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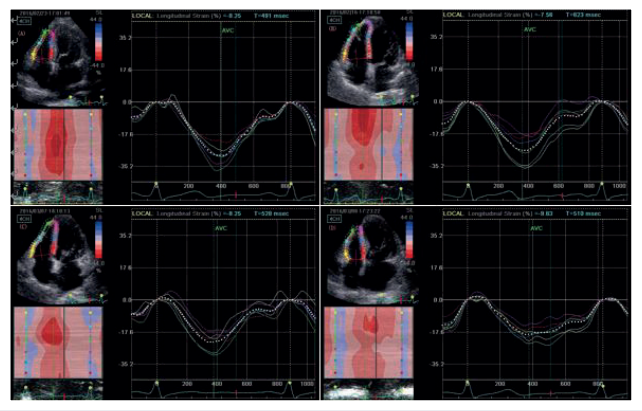

Figure 1 – *Longitudinal peak systolic strain (ε) curve was obtained in right ventricular free wall for basal, middle and apical segment by 2D-STE from the apical four-chamber view. (A) group A; (B) group B (systemic lupus erythematosus – SLE, without pulmonary hypertension); (C) group C (SLE with mild pulmonary hypertension); (D) group D (SLE with moderate-to-severe pulmonary hypertension). Page 79*

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Journal of Brazilian Society of Cardiology
REVISTA DA SOCIEDADE BRASILEIRA DE CARDIOLOGIA - Publicada desde 1948

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SUPPORT

The New Impact Factor of the Arquivos Brasileiros de Cardiologia (ABC Cardiol), 1.318: An Achievement of the SBC for Our Scientific Community

Carlos Eduardo Rochitte

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The *ABC Cardiol* is indexed in the main databases, such as ISI Web of Science, Cumulated Index Medicus - MEDLINE, Pubmed Central, EMBASE, SCOPUS, SCIELO and LILACS, and it has obtained an Impact Factor (IF) of 1.318 from JCR, as well as a B2 rating by the CAPES Qualis System. According to the list recently released by the Journal Citation Reports 2018,[1] 12,271 journals were ranked with a wide IF variability. Of these, 130 journals were in the field of Cardiology and Cardiovascular Sciences, and the *European Heart Journal* leads with 23,425. Around 58% of these publications have IFs below 2.0, among which the *Arquivos Brasileiros de Cardiologia* (*ABC Cardiol*), which has the best IF for journals in the area of Cardiology and Cardiovascular Sciences in Brazil, i.e., 1.318, with a total of 2,541 citations in 2017 (Figure 1).[1]

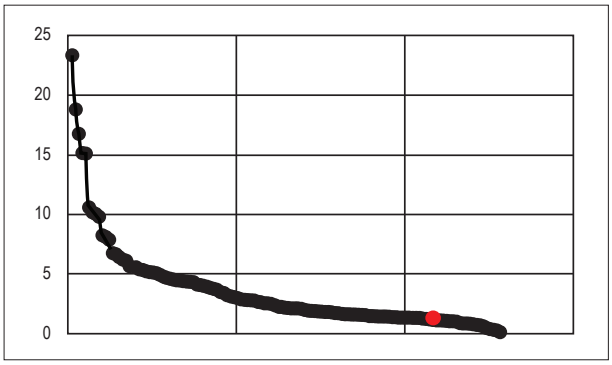

Figure 1 – *2017 Impact Factor for journals in the area of cardiology and cardiovascular sciences (from JCR). In red, the position of ABC Cardiol. Source: Journal Citation Reports 2018.*[1]

There has been a steady increase in *ABC Cardiol*'s IF in the last 5 years (Figure 2A),[1] resulting from the editorial policies adopted, among which the following stand out: peer-reviewed scientific contributions; members of the Editorial Board and reviewers selected among the most important researchers in Brazil and abroad; the rapid assessment of works which are accepted according to relevance and originality, scientific accuracy and level of importance for the advancement of science; indexing in the main databases; and bilingual open-access publication at no cost for authors. It is worth noting that self-citation was not focused on, as shown by Figure 2B,[2] which reinforces that the new impact factor is a solid achievement of our scientific community.

It should be noted that, for the period from 2010 to 2017, original articles were the ones that stood out most in the journal, followed by review articles, both accounting for most of citations (Figure 3). The articles published are divided in 10 areas of knowledge, with 64% of all articles being published in the areas of clinical cardiology, diagnostic methods, basic research and cardiovascular epidemiology (Figure 4), mostly from graduate programs in cardiology, medicine and related areas, which account for almost 60% of the original articles published (Figure 5). Since 2015, the Brazilian Society of Cardiology has annually held a meeting of graduate cardiovascular science program coordinators to discuss the evaluation conducted by CAPES, prospects for journals in the field and internationalization in order to congregate Brazilian researchers with their main national journal.

To promote the internationalization of the *ABC Cardiol*, international partnerships were fostered, accounting for 21% of the articles published in 2017, with the U.S., Portugal and Turkey standing out (Figure 6). It is also worth highlighting that 20% of the editorial staff is formed by members linked to foreign institutions. In 2017, the journal received 650 articles for evaluation, 171 of which were approved and 472 rejected, i.e., an approval rate of 26%.

According to the Web of Science Platform,[3] the average citation per article was 3.47, with the number of citations increasing each year. Such visibility growth can be attributed in part to the journal's website and to dissemination in social media. Our site was modernized in 2018 to integrate the SBC's scientific publications portal,[4] which had 45,000 visits in 2017. The *ABC Cardiol* keeps a page on Facebook and Twitter,[5,6] and in April 2018, it created its Instagram page,[7] where 4 highlight articles from each month's issue are monthly released, as well as videos of authors and editors, in addition to journal news and campaigns.

However, much remains to be done in order to increase both citations and the journal's IF. As of June 2018, *ABC Cardiol* began to use the ScholarOne manuscript management system,[8] thus accepting preprint articles and collecting the authors' ORCid. We also plan to implement Altimetric statistics in the second half of 2018.

This result, which we proudly celebrate, is largely due to the joint efforts of the editors-in-chief, area editors, editorial staff, reviewers and collaborators, who have worked so hard in recent years so that this new IF could be disseminated. Special reference and acknowledgement is made to Prof.

Keywords

Periodicals; Journal Impact Factor; Databases as Topic; Editorial Policies.

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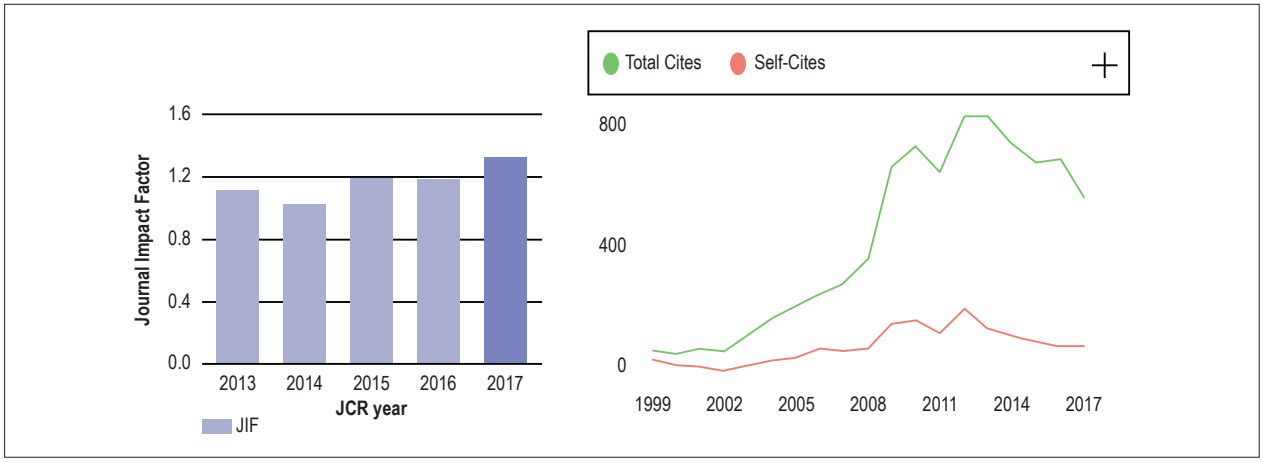

Figure 2 – *Chart A – Evolution of the ABC Cardiol's impact factor in the last 5 years. Source Journal Citation Reports 2018.[1] Chart B – Evolution of total and self-citations. Source: Scimago.[2]*

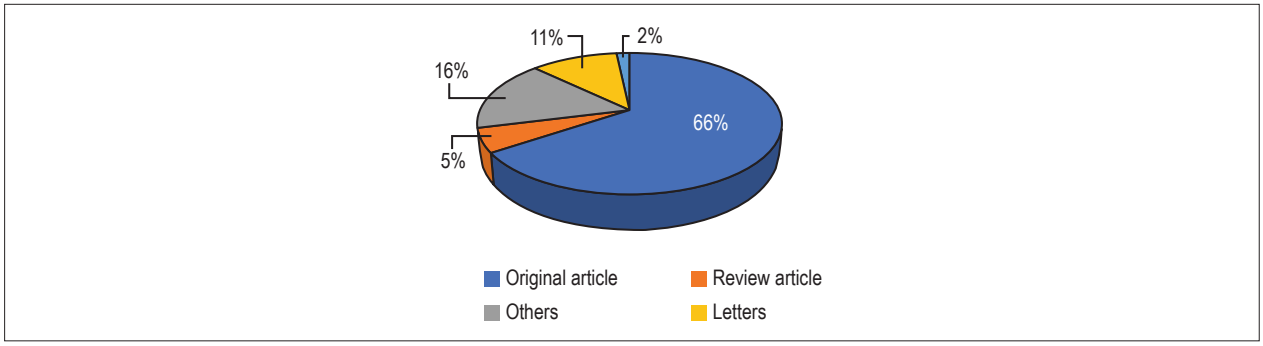

Figure 3 – *Articles Published (2010-2017).*

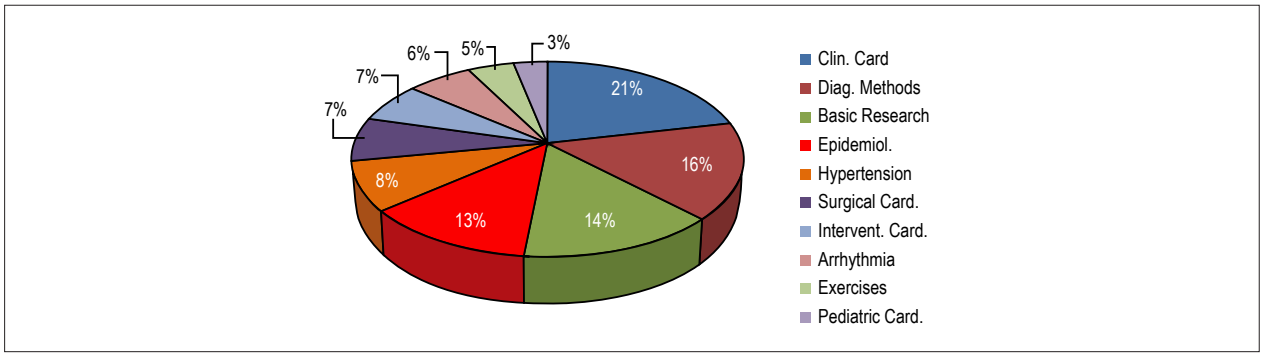

Figure 4 – *Areas of Knowledge (2010-2017).*

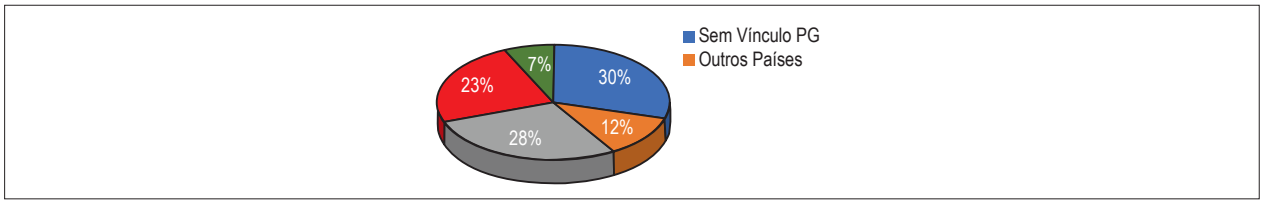

Figure 5 – *Origin of Publications (2010-2017)*

Figure 6 – *Articles by country (2010-2017). Source: Web of Science.*

Luiz Felipe Moreira, who has led the *ABC Cardiol* on this successful editorial line over the last 8 years. Our thanks to the entire "*ABC Cardiol* family", as well as to the SBC board members, who have remained faithful to the mission of the Society, which aims to broaden and disseminate knowledge in cardiovascular science, as well as represent and promote the development of Brazilian cardiologists.

