzer B, Cutter T. Cardiac arrest after labetalol and metoclopramide administration in a patient with scleroderma. Anesth Analg. 2002;95(6):1667-8

7. Grenier Y, Drolet P. Asystolic cardiac arrest: an unusual reaction following IV metoclopramide. Can J Anaesth. 2003;50(4):333-5.

8. Al-shaer MH, Mustafa MS, scalese MJ. Metoclopramide-induced asystolic cardiac arrest. Ann Pharmacother. 2015;49(5):610-1.

9. Rumore MM, Lee S, Wang S, Farmer B. Metoclopramide-induced cardiac arrest. Clin Pract. 2011;1(4):e83.

10. Cavero-redondo I, Álvarez-Bueno C, Pozuelo-Carrascosa DP, Díez-Fernández A, Notario-Pacheco B. Risk of extrapyramidal side effects comparing continuous vs. bolus intravenous metoclopramide administration: a systematic review and meta-analysis of controlled trials. J Clin Nurs. 2015;24(23-24):3638-46.

CASE REPORT

Complete Interruption of Aortic Arch and Non-Immune Hydrops Fetalis: A Case Report with Autopsy

Cesar Cilento Ponce

Universidade Metropolitana de Santos (UNIMES), Santos, São Paulo, SP – Brazil

Introduction

Interrupted aortic arch (IAA) occurs in three births per million, and accounts for approximately 1% of congenital heart diseases (CHDs).[1-3] The first case reported with these anomalies appears to be the one by Seidel in 1818.[1]

IAA is a severe form of CHD characterized by a lack of luminal continuity between the ascending and the descending thoracic aorta.[4] The two most common associated cardiac anomalies are ventricular septal defect (90%) and patent ductus arteriosus (98%).[4] Isolated IAA is very uncommon[2,4] and it is considered incompatible with life.[3]

To understand the pathogenesis of IAA, we must remember the embryological development of the main vessels. At approximately the third week of embryonic life, two aortas, a dorsal and a ventral, are connected by six paired arterial branches (aortic arches). In the course of development, a series of changes occur leading to the disappearance of several aortic arches, beginning with the first, the second and the fifth pairs. The third pair of arches persists to form the common carotid and external carotid arteries, and the fourth arches persist to form the permanent arch of the aorta on the left side and the proximal segment of the subclavian artery on the right side. The proximal portions of the sixth arches become the pulmonary arteries. On the right side, the distal segment disappears, while on the left the corresponding distal segment remains as the ductus arteriosus.[1] In IAA, there is a failure of development of the fourth left aortic arch, the pulmonary artery that transports the blood from the heart to the descending aorta via the ductus arteriosus. This absence of the aortic isthmus causes a discontinuity between the ascending and descending aorta.[5]

Symptoms usually occur early in the neonatal period and clinical deterioration is often rapid. The median age at death in untreated IAA with associated cardiac anomalies is 10 days.[2] In the embryo, the superior vena cava returns venous blood from the upper body. This less oxygenated blood leaves the heart via the pulmonary artery. A small amount reaches the lungs while the rest goes into the descending aorta through the ductus arteriosus. The umbilical vein transports oxygenated blood to the right auricle via the hepatic veins, ductus venosus and inferior vena cava; the main part flows through the ventricular septal defect into the left side of the heart,[2] and from there it is distributed to the head and arms.[1,2] In this type of circulation, in case of complete loss of continuity between the ascending and descending aorta it is important the re-establishment of a communication that allows the oxygenated blood that reaches the left heart passes into the right side for adequate supply of the lower portion of body.[2] The absence of a septal defect and a patent ductus arteriosus is incompatible with extra-uterine life.

Prenatal diagnosis of IAA has been reported in few case series.[6] The prenatal characterization of different IAA types based on echocardiographic examination has some limitations.[6] The clinician's knowledge of embryology and anatomy of the great vessels is essential for the diagnosis of IAA.

The aim of this study was to draw attention for possible cardiac abnormalities in hydropsy fetus and to report a case of fetal death by IAA with autopsy.

Keywords

Vascular Ring; Aorta/abnormalities; Aorta/surgery; Aortic Coarctation; Ductus Arteriosus; Perinatal Mortality; Autopsy.

Mailing Address: Cesar Cilento Ponce
Av. Conselheiro Nébias, 53. Postal Code: 11045-002, Encruzilhada, Santos, São Paulo, SP – Brazil.
E-mail: cesarcponce@gmail.com

DOI: 10.5935/2359-4802.20190045

Manuscript received on August 08, 2018, revised manuscript on November 14, 2018, accepted on January 02, 2019.