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Executive Summary – Guidelines for Mechanical Circulatory Support of the Brazilian Society of Cardiology

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Evaluation of candidates for mechanical circulatory support devices

In advanced heart failure (HF), the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) proposed seven clinical profiles (and modifiers) for a convenient, easy classification of disease status, risk of implantation of mechanical circulatory support devices (MCSDs) and adequate time for intervention (Chart 1).[1]

One of the main determinant factors for a successful MCSD implantation is patient eligibility. Correct selection of patients involves – (1) patients with advanced HF to which the risk of MCSD implantation surpasses mortality risk for current disease (making it a beneficial intervention); (2) patients with moderately advanced HF, i.e., implantation of MCSD would not increase patient's morbidity and mortality due to increased complication rate; (3) no contraindications for MCSD implantation.[2,3]

Perioperative renal failure, pre-existing right HF, liver dysfunction, mechanical ventilation in the pre-operative period, low weight or overweight and reoperation have been related to worse clinical outcomes after MCSD implantation.[3-5]

The main scores for risk prediction in MCSD implantation are described in Chart 2.

Echocardiography

Evaluation of patients candidates for MCDS should include a transthoracic echocardiogram (TEE) complemented by a transesophageal echocardiography (TEE).

The effects of MCDS on right ventricular function depend on the balance between the benefits of decompression of the left chambers (reduction of the left ventricular afterload) and greater volumetric load to the right atrium (RA; increase of the right ventricular preload). Decompression of left chambers also cause changes in the geometry of the right chambers, such as leftward shift of interatrial (IAS) and interventricular septum (IVS), structural changes of tricuspid annulus, which can aggravate a pre-existing tricuspid insufficiency (TI) and right ventricular overload.[10]

Keywords

Heart Failure/complications, Heart Failure/therapy; Myocardial Ischemia/complications; Assisted Circulation/instrumentation; Contraindicators; Risk Assessment.

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Considering that right ventricular cardiac output determines left ventricular preload, a significant reduction in right ventricular function results in decreased output by the MCSD. It is estimated that approximately 30% of patients with left ventricular assist device develop limiting right ventricular dysfunction. For these reasons, a careful evaluation of right ventricular function is mandatory before MCDS implantation. In the presence of moderate-to-severe dysfunction, the requirement of a permanent biventricular support cannot be ruled out.[11]

In the assessment of right ventricular function before MCSD implantation, it is recommended the measurement of the right ventricle, as well as a semiquantitative assessment of right ventricular longitudinal and radial contractility combined with quantitative parameters, including fractional area change (FAC; FAC < 20% are associated with increased risk of right ventricular dysfunction after MCSD implantation),[12] tricuspid annular plane systolic excursion (TAPSE) determined by M mode, peak systolic velocity of lateral tricuspid ring, measured by tissue Doppler (s'), and right ventricular performance index.[13,14]

Predictors of right ventricular dysfunction before mechanical circulatory support device implantation

Right ventricular dysfunction is multifactorial and includes an increase in preload, ventricular ischemia and mechanical interdependence of ventricular geometry. It is one of the most severe complications of left ventricular assist device, observed in up to 30% of cases and associated with a six-fold increase in morbidity and mortality (increased risk in up to 67%).[11,15]

Risk factors and the main risk score for right ventricular dysfunction after MCSD implantation are described in Charts 3 and 4.

Implantation of a MCSD in the left ventricle should be performed with caution in patients with important right ventricular dilation, moderate-to-severe tricuspid insufficiency, tricuspid valve annulus > 45 mm and CVP > 15 mmHg. By this means, hemodynamic variables directly reflect a preload or afterload increase and right ventricular contractility reductions, whereas venous congestion and organ hypoperfusion, consequence of right ventricular dysfunction, indicate hepatic and renal dysfunctions[15,21]

Positive hemodynamic indicators of adequate right ventricular function that might reduce the risk of post-MCSD implantation dysfunction are: CVP ≤ 8 mmHg; PCP ≤ 18 mmHg; CVP/PCP ≤ 0,66; pulmonary vascular resistance (PVR) < 2 wood units and right ventricular work index ≥ 400 mL/m^2.

Chart 1 – Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles

Profile	Description	Hemodynamic status	Time frame for definitive intervention
1	Critical cardiogenic shock	Persistent hypotension despite the use of inotropes and intra-aortic balloon pumps, associated with organic dysfunction	Hours
2	Progressive decline, but inotrope dependent	Deterioration of renal and hepatic function, nutritional status and lactate levels, despite use of inotropes in optimized doses	Days
3	Stable but inotrope dependent	Clinical stability on continuous inotropic therapy, and history of failure to wean from it	Weeks – months
4	Frequent hospitalization	Signs of water retention, symptoms at rest and frequent admissions to emergency departments	Weeks – months
5	At home, exertion intolerant	Intolerant to activity, comfortable at rest despite water retention	Intervention emergency depends on nutritional status and organic dysfunction severity
6	Exertion limited	Moderate limitation to activity; absence of signs of hypervolemia	Intervention emergency depends on nutritional status and organic dysfunction severity
7	NYHA III	Hemodynamic stability and absence of hypervolemia	Intervention is not indicated

NYHA: New York Heart Association.

Chart 2 – Risk predictors for mechanical circulatory support device implantation

Risk score for destination therapy[6]	Risk score for bridge/destination therapy (HMII score)[7]	Pre-operative risk score[8]	Pre-operative risk score[9]
Risk of 90-day in-hospital mortality (pulsatile flow)	Ninety-day mortality (continuous flow)	Mortality risk after MCSD implantation (mean of 84 days)	Mortality risk after MCSD implantation (mean of 100 days)
Platelets < 148.000/µL OR: 7.7	Age (for 10 years) OR: 1.32	Urine flow < 30 mL/hour RR: 3.9	Respiratory failure /sepsis OR: 11,2
Albumin < 3.3 mg/dL OR: 5.7	Albumin OR: 0.49	CVP > 16 mmHg RR: 3.1	Right heart failure OR: 3.2
INR > 1,1 OR: 5.4	Creatinine OR: 2.1	Mechanical ventilation RR: 3	Age > 65 years OR: 3.01
Use of vasodilator OR: 5.2	INR OR: 3.11	Prothrombin time > 16 seconds RR: 2.4	Postcardiotomy acute ventricular failure OR: 1.8
Pulmonary artery medium pressure < 25 mmHg OR: 4.1	Center volume < 15 implants OR: 2.24	Reoperation RR: 1.8	Acute myocardial infarction OR: 1.7
ALT > 45 U/mL OR: 2.6		Leucocytes > 15.000 RR: 1.1	
Hematocrit < 34% OR: 3,0		Temperature > 101.5 F RR: 0	
BUN > 51 U/dL OR: 2.9			
Intravenous inotropic support OR: 2.9			

HMII: HeartmateII; OR: odds ratio; RR: relative risk; CVP: central venous pressure; INR: international normalized ratio; ALT: alanine transaminase; BUN: Blood Urea Nitrogen. MCSD: mechanical circulatory support device

Temporary devices

Selection of strategies for temporary mechanical circulatory support devices

Temporary MCSD can be used for hemodynamic and clinical stability restoration, aiming at improvement of cardiac function and transplantation. Three strategies (which may be overlapped) can be defined:

1. **Bridge to decision**: should be considered in severely ill patients, who requires immediate hemodynamic support due to high risk of cardiac failure. It may occur in different situations – lack of neurological recovery, multiple organ failure, hemodynamic stabilization and requirement of other devices – in which the final strategy of therapy cannot be established during device implantation (e.g. after cardiorespiratory arrest).[22]
2. **Bridge to recovery:** situation in which support device is removed for ventricular function recovery, such as ventricular dysfunction following acute myocardial infarction, Takotsubo cardiomyopathy and myocarditis.[23]

Chart 3 – Risk factors for right ventricular dysfunction after mechanical circulatory support device implantation (MCSD)[16]

Indication of MCDS	Destination therapy
Sex	Female
Pre-implantation support	Intra-aortic balloon pump and vasopressor requirement
Organic dysfunctions	Respiratory: invasive ventilatory support
	Hepatic: ALT ≥ 80 UI/L. bilirubin > 2.0 mg/dL
	Renal: serum creatinine ≥ 2.3 g/dL History of kidney replacement therapy
	Nutritional: albumin ≤ 3.0 g/dL
	Coagulation: platelets < 120,000
	Others: increased BNP. PCR. Procalcitonin
Right ventricular dysfunction	Right ventricular diastolic diameter > 35 mm. FAC < 30%. Right atrium > 50 mm
Hemodynamic measures	CVP ≥ 15 mmHg or CVP/PCP ≥ 0.63. right ventricular work index ≤ 300 mmHg mL/m^2; low pulmonary artery pressures, low cardiac index or increased pulmonary vascular resistance
Others	Non-ischemic cardiomyopathy, reoperation, important TI, history of PTE

ALT: alanine transaminase; BNP: brain natriuretic peptide; CRP: C-reactive protein; FAC: fractional area change; CVP: central venous pressure; PCP pulmonary capillary pressure; TI: tricuspid insufficiency; PTE: pulmonary thromboembolism

Chart 4 – Main risk scores for right ventricular failure after left ventricular mechanical circulatory support device implantation

Score	Variables	Prediction
University of Michigan, RV Failure Risk Score, Matthews et al.[17]	Vasopressor requirement: 4 points TGP ≥ 80 IU/L: 2 points Bilirubin ≥ 2.0 mg/dL: 2.5 points Creatinine ≥ 2.3 mg/dL or hemodialysis: 3 points	Likelihood of right ventricular failure • ≥ 5.5 points: 7.6 • 4.0-5.0 points: 2.8 • ≤ 3.0 points: 0.49
Kormos et al.[18]	Pre-operative predictors for early left ventricular dysfunction: CVP/PCP > 0.63 Ventilatory support BUN > 39 mg/dL	One-year survival: • Absent right ventricular dysfunction: 78% • Early right ventricular dysfunction: 59% (p < 0.001)
University of Pennsylvania, RV Failure Risk Score, Fitzpatrick et al.[19]	Cardiac index ≤ 2.2 L/min/m^2: 18 points SVRI ≤ 0.25 mmHg-L/m^2: 18 points Important right ventricular dysfunction: 17 points Serum creatinine ≥ 1.9 mg/dL: 17 points Previous cardiac surgery: 16 points Systolic arterial pressure ≤ 96 mmHg: 13 points	< 30: 96%, isolated left ventricular assist device ≥ 65 points: 11%, isolated left ventricular assist device
CRITT score[20]	CVP > 15 mmHg: 1 point Severe right ventricular dysfunction: 1 point Pre-operative mechanical ventilation: 1 point Important tricuspid insufficiency: 1 point Tachycardia (> 100 bpm) = 1 point	1-2 points: low risk for right ventricular dysfunction 2-3 points: moderate risk for right ventricular dysfunction 4-5 points: high risk for right ventricular dysfunction

ALT: alanine transaminase; CVP: central venous pressure; PCP pulmonary capillary pressure; BUN: Blood Urea Nitrogen; SVRI: systemic vascular resistance index

3. **Bridge to transplantation:** situations in which the patient is in progressive severity and heart transplantation cannot be performed in a short term. Support devices may provide hemodynamic support and clinical stability until transplantation is performed.

Types of temporary mechanical circulatory support devices

Main characteristics of temporary MCSDs available in Brazil are described in Chart 5.[24]

Indications and contraindications

Although temporary MCSDs are primarily indicated for patients INTERMACS levels 1 and 2, INTERMACS level 3 patients, dependent of high doses of inotropes or at high risk of hemodynamic instability may also be considered eligible.

Contraindications for temporary MCDS include limiting clinical situations that require individualized approach and involvement of other professionals (e.g. oncologist for establishment of cancer prognosis).

Intra-aortic balloon pump (IABP)

The mechanism of action of the IABP is aortic counterpulsation, which increases diastolic pressure at aortic root, promoting an increase in coronary perfusion, afterload reduction, and consequently an increment in cardiac output by 15%.

Chart 5 – Temporary mechanical circulatory support devices available in Brazil

Characteristics	Intra-aortic balloon	ECMO	TandemHeart™	Impella 2.5® Impella CP® Impella 5.0®	CentriMag®	EXCOR®
Mechanism	Pneumatic	Centrifugal	Centrifugal	Axial	Centrifugal	Pulsatile
Access	Percutaneous	Percutaneous / thoracotomy	Percutaneous	Percutaneous Percutaneous Dissection	Thoracotomy	Thoracotomy
Cannulation	7-9 F	18-21 F Inflow 15-22 F Outflow	21 F Inflow 15-17 F Outflow	12 F 14 F 21 F	24-34 F	27-48 F Inflow 36-48 F Outflow
Insertion technique	Descending aorta via femoral artery	Percutaneous: - Inflow: right atrium via femoral or jugular vein - Outflow: descending aorta via femoral artery Thoracotomy: - Inflow: right atrium - Outflow: pulmonary artery (left mechanical circulatory assist device) or ascending aorta (biventricular assist device)	Inflow: left atrium via femoral vein and transseptal puncture Outflow: femoral artery	Insertion into left ventricle via femoral artery	ACM-E: - Inflow: left ventricle (via left atrium or apex of left ventricle) - Outflow: ascending aorta ACM-D: - Inflow: right atrium - Outflow: pulmonary artery	ACM-E: - Inflow: left ventricle (apex of left ventricle) - Outflow: ascending aorta ACM-D: - Inflow: right atrium - Outflow: pulmonary artery
Hemodynamic support	0.5 L/min	> 4.5 L/min	4 L/min	2.5 L/min 3.7 L/min 5.0 L/min	Up to 8-10 L/min	Up to 8 L/min

ECMO: Extracorporeal membrane oxygenation

Although IABP is still used in the clinical practice especially in younger patients with less severe cardiogenic shock, the efficacy of the method should be carefully evaluated based on improvement of objective parameters of tissue microperfusion. Lack of improvement of these variables in a short time period (hours) justifies the selection of more invasive devices.

Recommendations for intra-aortic balloon pump implantation

Recommendation	Class	Evidence level
Post-AMI cardiogenic shock	IIa	B
Post-AMI mechanical complication with cardiogenic shock	IIa	C
Refractory angina after standard therapy for acute coronary syndrome	IIa	C
Cardiogenic shock in ischemic / non-ischemic chronic cardiomyopathy	IIa	C
Intervention support for patients at high cardiac risk	IIb	C

AMI: acute myocardial infarction

Percutaneous circulatory devices

Definition and benefits

Percutaneous circulatory devices enable active support without requiring a synchronism with the cardiac cycle. The main benefits are maintenance of tissue perfusion, improvement of coronary perfusion, and reduction of myocardial oxygen consumption, filling pressures and ventricular wall stress, providing a circulatory support in cardiogenic shock.[25,26]

Recommendations for percutaneous circulatory support device implantation

Recommendation	Class	Evidence level
Post-AMI cardiogenic shock	IIa	C
Support for interventions in patients at high cardiac risk	IIb	C

AMI: acute myocardial infarction

Types of percutaneous circulatory devices

Impella®

Impella device is composed of a continuous axial flow pump, that aspirates blood directly from the left ventricle and directs it to the aorta (works in series with left ventricle). It allows the flow of 2.5 L/min (Impella® 2.5), 4.0 L/min (Impella® CP) or 5.0 L/min (Impella® 5.0). The model currently available in Brazil is Impella® CP.[24,27]

TandemHeart™

TandemHeart™ system is composed of a centrifugal extracorporeal pump, a femoral cannula, a transseptal cannula and a control console. It pumps blood from the left atrium through a transseptal cannula to the ileo-femoral arterial system. Both TandemHeart™ and the left ventricle work in parallel and contribute to aortic blood flow.[24,27]

Extracorporeal membrane oxygenation

Definition, types and benefits

Extracorporeal membrane oxygenation (ECMO) is an invasive temporary mechanical support that provides partial or total cardiopulmonary support for patients with cardiogenic shock and/or acute respiratory insufficiency. There are two types of ECMO – venoarterial and venovenous. With quick installation technology, ECMO promotes rapid reversal of circulatory failure and/or anoxia.

Recommendations for extracorporeal membrane oxygenation implantation

Recommendation	Class	Level of evidence
Bridge to decision or recovery	I	C
Bridge to transplantation	IIa	C

Paracorporeal circulatory support

Definition, types and benefits

Paracorporeal circulatory support devices are surgically implanted pumps that promote hemodynamic support in individuals with refractory cardiogenic shock with high mortality risk.

A CentriMag® is a continuous flow, magnetically levitated centrifugal blood pump. It provides up to 10 L/minute of blood flow and low shear stress, promoting low thrombogenicity, moderate anticoagulation levels and minimum hemolysis during support.[24]

Berlin Heart EXCOR® is a pulsatile-flow pump that provides up to 8 L/min of blood flow, with batteries connected to a transport system, allowing an up to ten hours of patient's mobility.

Other conventional centrifugal pumps may be used with the same purpose.

Recommendations for implantation of paracorporeal circulatory pumps

Recommendation	Class	Level of evidence
Bridge to decision or recovery	IIa	C
Bridge to transplantation	IIa	C

Long term devices

Types of long-term mechanical circulatory support devices

Due to technological progress, advances in long-term MCSD models have occurred during the last years, regarding pumping system and flow type, enabling its reduction in size, greater efficiency and lower complication rates (Figure 1).

The long-term MCSDs available in Brazil are described in Chart 6.

Indications and contraindications

In making decision process for long-term MCSDs, some important factors should be considered. In case of bridge to transplantation, transplant waiting time should be taken into account; for waiting time shorter than 30 days, there would be a low benefit-cost ratio. Also, the use of these devices in INTERMACS level 2 patients may have unfavorable results.

Recommendations for long-term mechanical circulatory support devices as bridge to transplant

Recommendation	Class	Level of evidence
Systolic heart failure - INTERMACS levels 2 and 3	Class IIa	C
Systolic heart failure - INTERMACS level 4	Class IIb	C
Systolic heart failure -INTERMACS levels 1, 5, 6 and 7	Class III	C

Recommendations for long-term mechanical circulatory support devices as destination therapy

Recommendation	Class	Level of evidence
Systolic heart failure - INTERMACS 3	Class IIa	B
Systolic heart failure - INTERMACS 2		C
Systolic heart failure - INTERMACS 4	Class IIb	C
Systolic heart failure - INTERMACS 1, 5, 6 e 7	Class III	C

Recommendations for long-term mechanical circulatory support devices as bridge to decision

Recommendation	Class	Level of evidence
Systolic heart failure - INTERMACS 2 and 3	Class IIa	C
Systolic heart failure - INTERMACS 4	Class IIb	C
Systolic heart failure - INTERMACS 1, 5, 6 and 7	Class III	C

Patients eligible for MCSD should be evaluated for the presence of factors that may contraindicate or negatively influence patients' survival after transplant. Main contraindications are listed in Chart 7.

Strategy for selection of long-term MCSDs

1. **Bridge to decision:** long-term MCSDs may be indicated for patients with clinical conditions that contraindicate heart transplantation, but if modified, patients may become eligible for transplant (for example: pulmonary hypertension and curable cancers).
2. **Bridge to transplant:** Situations in which MCSDs may provide hemodynamic support and clinical stability until heart transplant, in patients with progressive severity and when a short-term transplant is not possible.
3. **Destination therapy:** Situations in which MCSDs may provide hemodynamic support and clinical stability in patients with refractory heart failure with contraindication for cardiac transplant, promoting higher survival and better quality of life as compared with clinical treatment with drugs.

Optimization and management of right ventricular function

Right ventricular failure is still one of the main factors that affect patients' survival after MCSD implantation.[28] Its diagnostic criteria are – signs and symptoms for persistent right ventricular dysfunction; CVP > 18 mmHg with cardiac index < 2,0 L/min.m^2 in the absence of ventricular arrhythmias or pneumothorax; requirement of ventricular support devices; or requirement for inhaled nitric oxide or inotropic therapy for more than one week after device implantation.[29]

Implantation of a MCSD increases cardiac output and consequently causes an increment in venous return to the right ventricle. To counteract this preload increase, right ventricular compliance should improve with reduction of its afterload (decrease in left ventricular filling pressure and pulmonary arterial pressure). However, leftward shift of IVS may occur in case of excessive left ventricular emptying.[29]

In addition to its contractility, optimization of right ventricular preload and afterload is crucial to prevent right ventricular failure in the perioperative period. CVP and systolic pulmonary pressure should be maintained lower than 16 mmHg and 65 mmHg, respectively. For maintenance of coronary perfusion, use of inotropes that cause pulmonary vasodilation (milrinone or dobutamine) and maintain adequate systemic pressure (adrenaline) is recommended. In addition, the use of specific pulmonary vasodilators, such as nitric oxide should be considered (Figure 2).[30]

Complications after long-term MCSD implantation

The main complications related to long-term MCSD implantation are described in Chart 8.

Proposal of prioritization criteria for cardiac transplant in patients with MCSD

With increasing number of MCDSs, this document proposes a change in the prioritization criteria for patients in the cardiac transplant waiting list. These new criteria are described in Chart 9.

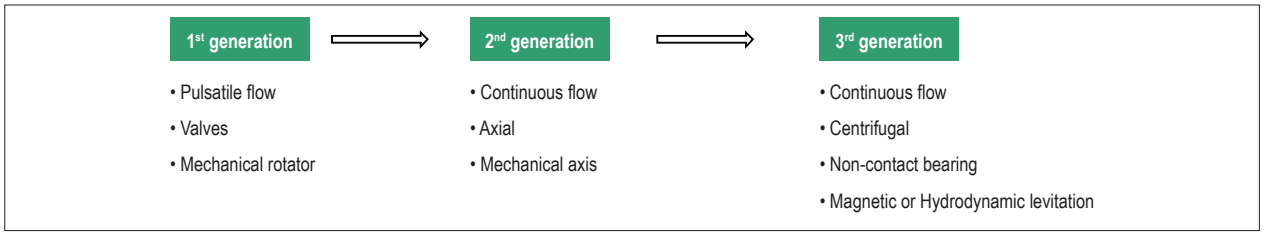

Figure 1 – *Progress of long-term mechanical circulatory support devices.*

Chart 6 – Long-term mechanical circulatory support devices available in Brazil

Name	Company	Type of pump	Type of support	Presence of bearing	Anvisa Approval
HeartMate II®	Thoratec	Axial flow	Left	Yes	Yes
INCOR®	Berlin Heart	Axial flow	Left	No (electromagnetic levitation)	Yes
HeartWare®	HeartWare	Centrifugal flow	Left	No (electromagnetic levitation)	Yes

Anvisa: Agência Nacional de Vigilância Sanitária (The Brazilian Health Regulatory Agency); NA: not applicable

Chart 7 – Contraindications for long-term mechanical circulatory support devices

Absolute	Coumarin intolerance
	Absence of trained caregivers
	Severe psychiatric disorders or nonadherence to the staff instructions
	Severe motor deficit or cognitive deficit related after stroke
	Neoplastic disease with unfavorable prognosis
	Vascular malformation of the small bowel that predisposes to bleeding
	Severe pulmonary obstructive disease
	Severe hepatic dysfunction
	Active infection
	Hematologic changes (platelets < 50,000 mm^3 and thrombophilia)
	Moderate-to-severe right ventricular dysfunction
	Dialytic therapy for renal failure
Relative	Difficult-to-control diabetes
	Partial motor deficit after stroke
	Severe malnutrition
	Significative peripheral artery disease