Case report

A multiparous 43-year-old woman in prenatal care with negative serological tests for infectious diseases was referred for fetal cardiovascular evaluation at 33 weeks of gestation. Her past medical and family histories were unremarkable. A morphology ultrasound in the third trimester showed a hydrops fetus with probable atrioventricular septal defect (AVSD) and heart failure with pericardial effusion in utero. Fetal echocardiography was not performed. Based on perinatal outcomes, amniocentesis for fetal karyotyping was recommended, but the parents declined. Examination during the 35 weeks' follow-up visit revealed that the fetus had died. A female stillborn infant was delivered vaginally. Permission for autopsy was obtained from the parents.

Autopsy findings

An autopsy was performed based on the guidelines of the Committee of the College of American Pathologists.[7] The stillborn weighed 1,510 grams and measured 40 cm in length. The pertinent findings were as follows: macerated skin, hydrops fetalis facies and no other external malformation. At this time, the umbilical cord blood was already clotted, not allowing a suitable sample for the karyotype.

The cephalic, thoracic, and abdominal organs showed moderate autolysis. The heart was dilated and had increased weight for the gestational age, with 20.5 g (mean reference value [mRV]; 14.5 ± 3.7 g) and discrete hydropericardium. The ascending aorta ended at the innominate and left common carotid arteries (Figure 1A). The descending thoracic aorta was a continuation of the pulmonary artery with a widely dilated ductus arteriosus (Figure 1B). The left subclavian artery originated from the descending aorta (Figure 1B). There was a complete absence of the segment of aorta between the origin of the left common carotid and the left subclavian arteries (absence of the aortic isthmus). The venous return to the heart was normal. The aortic and pulmonary valves showed no abnormalities (Figure 2A and 2B). Proximally to the pulmonary artery opening, we noticed the ostium of the left pulmonary artery and distally the ostium of the right pulmonary artery (Figure 2A), and a single coronary artery ostium was identified (Figure 2B). There was a complete AVSD, Rastelli's type A,[8] with both atrial and ventricular septal defect and common atrioventricular valve that bridges both sides of heart (Figure 2B). The lungs were immature. The liver was enlarged, weighing 111.5 g (mean reference value [mRV]; 81.8 ± 22.3 g). No other syndromic features or other malformations were noted.

The placenta weighed 220 grams previously fixed in formaldehyde was received in the Pathology Laboratory, which precluded a karyotype test. Histological sections stained with hematoxylin and eosin (H&E) revealed acute purulent inflammation of the fetal membranes and large areas of placental infarction. No changes were detected in the umbilical cord.

Discussion

IAA was anatomically classified by Celoria and Patton in 1959[9] according to the level of arch interruption: type A, IAA distal to the left subclavian artery, accounting for approximately 30% – 40% of cases; type B, IAA between the left common carotid and left subclavian arteries; it is the most common form, representing 53% of cases; and type C the arch is interrupted between the innominate and left common carotid arteries. This is the most uncommon, accounting for about 4% of cases.[2,4] The case reported herein can be classified as type B based on the site of aortic arch interruption. This subtype is found when the left fourth arch segment regresses early, prior to cephalad migration of the left subclavian artery.[4]

IAA type B is usually syndromic; it is the most common cardiac defect occurring in DiGeorge syndrome, which is associated with microdeletions of the segment 22q11.2.[3,6] Although fetal karyotyping was indicated by the medical team, the parents did not agree with it.

In our case, the blood from the vena cava emptied into the right atrium and then into the right ventricle. Because of complete AVSD, part of this blood passed into the left atrium and into the left ventricle. From the pulmonary artery, some of this blood flew into the branches of this vessel, and the other part emptied through the ductus arteriosus into the descending aorta.[1,4,5] In intrauterine life, the fetus receives the oxygenated blood from the placenta through the umbilical vein. The intercavitary flow promoted by septal defect and ductus arteriosus allows a mixed-blood condition *sine qua non* for survival.[6] However, in the case described here, the septal defect and the large ductus arteriosus exerted no positive effect on gestational outcome.

Chorioamnionitis is an inflammation of the fetal membranes due to infection. The presence of polymorphonuclear leukocytes indicates acute

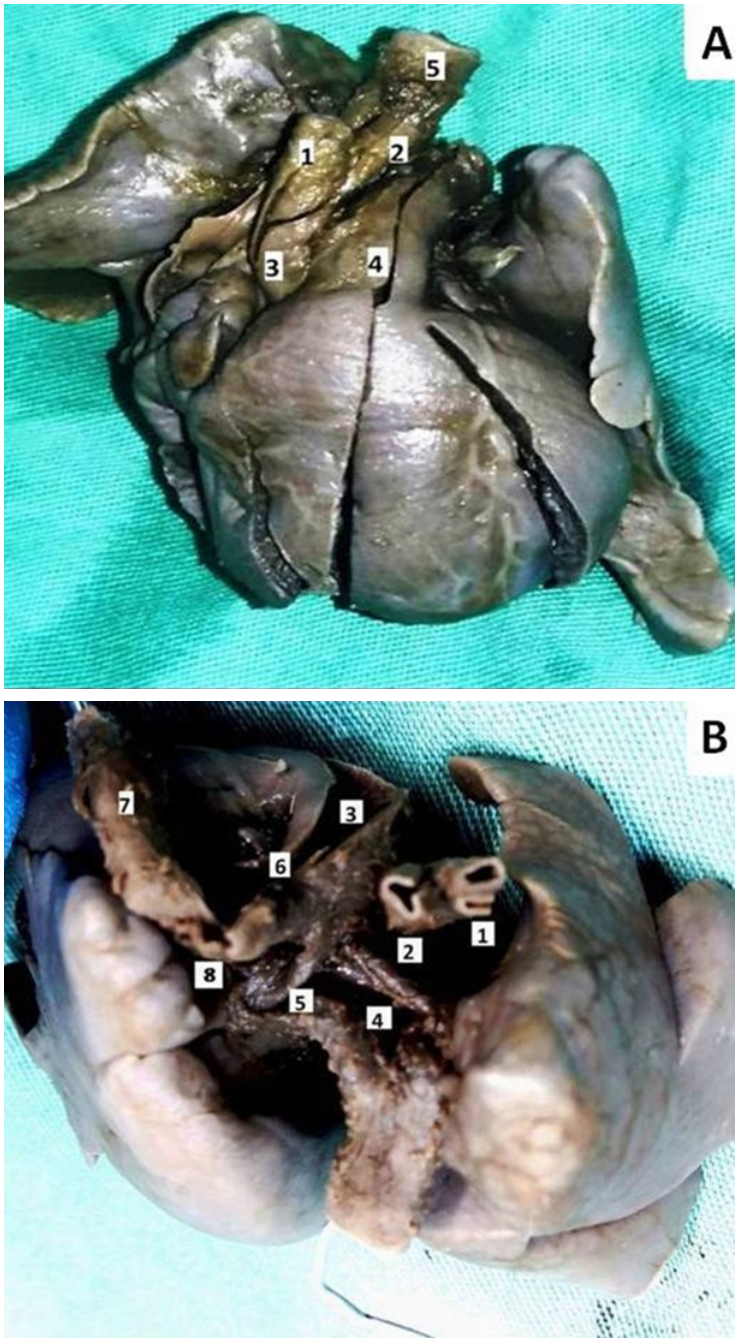

Figure 1 - A: Ascending aorta ending in innominate and left common carotid arteries (anterior view): 1. Innominate artery. 2. Left common carotid artery. 3. Ascending aorta. 4. Pulmonary artery. 5. Trachea. B: The pulmonary artery continues as a descending thoracic aorta via a widely dilated ductus arteriosus (upper view): 1. Innominate artery. 2. Left common carotid artery. 3. Pulmonary artery. 4. Right pulmonary artery. 5. Left pulmonary artery. 6. Dilated ductus arteriosus. 7. Descending thoracic aorta. 8. Left subclavian ostium.

infection. Studies have provided evidence that placental inflammation may be associated with fetal growth abnormalities culminating in stillbirth.[10] Infarcts are the most common lesions seen in the placenta. Large parenchymal infarctions identified in any location of the placenta cause placental abnormalities.[11] In the