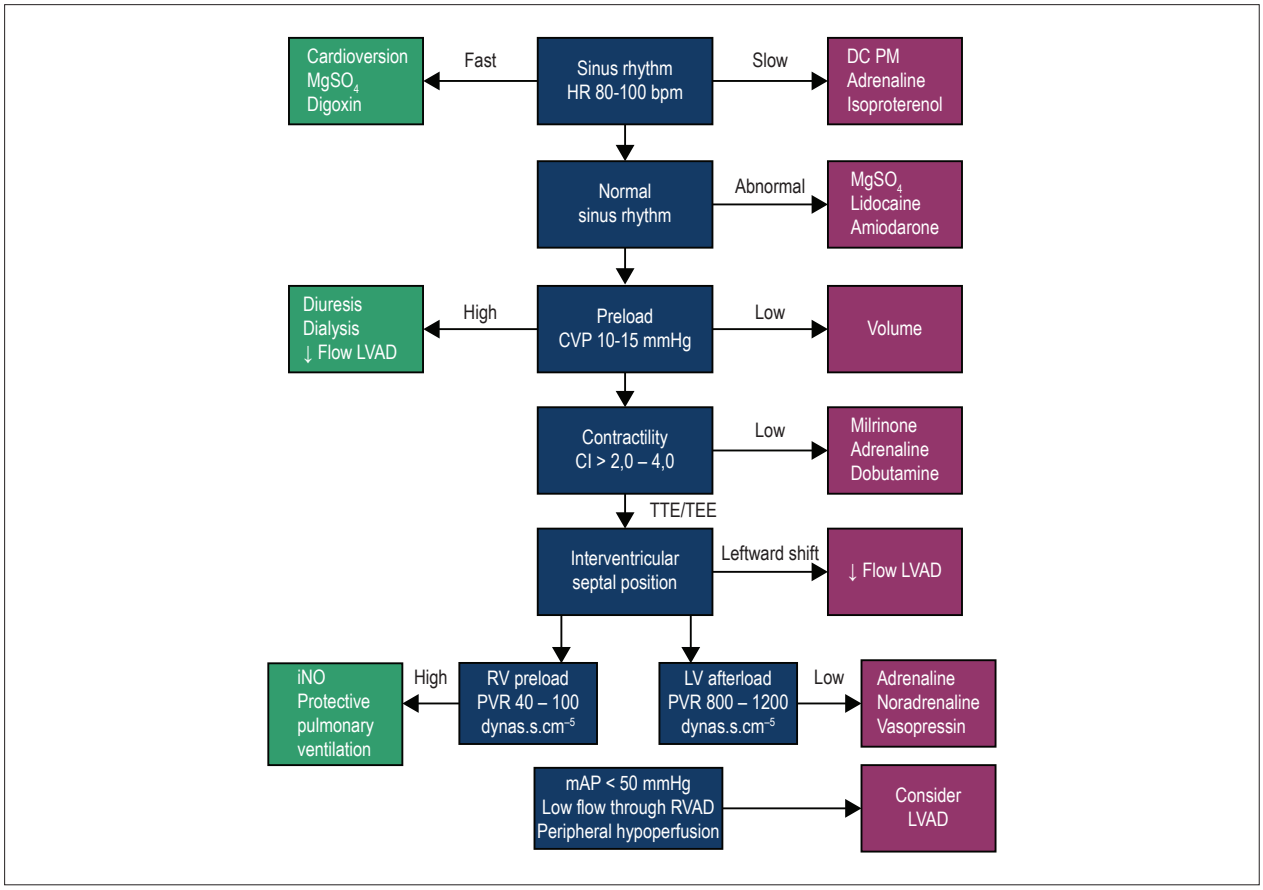

Figure 2 – *Optimization and management of right ventricular function. $MgSO_4$: magnesium sulfate; HR: heart rate; DC PM: dual-chamber pacemaker with right atrial and ventricular stimulation and sensitivity; LVAD: Left ventricular assist device; CVP: central venous pressure; CI: cardiac index; TTE: transthoracic echocardiogram; TEE: transesophageal echocardiography; RV: right ventricular; PVR: pulmonary vascular resistance; LV: left ventricular; SVR: systemic vascular resistance; RVAD: right ventricular assist device; mAP: mean arterial pressure.*

Chart 8 – Complications of long-term mechanical circulatory support devices (MCSDs)

Bleeding	Pericardial effusion	Respiratory insufficiency
Right ventricular dysfunction	Hypertension	Non-neurological arterial thromboembolism
Neurological events	Arrhythmias	Venous thromboembolism
Infections	Myocardial infarction	Surgical wound dehiscence
MCSD malfunction	Hepatic dysfunction	Psychiatric / behavioral change
Hemolysis	Renal dysfunction	

Chart 9 – Proposal of prioritization criteria for cardiac transplant

Priority	Criterium
1	Cardiogenic shock in patients using short/medium-term paracorporeal MCDS (including intra-aortic balloon) Long-term MCDS with complications and substitution of device is not possible
2	Cardiogenic shock in patients using inotropes or vasopressors
3	Stable long-term MCDS without complications
4	Outpatient management of advanced heart failure

MCDS: mechanical circulatory device support

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Cohort of Patients Referred for Brugada Syndrome Investigation in an Electrophysiology Service - 19-Year Registry

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Abstract

Background: **Brugada syndrome (SBr) is an arrhythmic condition characterized by ST-T segment abnormalities in the right precordial leads associated with a high risk of ventricular arrhythmias and sudden death. Local data regarding the clinical characteristics of patients with a typical electrocardiographic (ECG) pattern undergoing electrophysiological study are scarce.**

Objective: **To evaluate patients with an ECG pattern suggestive of SBr referred for electrophysiological evaluation in a specialized center.**

Methods: **Cohort study of patients referred for electrophysiological study because of an ECG pattern compatible with SBr between January 1998 and March 2017.**

Results: **Of the 5506 procedures, 35 (0.64%) were for SBr investigation, 25 of which (71.42%) were performed in men. The mean age was 43.89 ± 13.1 years. The ECG patterns were as follows: type I, 22 (62.85%); type II, 12 (34.30%); and type III, 1 (2.85%). Twenty-three patients (65.7%) were asymptomatic, 6 (17.14%) had palpitations, 5 (14.3%) had syncope, and 3 (8.6%) had a family history of sudden death. Electrophysiological study induced ventricular tachyarrhythmias in 16 cases (45.7%), the mean ventricular refractory period being 228 ± 36 ms. Ajmaline / procainamide was used in 11 cases (31.4%), changing the ECG pattern to type I in 7 (63.6%). Sixteen cases (45.7%) received an implantable cardioverter defibrillator (ICD). In a mean 5-year follow-up, 1 of the 16 patients (6.25%) with ICD had appropriate therapy for ventricular fibrillation. There was no death. Other arrhythmias occurred in 4 (11.4%) cases.**

Conclusions: **Most patients are men, and a type I ECG pattern is the main indication for electrophysiological study. Class IA drugs have a high ECG conversion rate. The ICD event rate was 6%. (Arq Bras Cardiol. 2018; 111(1):13-18)**

Keywords: **Brugada Syndrome; Ventricular Tachycardia; Sudden Death.**

Introduction

Brugada syndrome (BrS) is a genetic arrhythmogenic disorder characterized by typical electrocardiographic changes of the ST-T segment in the right precordial leads (V1-V3), associated with an increased risk for sudden death due to ventricular arrhythmias, mainly polymorphic ventricular tachycardia, in the absence of structural heart disease.[1]

The BrS was first described in 1992, relates to the loss of function in the sodium ion channels of ventricular cardiomyocytes and results from the decrease in that channel amount and failure of expression, its voltage change, time-dependent action and accelerated or prolonged inactivation recovery,[2] leading to a reduction in the sodium ion inflow and in the physiological duration of the action potential. Despite its autosomal dominant inheritance, BrS is currently known to be sporadic in two-thirds of its cases (65%),[3] due to mutations leading to the failure of the SCN5A gene function that encodes sodium channels – initially re-written in 1998[4] – or to other 350 pathogenic mutations in several sodium, potassium or calcium channel genes, currently representing percentages of genetic changes lower than 35%.

Because of its multifactorial etiology that involves the contribution of genetic, environmental and hormonal factors, the clinical manifestation varies, affecting mainly men (proportion of 8-9:1),[5] with clinical onset, on average, at the age of 40 years, and major outcome of sudden death triggered by sleep, vagotonia or fever. Brugada syndrome accounts for 20% of the sudden cardiac deaths with structurally normal hearts[6] and 4-12% of all sudden cardiac deaths.[7]

This study describes a cohort of patients referred for electrophysiological study at the Instituto de Cardiologia/ Fundação Universitária de Cardiologia do Rio Grande do Sul (ICFUC), over the past 19 years (1998-2017), after finding an electrocardiographic pattern suggestive of BrS in different situations of medical care.

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Methods

This is a cohort study of patients referred for electrophysiological study at the ICFUC electrophysiology laboratory between January 1998 and March 2017. Of the 5506 studies performed in that period, 35 (0.67%) corresponded to assessment of patients with electrocardiographic pattern compatible with BrS (Brugada pattern), who were followed up from that study on.

The inclusion criteria were: absence of structural heart disease, absence of personal history of aborted sudden death, electrocardiogram (ECG) compatible with type I, II or III Brugada pattern, and electrophysiological study under a preestablished protocol of ventricular stimulation with three baseline cycles (600, 500 and 400 ms) and introduction of up to three extra stimuli. Diagnostic challenge with infusion of class IA antiarrhythmic drugs according to the Vaughan Williams classification (ajmaline at the dose of 1 mg/kg for 10 minutes or procainamide 10 mg/kg for 10 minutes) was performed in type II electrocardiographic presentations, in accordance with the most used drugs in European and American studies.[8]

From the electrophysiological study on, the patients were followed up through medical appointments at regular six-month intervals, medical record review and/or telephone contact.

Statistical analysis

Our data bank was stored in Microsoft Excel sheets and analyzed by use of the Statistical Package for Social Sciences (SPSS) software, version 20.0 (Armonk, NY, USA: IBM Corp). The continuous variables were expressed as mean (± standard deviation) and compared by use of independent samples *t* test. The continuous variables of non-gaussian distribution were expressed as median [interquartile range (IQR)] and compared by using Mann-Whitney U test. The categorical variables were expressed as percentages and compared by use of chi-square test. The comparisons between groups were performed by using *z* test, with post-hoc Bonferroni analysis to identify the statistical difference. Kaplan-Meyer event-free survival analysis was performed, with percentage survival and standard error. Differences between the frequency of events over time according to the variables identified were compared by use of log-rank test. A p value < 0.05 was considered statistically significant.

Follow-up outcomes

By use of electronic medical record review or telephone call, the occurrence of the following events was investigated: death, syncope, hospitalization due to arrhythmia, and recurrent palpitations requiring medical care. In patients receiving an implantable cardioverter defibrillator (ICD), the occurrence of shock was investigated, and, when present, the appropriateness (shock due to ventricular arrhythmia) or inappropriateness (shock due to supraventricular tachycardia, increased T-wave sensitivity or electromagnetic interference) of the event was assessed.

Results

Of the 35 patients included in the cohort, 22 (62.85%) showed a type I electrocardiographic pattern, 12 (34.30%) showed a type II, and 1 patient (2.85%), a type III pattern. Regarding sex, 25 patients (71.42%) were of the male sex. The mean age was 43.89 ± 13.1 years, and most patients (65.71%) were asymptomatic at the time of inclusion. Regarding the symptoms, 6 patients (17.14%) had palpitations, 5 (14.28%) reported syncope, and 3 (8.57%) reported sudden death of a first-degree relative. Sixteen patients (45.7%) had induced ventricular tachyarrhythmias on stimulation – mean refractory ventricular period of 228 ± 36 ms. Eleven patients (31.4%) with type II ECG pattern received ajmaline or procainamide, and 7 of them (63.6%) changed to type I ECG pattern. Table 1 summarizes the clinical, electrocardiographic and electrophysiologic characteristics of the patients included in this study. No difference was observed between the groups with and without induced arrhythmia (Table 2).

Sixteen patients (45.7%) received an ICD. Of those patients, only 2 had no arrhythmia triggered (reason for implantation: history of sudden death and syncope). Two patients with ventricular arrhythmia (1 with nonsustained ventricular tachycardia and another with ventricular fibrillation) refused to receive the ICD despite the clinical indication. In a mean follow-up of 5 years, 1 of the 16 patients (6.25%) who received the ICD had appropriate therapy for ventricular fibrillation, and 1 (6.25%) attended no consultation after implantation (Figure 1). No death was reported during follow-up. Four patients (11.4%) had other arrhythmic events, such as episodes of nonsustained supraventricular tachyarrhythmias and frequent premature ventricular complexes. Figure 2 shows the discrimination of events in patients with ICD.

Discussion

The long-term event rate of patients diagnosed with BrS or electrocardiographic pattern of BrS is little known, because of the relative short time since that syndrome initial description in 1992,[1] in addition to the limited follow-up duration of current studies, most of which no longer than 3 years.

Table 1 – Clinical, electrocardiographic and electrophysiological study characteristics

Clinical presentations	N = 35
Men	25 (71.42%)
Age	43.89 ± 13.1 years
Asymptomatic	23 (65.7%)
Syncope	5 (14.3%)
Palpitation	6 (17.14%)
Electrocardiographic presentations	
Type I	22 (62.85%)
Type II	12 (34.30%)
Type III	1 (2.85%)
Electrophysiological study	
Ventricular tachyarrhythmia	16 (45.7%)
Refractory period	228 ± 36 ms
HV interval	49 ± 8.6 ms
Ajmaline / Procainamide	11 (31.4%)

Table 2 – Characteristics regarding arrhythmia induction during the electrophysiological study

	With induced arrhythmia	Without induced arrhythmia	p
Number (%)	16 (45.7)	19 (54,3)	
Age	44.625 (±13.69)	43,26 (± 13,30)	0.768¶
Male sex	12 (75)	13 (68,42)	0.7304¶
Electrocardiographic pattern			
Type I	10	11	0.8034†
Type II	6	7	
Type III	-	1	
Clinical manifestation			
Asymptomatic	10	13	0.99†
Palpitations	2*	4**	0.82†
Syncope	3	2**	0.83†
FH of sudden death	2*	1	0.87†

** In the group of patients with induced arrhythmia, one had palpitations and sudden death in the family. ** In the group of patients without induced arrhythmia, one had palpitations and syncope. FH: family history. ¶: Student t test; †: Chi-square / Fisher exact test.*

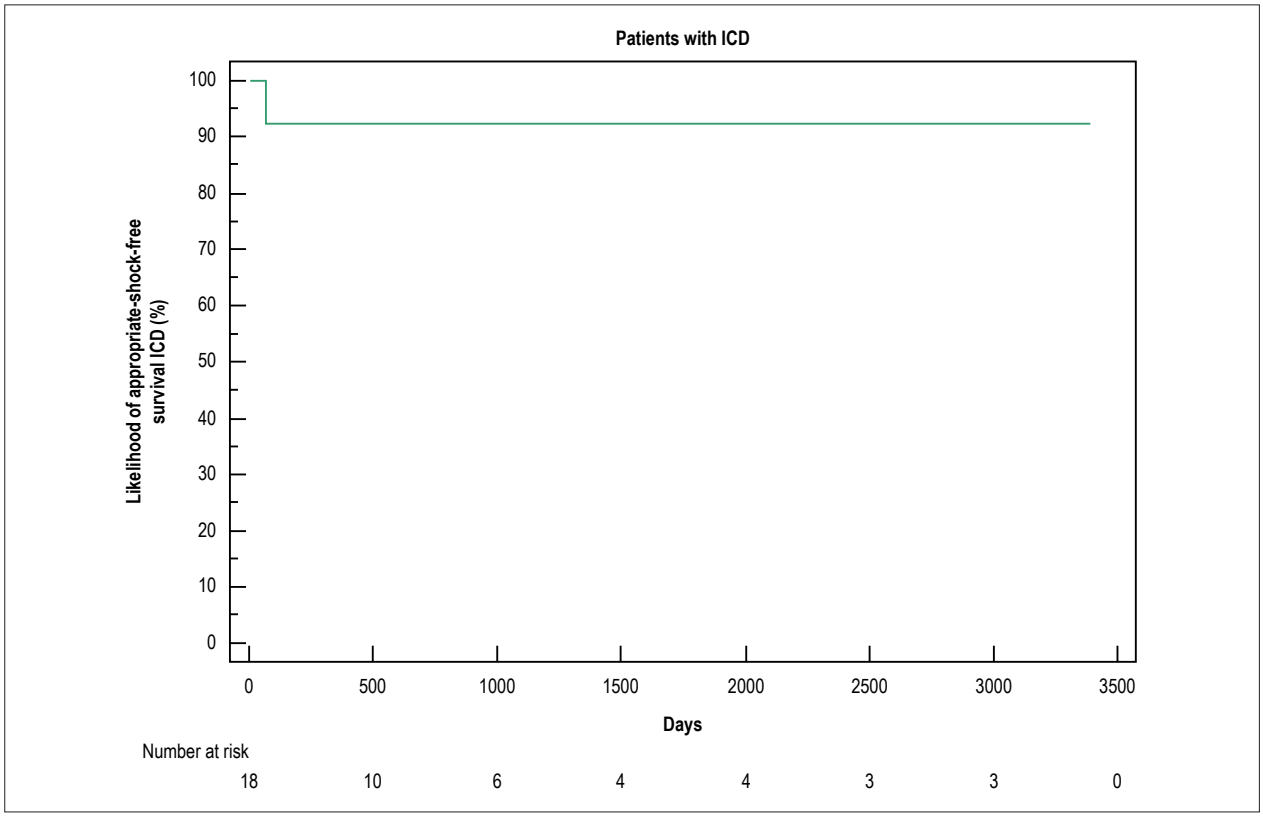

Figure 1 – *Event-free survival curve of the patients with implantable cardioverter defibrillator (ICD).*

The worldwide prevalence of BrS is heterogeneous, because of its nonpermanent electrocardiographic tracings, disparate genetic changes or undiagnosed patients. In addition, potential arrhythmic events and sudden death can occur, making long-term follow-up important to understand the disease and elaborate tools for risk stratification and therapy, mainly because of the involvement of young individuals and the long exposure to possible outcomes.

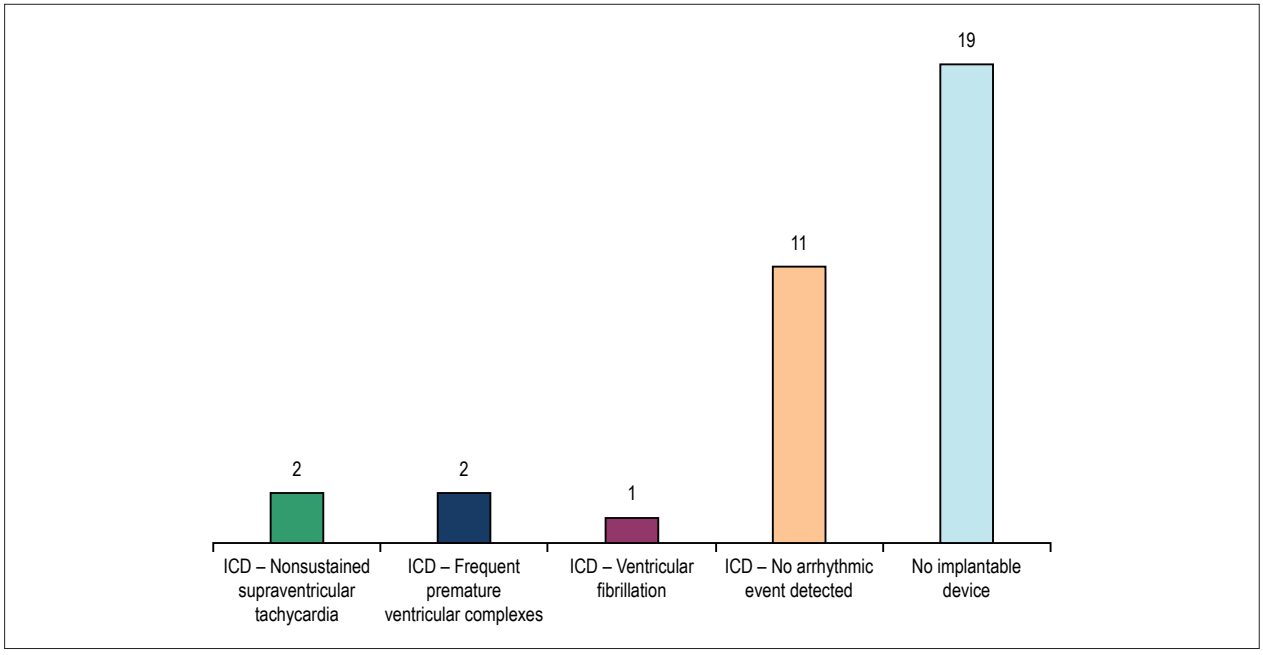

Figure 2 – *Discrimination of events in patients with implantable cardioverter defibrillator (ICD).*

The male predominance found in this study, already reported in the initial description of the disorder as 75%,[1] is in accordance with data from the global literature, whose percentages range according to the geographic location: 84.3% in a large Japanese cohort,[5] 70% in a Spanish cohort,[9] and 57.9% in a Belgian study.[10] The proportion is maintained in geographically close populations, such as an Argentinian cohort of similar size to ours (43 patients), whose male percentage reached 85%.[11] Likewise, the mean age of 43.89 years coincides with the findings of several populations studied, even those with larger samples,[12-14] clearly and repeatedly showing the impairment of young individuals with high productive capacity, emphasizing the importance of the correct identification of those at higher risk based on a common epidemiological profile.

Although the history of ventricular arrhythmias of the fibrillation or tachycardia type is a predictor of mortality in patients with BrS, and the arrhythmia recurrence rates are around 7.7% per year,[14] most of our patients were asymptomatic at the time of the electrophysiological study. If, on the one hand, asymptomatic patients without additional risk factors are currently classified as of low risk,[14,15] on the other it is difficult to predict the potential risk based solely upon the ECG assessment, requiring a multifactorial approach in the search for other complications, such as family history of sudden death, personal history of syncope or induced arrhythmia, because the electrocardiographic pattern in isolation seems insufficient to define high risk for events.[16]

The incorporation of the advances in cardiology in the search for risk predictors has diverging results in a scenario where the identification of susceptibility is the key point, and, because therapy showed no significant changes in past years, it remains without any effective pharmacological alternative, being limited to implantable antiarrhythmic devices. Such devices are known to have a significant, although indirect, contribution to the patients' quality of life because of their daily social or professional repercussions,[17] adding arguments to the already challenging process of identifying its real beneficiaries.

In 2003, the assessment of 547 patients with the BrS pattern and no previous history of sudden death, with a mean 24-month follow-up, a positive electrophysiological study was associated with arrhythmic outcomes on a multivariate analysis, with a 6-fold higher risk in 2 years *versus* a 2.5-fold for the second better predictor, the previous history of syncope.[13] In a cohort[14] of 1029 patients (72% of men, mean age of 45 years, and 64% asymptomatic - a population profile similar to ours), the electrophysiological study was performed in 638 individuals and had a 41% positivity, but was not a risk predictor on multivariate analysis, leaving only personal history and electrocardiographic pattern correlated with events.

Two years later, a prospective multicenter study,[15] assessing specifically the accuracy of arrhythmia induced by stimulation and the identification of new risk predictors, evidenced that induced arrhythmia was not an event predictor in a 36-month follow-up (and only 34% of the patients with induced arrhythmia experienced a new induction when repeating the protocol), in addition to the same findings regarding type I ECG and personal history of syncope, and the additional positive finding for ventricular refractory period shorter than 200 ms and QRS fragmentation. Of the 14 events, only 1 showed no spontaneous type I pattern, with a number needed to treat (NNT) of 25.2.

In 2016, however, a systematic review of eight prospective observational studies involving 1312 patients (n ranging from 575 to 23) with BrS, no previous history of sudden death, undergoing ventricular stimulation, showed that induced arrhythmia correlated with events in a mean 38.3-month

follow-up, with higher risks for patients induced with one or two extra stimuli.[18] The overall analysis of data indicates that the electrophysiological study is useful, mainly in patients at intermediate risk, to whom the clinical characteristics cannot provide a dichotomous classification of high or low risk.