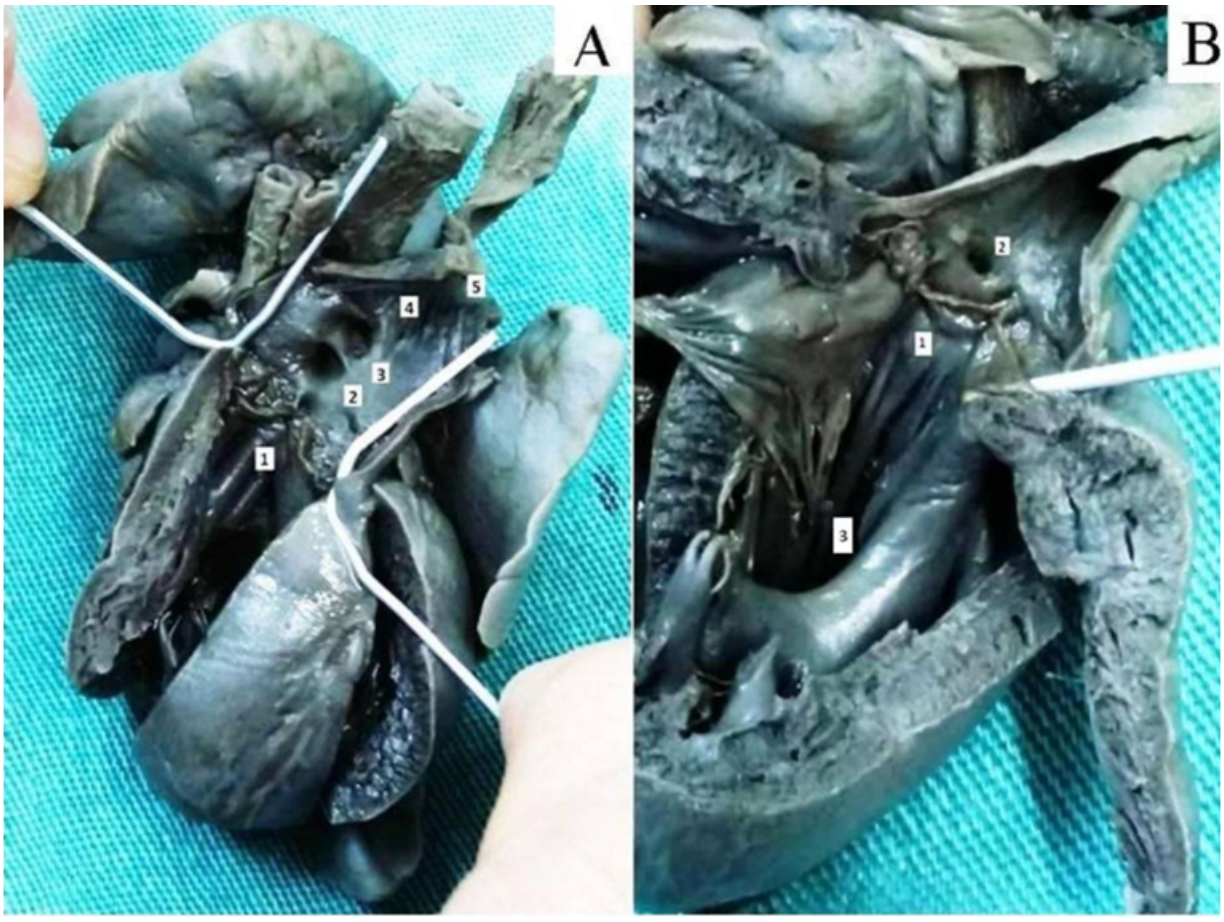

Figure 2 - A: Pulmonary valve, ostium of the left pulmonary artery (below) and ostium of the right pulmonary artery (above). 1. Pulmonary valve. 2. Ostium of the left pulmonary artery. 3. Ostium of the right pulmonary artery. 4. Ductus arteriosus. 5. Descending thoracic aorta. B: Aortic valve and single coronary artery ostium. 1. Aortic valve. 2. Single coronary artery ostium. 3. Complete atrioventricular septal defect with common atrioventricular valve

reported case, we hypothesized that the combination of chorioamnionitis and placental infarction with reduced oxygenation, pertinent to the IAA, may have caused anemia, hidrops, and intrauterus heart failure that culminated in fetal death. Failure to perform the fetal karyotype analysis was a limitation of the reported case.

An important echocardiographic finding in the prenatal diagnosis of IAA is the size discrepancy between the large arteries, with the aortic artery being much smaller in diameter than the main pulmonary artery. In all these cases, it is important to check the continuity of the aortic arch.[6] This difference in diameter between the great vessels was readily observed in the autopsy of the case described, but fetal echocardiography was not performed.

This case is particularly interesting because it emphasizes the importance of a detailed diagnostic investigation in suspicion of fetal hydrops in gestational ultrasound. Although cases of IAA are rare, this entity should be considered as a possible cause of fetal hydrops.