In 2017, Sieira et al.[19] proposed a model of risk classification based on a cohort of 400 patients from a single Belgian center, with mean age and percentage of asymptomatic individuals similar to those of our cohort, in which the clinical factors associated with outcomes were categorized into a score model including the following variables: type I electrocardiographic pattern, history of sudden death of a first-degree relative younger than 35 years, arrhythmia induced on electrophysiological study, syncope, sinus node disease and history of sudden death. In the model proposed, a score equal to or greater than 2 represents high risk for outcome, with positive predictive value of 90%, maintained at 81% when having external validity.

In the present study, the rate of the implantable device events was lower than that reported in the literature, including national studies with patients with BrS,[20] and the one patient with appropriate therapy received it in the first year of follow-up. Nevertheless, the mean 5-year follow-up showed a temporal gain as compared to many similar studies, allowing for the analysis of events in a larger time window – knowing that the risks are continuous throughout life – with the potential advantage of overcoming occasional inaccurate clinical data, manly family history, because the information is patient-dependent and previous data might not be well characterized in the generation immediately before the proband.

Although controversial, the use of electrophysiological study for stratification has shown to be a useful tool to identify high-risk patients, representing a clear signal that the ventricle is more excitable, and, thus, prone to arrhythmic events.[21]

Limitations

This study has limitations such as the fact that the cohort is not constituted by patients identified by ECG, but by those, who, according to their attending doctors would benefit from an electrophysiological study for risk stratification, a fact that limited the sample size and can be a bias by selecting patients that raise more concern about future events. Another fact is that, of the 35 patients, 5 did not undergo follow-up at the same institution where the electrophysiological study was performed. In such cases, data were limited to information collected via telephone, with checking up on neither the electronic medical records nor the devices. Moreover, we performed no genetic study of the population assessed, because it is not routinely available in the healthcare system in addition to its costs.

Conclusion

Brugada syndrome is a potentially fatal arrhythmic condition, and reports on it increased substantially in past years. In this cohort, similarly to the world literature, most patients are of the male sex and had spontaneous type I electrocardiographic pattern. Class IA antiarrhythmic drugs of the Vaughan Williams classification have high rates of electrocardiographic conversion when used for diagnostic challenge. The rate of arrhythmic event was 6.25%, and mortality was lower than that in the literature. The electrophysiological study for risk assessment, although controversial, is currently a useful tool for patient's stratification, mainly when the clinical characteristics are poor and do not allow for estimating accurately the risks of future events.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Statistical analysis, Obtaining financing, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Warpechowski Neto S, Lima GG, Ley LLG, Ley ALG, Dutra LZ, Pires LM, Kruse ML, Leiria TLL.

Potential Conflict of Interest

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

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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 Instituto de Cardiologia do Rio Grande do Sul under the protocol number UP 5374/17. 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.

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Cohort of Patients Referred for Brugada Syndrome Investigation in an Electrophysiology Service – 19-Year Registry

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Short Editorial regarding the article: Cohort of Patients Referred for Brugada Syndrome Investigation in an Electrophysiology Service - 19-Year Registry

Brugada syndrome (BrS) was described by Pedro and Josep Brugada in 1992 as a new clinical entity characterized by specific electrocardiographic (ECG) changes, such as the patterns of right bundle-branch block and persistent ST-segment elevation in right precordial leads, associated with increased risk for sudden death.[1]

Brugada syndrome is an autosomal dominant channelopathy, with clinical manifestation at the age of 30 to 40 years, affecting mainly men. Currently, BrS is estimated to account for 12% of all sudden cardiac deaths and up to 20% of the sudden cardiac deaths in individuals with no structural heart disease.[2] The real prevalence of BrS in the general population is difficult to establish, being estimated at 5 to 20 in every 10,000 individuals.[2] Several genetic mutations have been associated with BrS, most of them related to the encoding of sodium channel proteins (INa), calcium channel proteins (ICa) or potassium channel proteins (usually Ito) of the sarcoplasmatic membrane.[2-5]

The usual clinical manifestation of BrS is arrhythmic syncope, nocturnal agonal respiration or sudden death secondary to polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF). The symptoms usually occur during sleep, at rest during the day or in situations with increased vagal tone, such as binge drinking or heavy meals. In addition, fever is a common trigger, mainly among children.[2-5]

The diagnosis and risk stratification of BrS are mainly based on clinical history and ECG pattern, which can generate controversy because of the incomplete penetrance of the channelopathy and the dynamic pattern of ECG manifestations.[2-5] Although three ECG patterns have been described, the diagnosis of BrS can only be established in patients with type 1 ECG pattern (coved-type), characterized by a concave ST-segment elevation ≥ 2 mm in at least two right precordial leads (V1, V2) positioned on the 2nd, 3rd and 4th intercostal spaces, occurring spontaneously or after provocative drug test with the intravenous administration of class I antiarrhythmic drugs (ajmaline, flecainide or procainamide). The other ECG patterns (types 2 and 3) do not establish the diagnosis of BrS.[2-5]

In BrS risk stratification and treatment, individuals with history of resuscitated cardiac arrest (class I indication) and those with history of syncope and type 1 ECG pattern (class IIa indication) are at high risk for sudden death and have indication for implantable cardioverter-defibrillator (ICD) placement for secondary prevention. Several studies have reported that asymptomatic patients with type 1 ECG pattern only after infusion of class I antiarrhythmic drugs are at low risk for arrhythmic events during clinical follow-up.[6-8] Thus, in those patients, ICD placement should be avoided because of the risk of complications, such as inappropriate shocks.[3-5]

The role of programmed ventricular stimulation (PVS) during invasive electrophysiological study for risk stratification and management of asymptomatic patients with BrS is controversial. While some studies have shown that the induction of ventricular tachyarrhythmias (polymorphic VT or VF) during PVS is an independent predictor of arrhythmic events during clinical follow-up, emphasizing their negative predictive value,[9,10] other studies have questioned those findings.[6,7] It is worth noting the results of a recent systematic review of eight observational prospective studies, including 1,312 patients with BrS and no history of cardiac arrest, in which the induction of polymorphic VT or VF during PVS could predict an increased risk for arrhythmic events (cardiac arrest or ICD shocks) during clinical follow-up, with an increased risk for events when VT/VF induction occurred with only one or two extra-stimuli. However, those authors have reported that the lack of VT/VF induction could not predict a lower risk of arrhythmic events, especially in the subgroup of patients with type 1 ECG pattern and history of syncope.[8] Thus, the most recent expert consensus recommend caution when indicating ICD placement in asymptomatic patients with BrS when ventricular tachyarrhythmias were induced by PVS, emphasizing the need to consider an individualized approach for ICD implantation (class IIb indication) in those patients.[3-5]

It is worth noting that, despite the description of BrS by the Brugada brothers more than 25 years ago,[1] its genetic changes, arrhythmogenic mechanisms and clinical management continue to be debated. This is attributed to the continuous report of new information on BrS and its constantly evolving understanding, driven by new clinical and basic research findings.[2-8,10]

In the present *Arquivos Brasileiros de Cardiologia* issue, Warpechowski Neto et al.[11] report the clinical characteristics, management and follow-up of patients with an ECG pattern suggestive of BrS, who had been referred to a tertiary center for risk stratification by use of invasive electrophysiological study. In the study, aligned with those previously reported in the literature, most patients were of the male gender, adults and had spontaneous type 1 ECG pattern. The study provides a timely and updated overview of the complexity of the BrS clinical management, discussing the controversies of using PVS for risk stratification of asymptomatic patients, as well as ICD placement to treat those at higher risk for fatal arrhythmias in the long-term clinical follow-up.

Keywords

Brugada Syndrome; Bundle-Branch Block; Death, Sudden; Tachycardia, Ventricular; Syncope.

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Mid- and Longterm Neo-Aortic Valve Regurgitation after Jatene Surgery: Prevalence and Risk Factors

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Abstract

Background: Jatene surgery became the surgical procedure of choice to repair transposition of the great arteries (TGA) in neonates and infants. Late complications, mainly related to the pulmonary outflow tract and coronary arteries, are well known. The behavior of the neo-aortic valve is a cause of concern because of its potential for requiring late reoperation.

Objectives: To assess the prevalence and risk factors of neo-aortic valve regurgitation in 127 patients in the late postoperative period of the Jatene surgery.

Methods: Of the 328 survivors of the Jatene surgery at the Biocor Institute from October 1997 to June 2015, all patients undergoing postoperative follow-up were contacted via telephone, 127 being eligible for the study. The patients were divided into two groups, simple TGA and complex TGA groups, with follow-up means of 6.4 ± 4.7 years and 9.26 ± 4.22 years, respectively. Echocardiography was performed with adjusted measurements (Z-score) of the neo-aortic annulus, sinus of Valsalva, sinotubular region and ascending aorta, as well as quantification of the neo-aortic valve regurgitation grade.

Results: The incidence of mild neo-aortic valve regurgitation was 29% in a follow-up of 7.4 ± 4.7 years. Moderate regurgitation was identified in 24 patients with age mean (± standard-deviation) of 9.81 ± 4.21 years, 19 of whom (79%) in the complex TGA group. Those patients had a higher aortic annulus Z-score. The reoperation rate due to neo-aortic regurgitation associated with aortic dilation was 1.5%, all patients in the complex TGA group.

Conclusion: This study shows that, despite the low incidence of reoperation after Jatene surgery due to neo-aorta dilation and neo-aortic valve regurgitation, that is a time-dependent phenomenon, which requires strict vigilance of the patients. In this study, one of the major risk factors for neo-aortic valve regurgitation was the preoperative pulmonary artery diameter ($p < 0.001$). (Arq Bras Cardiol. 2018; 111(1):21-28)

Keywords: Heart Defects, Congenital; Transposition of Great Vessels; Transposition of Large Vessels, Aortic Valve Insufficiency.

Introduction

Transposition of the great arteries (TGA) has been known for almost 300 years.[1] In 1797, Matthew Baille described a condition in which the aorta originated from the right ventricle and the pulmonary artery, from the left ventricle.[2] In 1814, Farré used the term "transposition" to characterize the malformation described by Baillie. The history of the surgical correction of TGA begins in the 1950s with palliative procedures, progressing to techniques of atrial correction (Mustard/Senning).[3]

The surgical treatment of TGA was modified with the publication of the anatomical correction technique by Adib Jatene[4] in 1976, changing patients' outcome. Throughout the years, thus, the Jatene surgery has been established as the arterial switch operation of choice, with complete physiological and anatomical corrections. Its superiority has been corroborated by long-term results showing the preservation of good left ventricular (LV) function[5] and sinus rhythm, as well as low mortality, with a survival rate over 88% in the 10-to-15-year follow-up.[6]

Complications are not frequent in the immediate postoperative period, being mainly related to the patient's preoperative condition, prolonged cardiopulmonary bypass duration and coronary artery obstruction, with consequent myocardial ischemia. Despite the excellent clinical outcome of most patients in the mid and long run,[5] the rate of late reoperation is significant after the Jatene surgery. The major reasons for reintervention are right ventricular (RV) outflow tract and coronary obstructions and progressive neo-aorta dilation associated with aortic regurgitation. Although technical modifications have determined a significant reduction in reinterventions for RV outflow tract[7] and coronary obstructions,[8] the late progression of neo-aorta dilation and neo-aortic valve regurgitation is of great concern.

This study was aimed at investigating the factors that could contribute to the progression of neo-aortic valve regurgitation by use of a retrospective review of a group of patients who had had surgery at a single institution.

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Methods

From October 1997 to June 2015, 367 patients with TGA were submitted to the Jatene surgery at the Biocor Institute of Cardiovascular Diseases from Minas Gerais, 328 of whom survived and were discharged from the hospital. This observational study was performed from November 2015 to May 2016 at the Biocor Institute as part of a Master's thesis. Of the 328 survivors, 251 were on regular outpatient follow-up, and 127 participated in this study, being divided into two groups based on their anatomical characteristics.

In the simple TGA group, 84 patients with TGA and intact ventricular septum were included.

The complex TGA group included 43 patients with TGA and intermediate to large ventricular septal defect (VSD) and patients with double RV outflow tract without pulmonary stenosis (Taussig Bing), with or without obstruction of the aortic arch.

Patients with the following characteristics were excluded from the study: children with a postoperative period shorter than 2 years (n = 18); patients submitted to ventricular preparation (n = 3); patients submitted to pulmonary artery reduction plasty (n = 27), a technique for patients with great disproportion in the sizes of the neo-aorta and neo-pulmonary artery, which began to be used at the Biocor Institute in 2006; and those who could not attend the consultations (n = 76). Seventy-five patients were lost to follow-up and two had late death.

Preoperative data collection

The medical records were reviewed for collection of pre-, perioperative and immediate postoperative demographic data, such as anatomical characteristics of the defect, age in days and body surface at the time of surgical correction, adjusted pulmonary artery measurement, and presence of associated anomalies.

Postoperative data collection

During postoperative assessment, all patients underwent clinical examination by a pediatric cardiologist of the institution, with weight and height measurement to calculate body surface. Transthoracic echocardiography was performed with no cost to the patient. The Secretariats of Health of the respective municipalities were responsible for the patients' transportation, and when that was not available, this study's author responded to that need. This study was approved by the local Ethics Committee, in accordance with the Declaration of Helsinki, regarding research in human beings. All individuals or their legal guardians provided written consent for this study.

Surgical technique

The Jatene surgery technique used at the Biocor Institute was the same during the entire study period. Lecompte maneuver was used for almost all patients (96%) and coronary reimplantation was performed with the neo-aorta distended and always in the sinuses of Valsalva, never in the suture line ("trap door"). The approach to the VSD varied according to its anatomical location: via the right atrium, aorta or pulmonary artery. Pulmonary reconstruction was performed with autologous pericardium (two patches or monopatch).

Methodology of the echocardiographic study

The echocardiographic study was performed by the author, the pediatric echocardiographer at the Biocor Institute, with a Phillips HD11 device and four sequential measurements of the aorta, quantifying the neo-aortic valve regurgitation grade. Another equally trained echocardiographer performed the same exam, and the measurements were compared.

There was no discrepancy between the echocardiographers regarding the measurements. Thus, no other checking was necessary, because the guidelines regarding measurements are very clear.[9]

Serial measurements of the neo-aortic annulus, sinus of Valsalva, sinotubular region and ascending aorta were taken in the parasternal view of the long axis of the left ventricle and adjusted for body surface, following the American Society of Echocardiography (ASE) guidelines (Figure 1). In accordance with those guidelines, the aortic root was considered to extend from the implantation of the aortic leaflets in the LV outflow tract to the tubular portion of the aorta (sinotubular junction).[9]

The aortic root is a geometrically complex structure that includes: (1) aortic valve annulus; (2) interleaflet triangles; (3) semilunar aortic leaflets and their attachments; (4) sinuses of Valsalva; (5) sinotubular junction.[10]

The aortic measurements were taken at the following sites: (1) aortic valve annulus; (2) maximum diameter of the sinus of Valsalva; (3) sinotubular junction (usually a well-defined transition between the sinuses of Valsalva and the tubular portion of the ascending aorta); (4) maximum diameter of the proximal ascending aorta, recording the distance between the measurement site and the sinotubular junction.[9]

The measurements of the aortic annulus, sinus of Valsalva, sinotubular region and ascending aorta were adjusted by using the Z-score.[11,12] Similarly, the measurements of the aortic annulus were taken in accordance with the ASE recommendations.[9] Thus, they were taken in the zoom mode, in mid systole, when the annulus is slightly larger and rounder than in diastole, between the hinging points of the aortic valve leaflets (usually between the hinging point of the right coronary leaflet and the border of the sinus at the side of the commissures between the left coronary leaflet and the noncoronary leaflet) in its internal border. In accordance with the ASE recommendations, all other aortic measurements were taken at the end of diastole, along a strictly perpendicular plane to the long axis of the aorta.[9]

The neo-aortic valve regurgitation was assessed on color Doppler echocardiography and quantified as absent or trivial, mild, moderate and severe, depending on the relationship between the regurgitating jet and the LV outflow tract diameter.[13] If that relationship was smaller than 0.25, the regurgitation was quantified as mild; if between 0.25 and 0.5, moderate; and if higher than 0.5, severe. However, considering the possibility of underestimating the regurgitation grade in patients with aortic annulus dilation, the flow in the descending aorta was analyzed by use of Doppler echocardiography. In the presence of holodiastolic flow reversal in the descending aorta, regurgitation was considered moderate or severe.[14]

The regurgitation grade was compared to the neo-aorta diameter in its respective measurements.

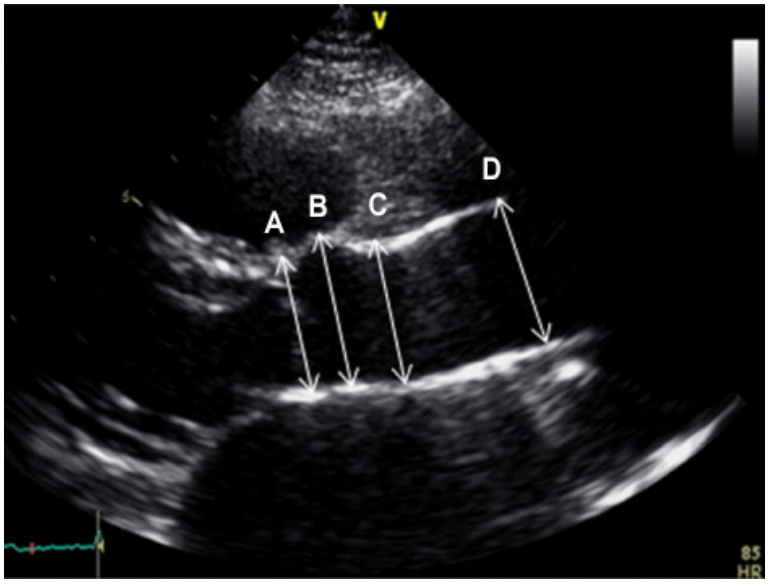

Figure 1 – *Measurements of the aorta. Two-dimensional echocardiogram of the neo-aorta, parasternal view of the long axis of the left ventricle. The measurement sites are shown: A- aortic annulus; B- sinus of Valsalva; C- sinotubular region; D- ascending aorta.*

The body surface was calculated by using the Mosteller formula: A = √ (height x weight) / 3600).[15]

Statistical analysis

The Epi Info software, version 6, was used for data collection and database management. The Epi Info and Microsoft Office Excel, version 2000 were used for the statistical analyses, the latter being also used to elaborate and edit the tables.

The categorical variables were compared by using Pearson chi-square and Fisher Exact tests, when necessary. To compare the means of continuous variables, Student *t* test was used for independent samples when the distribution was normal, paired *t* test was used for paired samples, and Kruskal-Wallis test was used to compare the medians.

Analysis of variance (ANOVA) was used to compare several groups of continuous variables at one time.

A p value < 0.05 was adopted for statistical significance.

Results

Analysis of the preoperative characteristics of the simple and complex TGA groups

Table 1 shows the following pre- and perioperative characteristics of the two groups: sex, body surface, age and pulmonary annulus adjusted to body surface.

Of the 127 patients assessed, 84 were in the simple TGA group and 43, in the complex TGA group. The follow-up duration was 7.4 ± 4.7 years.

The body surface means were 0.20 ± 0.04 m^2 and 0.21 ± 0.08 m^2 for the simple TGA and complex TGA groups, respectively.

When comparing the preoperative Z-score of the pulmonary annulus (Table 1), the complex TGA group had the highest Z-score, a finding of statistical significance.

Table 2 shows the associated anomalies found in 21 patients (16.5%), the most frequently one being the aortic arch anomaly, identified in 7 patients (5.5%), 6 of which in the complex TGA group.

Analysis of the postoperative characteristics of the simple TGA and complex TGA groups

Analysis 2.1 - Table 3 shows that the mean ages for the simple TGA group and the TGA with VSD group were 6.4 ± 4.73 years and 9.26 ± 4.22 years, respectively.

Analysis 2.2 - Table 4 compares the preoperative Z-score mean of the pulmonary artery with the postoperative Z-score mean of the neo-aorta of 84 patients in the simple TGA group and 43 patients in the complex TGA group, showing a statistically significant difference between the means.

Analysis 2.3 - Table 5 shows no or trivial neo-aortic valve regurgitation in 74 patients of the simple TGA group (88%) and in 16 patients of the complex TGA group (37.2%). Mild regurgitation was observed in 5 patients of the simple TGA group (5.9%) and in 8 patients of the complex TGA group (18.6%). Moderate regurgitation was identified in 5 patients of the simple TGA group (5.9%) and in 19 patients of the TGA with VSD group (44.8%). Absent or trivial regurgitation predominated in the simple TGA group ($p < 0.0001$).

Analysis 2.4 - In patients with no or trivial regurgitation (90 patients), the aortic annulus Z-score mean ± standard-deviation was 1.72 ± 0.98 cm. In patients with mild regurgitation (13 patients), the Z-score mean ± standard-deviation was 2.18 ± 0.83 cm, and, in those with moderate

Table 1 – Means, standard deviations and medians of the patients of the simple TGA and complex TGA groups submitted to Jatene surgery

Variables	n	Mean ± standard-deviation	Median	Statistical test
Sex				
Simple TGA				
Male	60			Chi-square = 0.83
Female	24			
Complex TGA				
Male	30			
Female	13			
Body surface				
Simple TGA	84	0.20 ± 0.04 m^2	0.20	p = 0.86
Complex TGA	43	0.21 ± 0.08 m^2	0.20	
Pulmonary annulus Z-score				
Simple TGA	84	1.6 ± 0.6	0.2 ± 0.3	p = 0.18
Complex TGA	43	1.9 ±1.1	0.3 ± 0.4	

(*) Statistically significant difference. TGA: transposition of the great arteries.

Table 2 – Associated anomalies in the simple TGA and complex TGA groups

Associated anomalies (n = 21)	Simple TGA	Complex TGA
Dextrocardia *situs solitus*	2	0
Dextrocardia *situs inversus*	0	1
Juxtaposition of atrial appendages	3	1
L-position of the aorta	0	3
Tricuspid straddling	0	2
Superoinferior ventricle	0	2
Aortic arch anomalies	1	6
TOTAL	6	15

TGA: transposition of the great arteries.

Table 3 – Means and standard deviations of the ages of the patients of the simple TGA and complex TGA groups at the time of control

Variables	n	Mean ± standard deviation	Statistical test	P value
Age in control				
Simple TGA	84	6.40 ± 4.73 anos	Student *t* test	< 0.0001
Complex TGA	43	9.26 ± 4.22 anos		(*)

**t = 3.34. TGA: transposition of the great arteries.*

regurgitation (24 patients), 2.60 ± 1.40 cm. The results show that, the larger the aortic annulus, the higher the regurgitation grade ($p < 0.001$).

Analysis 2.5 - Table 7 shows that patients submitted to the Jatene surgery with a moderate neo-aortic valve regurgitation had a higher age mean ($p=0.0145$). Of the 127 patients studied, 2 patients in the complex TGA group required valve change because of regurgitation progression during data collection, the reoperation rate being 1.5%.

Discussion

Reintervention due to neo-aortic valve regurgitation after Jatene surgery was first reported in 2009 in a 16-year-old adolescent.[16] That report concluded that neo-aorta dilation was present in two thirds of the patients and that moderate regurgitation was observed in 15%, emphasizing the need for careful follow-up in that group of patients.

Although the overall incidence of the surgery for neo-aorta dilation and neo-aortic valve regurgitation after Jatene surgery

Table 4 – Comparison between the preoperative Z-score mean of pulmonary artery and the postoperative Z-score mean of aortic annulus of the simple TGA and complex TGA groups

Z-score (Complex TGA)	Mean ± standard-deviation	Difference between the means	Paired *t* test	P value
Pre	1.9 ± 1.1	-0.3 ± 0.4	4.88	< 0.0001
Post	2.2 ± 1.3			
Z-score (Simple TGA)	**Mean ± standard-deviation**	**Difference between the means**	**Paired *t* test**	**P value**
Pre	1.6 ± 0.7	-0.2 ± 0.3	4.81	< 0.0001
Post	1.8 ± 1.0			

**p < 0.0001. TGA: transposition of the great arteries.*

Table 5 – Assessment of the neo-aortic valve regurgitation grade of 127 patients of the simple TGA and complex TGA groups submitted to Jatene surgery

Groups	Absent/trivial regurgitation	Mild regurgitation	Moderate regurgitation	Total
Simple TGA	74 (82.2%)	5 (38.4%)	5 (20.8%)	84
Complex TGA	16 (17.7%)	8 (61.5%)	19 (79.1%)	43
Total	90 (70.8%)	13 (10.2%)	24 (18.9%)	127

Chi-square = 34.85; p < 0.0001. TGA: transposition of the great arteries.