Author contributions

Conception and design of the research: Ponce C. Acquisition of data: Ponce C. Analysis and interpretation of the data: Ponce C. Statistical analysis: Ponce C. Obtaining financing: Ponce C. Writing of the manuscript: Ponce C. Critical revision of the manuscript for intellectual content: Ponce C. Supervision / as the major investigador: Ponce C.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Universidade Metropolitana de Santos* under the protocol number 2.965.717. 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. Everts-Suarez EA, Carson CP. The triad of congenital absence of aortic arch (isthmus aortae), patent ductus arteriosus and interventricular septal defect; a trilogy. Ann Surg.1959;150(1):153-9.
2. Kumanan T, Guruparan M, Gnanakanthan K, Ratnayake UK. Interrupted aortic arch in an adult. Ceylon Med J. 2016;61(3):135-6.
3. Kattea MO, Smettei OA, Kattea A, Abazid RM. Interrupted aortic arch with isolated persistent left superior vena cava in patient with Turners syndrome. Avicenna J Med. 2016;6(4):117-9.
4. Reardon MJ, Hallman GL, Cooley DA. Interrupted aortic arch: brief review and summary of an eighteen-year experience. Tex Heart Inst J.1984;11(3):250-9.
5. Gáspár I. Two of the rarer congenital anomalies of the heart. Am J Pathol. 1929;5(3):285-294.3
6. Volpe P, Tuo G, De Robertis V, Campobasso G, Marasini M, Tempesta A, et al. Fetal interrupted aortic arch: 2D-4D echocardiography, associations and outcome. Ultrasound Obstet Gynecol. 2010;35(3):302-9.
7. Bove KE. Practice guidelines for autopsy pathology: the perinatal and pediatric autopsy. Autopsy Committee of the College of American Pathologists. Arch Pathol Lab Med.1997;121(4):368-76.
8. Rastelli G, Kirklin JW, Titus JL. Anatomic observations on complete form of persistent common atrioventricular canal with special reference to atrioventricular valves. Mayo Clin Proc. 1966;41(5):296-308.
9. Celoria GC, Patton RB. Congenital absence of the aortic arch. Am Heart J. 1959 Sep;58:407-13.
10. Bukowski R, Hansen NI, Pinar H, Willinger M, Reddy UM, Parker CB, et al. Altered fetal growth, placental abnormalities, and stillbirth. PLoS One. 2017;12(8):e0182874.
11. Pinar H, Koch MA, Hawkins H, Heim-Hall J, Shehata B, Thorsten VR, et al. The Stillbirth Collaborative Research Network (SCRN) placental and umbilical cord examination protocol. Am J Perinatol. 2011;28(10):781-92.

NEWS

Calendar

22º Congresso de Cardiologia de Brasília e 10º Congresso de Imagem Cardiovascular Centro Internacional de Convenções de Brasília
De 02 a 04 de abril de 2020

32º Congresso de Cardiologia do Estado da Bahia
Hotel Deville Prime Salvador
De 30 abril a 02 de maio de 2020

37º Congresso De Cardiologia da SOCERJ
Centro de Convenções SulAmérica
De 06 a 08 de maio de 2020

47º Congresso da Sociedade Brasileira de Cirurgia Cardiovascular
PUCRS - POA
De 15 e 16 de maio de 2020

41º Congresso da Sociedade de Cardiologia do Estado de São Paulo
Transamerica Expo Center
De 11 a 13 de junho de 2020

Congresso SBHCI 2020
Expominas - BH/MG
De 24 a 26 de junho de 2020

DEIC 2020
Hotel Royal Palm Plaza - Campinas
De 25 a 27 de junho de 2020

30º Congresso do Sociedade Mineira de Cardiologia
Ouro Minas Palace Hotel
De 02 a 04 de julho de 2020

XLVII Congresso Paranaense de Cardiologia & International Cardiology Meeting
Centro de Eventos Expo Unimed
De 14 e 15 de agosto de 2020

XXXII Congresso da SBC/ES
Aroso Paço Hotel
De 20 a 23 de agosto de 2020

75º Congresso Brasileiro de Cardiologia
De 25 a 27 de setembro de 2020
Centro de Convenções do Ceará
http://cientifico.cardiol.br/

XVII Congresso DHA
Goiânia
De 22 a 24 de outubro de 2020

XXVI Congresso Nacional do DERC - da prevenção ao tratamento
Centro Fecomércio de Eventos - SP
De 26 e 28 de outubro de 2020

XVII Congresso Brasileiro de Cardiogeriatria - DECAGE 2020
Hotel Plaza São Rafael - POA
De 30 e 31 de outubro de 2020

SOBRAC 2020
Hotel Sharaton Santos - SP
De 5 a 7 de novembro de 2020

26º Congresso Brasileiro de Cardiologia e Cirurgia Cardiovascular Pediátrica
Royal Tulip Brasília Alvorada
De 26 a 28 de novembro de 2020

SEE IN THE NEXT EDITION

Vol. 33, Nº 2, March and April 2020

SBC CLUBE

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

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

Acesse já!
cardiol.br/sbc-clube

INTERNATIONAL JOURNAL OF

Cardiovascular SCIENCES