Table 6 – Z-score means of the aortic annulus according to the regurgitation grade in the postoperative follow-up of 127 patients submitted to Jatene surgery

Regurgitation grade	n	Mean ± standard-deviation	Analysis of variance	F
Absent/trivial	90	1.72 ± 0.98 cm		
Mild	13	2.18 ± 0.83 cm	F	6.66
Moderate	24	2.60 ± 1.40 cm		

F = 6.6

Table 7 – Age means at the control times according to the neo-aortic valve regurgitation grade during the follow-up of 127 patients submitted to Jatene surgery

Regurgitation grade	n	Mean ± standard-deviation	Analysis of variance	F
Absent/trivial	90	7.08 ± 4.74 anos		
Mild	13	5.60 ± 4.16 anos	F	5.4
Moderate	24	9.81 ± 4.21 anos		

F = 5.4

in 10 years is still low (2-2.5%),[6,16-19] several authors have reported that the development of neo-aorta regurgitation and dilation is a time-dependent phenomenon, requiring a strict vigilance of the patients.[6,20,21] McMahon et al.[22] have found a moderate enlargement in the neo-aortic root (Z-score between 3 and 4) in 52% of the patients, and a severe enlargement of the neo-aortic root (Z-score > 5) in 25%. In addition, those authors have shown that the development of significant neo-aortic valve regurgitation strongly associated with the development of neo-aorta dilation, which has been confirmed by other authors.[23] Schwartz et al.[24] have concluded that, after Jatene surgery, neo-aortic root dilation and neo-aortic valve regurgitation continue to develop over time, but aortic root dilation does not tend to be progressive during late follow-up. However, in that series, the last follow-up was up to 16 years, while Walter et al.[19] have concluded that neo-aortic regurgitation can develop in up to 15 years. In our sample, two patients required reintervention for progressive neo-aortic root dilation associated with neo-aortic regurgitation in a follow-up of 9.81 ± 4.21 years. Some studies have shown the significance of several risk factors to the development of late neo-aortic valve regurgitation and aortic root dilation, such as preoperative pulmonary artery dilation, patient's age over one year at the

time Jatene surgery is performed, and presence of VSD and complex TGA,[6,18-21] but such findings could not be repeated in some other large series.[8,23] In our series, as in others,[6,21,23] we observed that the most relevant factor for neo-aortic regurgitation was the great disproportion in the sizes of the neo-aorta and neo-pulmonary artery at the time of surgery, which was present in the complex TGA group, especially when aortic arch anomalies were associated.

In addition, the VSD found in the complex TGA group is related to two factors that increase the risk for developing valvular regurgitation, pulmonary root dilation and pulmonary artery pressure elevation, which can change the arrangement of the muscle fibers and generate permanent disarrangement of the pulmonary artery, even after anatomical correction.[25]

The presence of neo-aortic valve regurgitation in patients without risk factors, such as simple TGA, can be explained in histopathological studies revealing a reduction in the amount of collagen in the arterial roots in hearts with TGA as compared to that of normal hearts, in addition to less extensive anchorage and embedding of both arterial roots in the myocardium.[26] The pulmonary root dilation can be compared to that observed after the Norwood surgery for hypoplastic left heart syndrome,[27] indicating the pulmonary artery included in the systemic circulation is a risk factor per se. From the morphological and histological viewpoints, the pulmonary and aortic valves are indistinguishable at birth. In normal hearts, studies have shown gross and microscopic changes in those valves, probably due to pressure changes resulting from the transition from the fetal to post-natal circulation, resulting in pulmonary valve with thin leaflets, less collagen and a smaller amount of elastic tissue. After surgical repair, the more delicate valve is integrated into the systemic circulation and can be damaged by the high-pressure regime.[27]

Briefly, the etiology of neo-aortic valve regurgitation and neo-aorta dilation is very likely multifactorial. In addition to external risk factors, there are intrinsic structural problems of the pulmonary root integrated into the systemic circulation. Thus, according to our clinical observations, the increase in the number of surgical interventions to treat aortic root dilation and neo-aortic valve regurgitation should be the reason for the constant monitoring of patients with or without additional risk factors.

The present study, similarly to others,[21-23] showed that the most relevant factor for neo-aortic valve regurgitation was the disproportion in the sizes of the neo-aorta and neo-pulmonary artery at the time of surgery, which was present in the complex TGA group, especially when associated with aortic arch anomalies.

Conclusion

In the present study, the complex TGA group had a higher preoperative pulmonary artery Z-score as compared to that of the simple TGA group, and a higher incidence of associated anomalies, such as aortic arch anomalies ($p = 0.0064$). In addition, the neo-aorta dilation is maintained in the postoperative period.

Our results showed that the larger the aortic annulus, the higher the regurgitation grade ($p < 0.001$). In addition, moderate regurgitation was associated with a higher mean age ($p = 0.0145$) in both simple TGA and complex TGA groups, indicating the need for the constant monitoring of the patients.

Limitation

The present retrospective study results from the data collection of two groups of patients with distinct anatomical characteristics, submitted to the same surgical technique.

Some variations related to the presence of aortic regurgitation in the long run reported by other authors (techniques of coronary reimplantation, VSD closure and previous pulmonary artery cerclage) were not approached in this study.

Author contributions

Conception and design of the research and Writing of the manuscript: Martins CN, Gontijo Filho B, Lopes RM, Lima e Silva FC; Acquisition of data: Martins CN; Analysis and interpretation of the data: Martins CN, Gontijo Filho B, Lima e Silva FC; Statistical analysis: Martins CN, Lima e Silva FC; Critical revision of the manuscript for intellectual content: Martins CN, Gontijo Filho B, Lima e Silva FC.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto de Ensino e Pesquisa Santa Casa-BH under the protocol number 7.345. 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.

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The Economic Burden of Heart Conditions in Brazil

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Abstract

Background: Heart conditions impose physical, social, financial and health-related quality of life limitations on individuals in Brazil.

Objectives: This study assessed the economic burden of four main heart conditions in Brazil: hypertension, heart failure, myocardial infarction, and atrial fibrillation. In addition, the cost-effectiveness of telemedicine and structured telephone support for the management of heart failure was assessed.

Methods: A standard cost of illness framework was used to assess the costs associated with the four conditions in 2015. The analysis assessed the prevalence of the four conditions and, in the case of myocardial infarction, also its incidence. It further assessed the conditions' associated expenditures on healthcare treatment, productivity losses from reduced employment, costs of providing formal and informal care, and lost wellbeing. The analysis was informed by a targeted literature review, data scan and modelling. All inputs and methods were validated by consulting 15 clinicians and other stakeholders in Brazil. The cost-effectiveness analysis was based on a meta-analysis and economic evaluation of post-discharge programs in patients with heart failure, assessed from the perspective of the Brazilian Unified Healthcare System (Sistema Unico de Saude).

Results: Myocardial infarction imposes the greatest financial cost (22.4 billion reais/6.9 billion USD), followed by heart failure (22.1 billion reais/6.8 billion USD), hypertension (8 billion reais/2.5 billion USD) and, finally, atrial fibrillation (3.9 billion reais/1.2 billion USD). Telemedicine and structured telephone support are cost-effective interventions for achieving improvements in the management of heart failure.

Conclusions: Heart conditions impose substantial loss of wellbeing and financial costs in Brazil and should be a public health priority. (Arq Bras Cardiol. 2018; 111(1):29-36)

Keywords: Cardiovascular Diseases/economics; Hypertension; Heart Failure; Myocardial Infarction; Atrial Fibrillation.

Introduction

Heart conditions impose physical, social, financial and health-related quality of life limitations on individuals. These conditions result in an economic burden and impact on society due to expenditures on healthcare treatment, productivity losses from employment impacts, costs of providing formal and informal care, and lost wellbeing. Circulatory diseases presently represent the biggest health burden worldwide, accounting for over 17 million deaths every year; this represents half of all noncommunicable disease deaths.[1]

At the 2016 World Congress of Cardiology & Cardiovascular Health, the Mexico Declaration for Circulatory Health was signed by leading global organisations committed to improving circulatory health and reducing deaths and disability from heart diseases and stroke around the world. This is aligned with a clear target, set by the World Health Organization (WHO) and signed by country signatories, of reducing deaths from noncommunicable disease by 25 per cent by 2025.[1] Our analysis identifies the current burden heart conditions have on Brazil and consequently the potential economic benefits that could result from addressing it.

This study aims to assess the economic (health system and productivity) impact of four heart conditions in Brazil, providing estimates of the annual cost for the year 2015: hypertension (HTN), myocardial infarction (MI), atrial fibrillation (AF) and heart failure (HF). This study also analyzes the cost-effectiveness of two interventions for HF: telemedicine (TM) and structured telephone support (STS).

Method

This research is part of a larger study of the Latin American region, with country-specific results also identified for Mexico, Chile, Peru, Venezuela, Colombia, Ecuador, Panama and El Salvador. These results for Brazil were presented at ISPOR Vienna (November 2016) and the World Cardiovascular Congress (June 2016).

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Cost of illness

The analysis was based on estimating the prevalence, incidence, loss of wellbeing, health system and productivity losses attributed to the four heart conditions. Total cost estimates were adjusted based on the comorbidity between conditions. Underpinning the study was a literature search that used search terms associated with the country, region, epidemiology and economic impact of the four heart conditions. Sources included PubMed, government, healthcare and patient organization websites, and general internet search engines.

Prevalence/incidence of conditions

The sources used for estimating the prevalence or incidence are outlined in Table 1. Whenever possible, Brazil specific rates were used. All estimates were checked with stakeholders interviewed for the project. Identified rates were applied to projections from the United Nations World Population Prospects.[2]

Loss of wellbeing

Disability weights were based on the WHO Global Burden of Disease studies[3,4] as shown in Table 2. These were then multiplied by the prevalence estimates to identify the years lost to disability for 2015. Years lost to life were based on reported mortality for each condition.

Health system costs

The discharges and average length of stay for each of the conditions[5] were combined with cost estimates for each of the four condition categories[5] to estimate each condition's burden on the health system as a share of all conditions treated. This was then combined with an estimate of total relevant health expenditure for Brazil[6] to result in the cost of treating each of the four conditions. Health costs were estimated from the perspective of health care payers, i.e. both public and private payers. Cost breakdowns were based on those reported for Brazil.[7] This method allows us to reflect most appropriately the impacts based on the number, length of stay and cost intensity of each condition for Brazil specifically. However, data on condition-specific health expenditures are not available for other components of the health system (e.g. primary care). Accordingly, each condition's share of total health system expenditure was assumed to be the same as its share of total hospital expenditure.

Productivity losses

Consistent with the 'full or near-full employment' criterion,[a] a human capital approach to the estimation of productivity losses was adopted. Calculations involving productivity losses were based on employment rates by age-gender groups. It was assumed that those with heart conditions were, in the absence of the condition, as likely to be employed as others in their corresponding age-gender group. Forgone wage income was based on wage data for Brazil.[7]

Absenteeism was associated with all of the conditions. For HF it was estimated as 12.66 days for those with NYHA III/IV and 3.04 days per year for those with NYHA I/II.[8] Absenteeism was estimated as 3.03 days per year[8] for HTN, 75 days per year for those admitted to hospital[9] with MI, and 2.1 days per year[10] for AF. Reduced employment participation, where individuals are no longer able to be employed due to their condition, was identified for both HF and MI, but not for AF or HTN. For HF, there was 13% lower employment participation rate (based on those with coronary heart disease).[11] The study also showed increased withdrawal of unemployed people from the labor force, especially those aged below 60 years and those engaged in manual work. For MI, there was a 21% lower employment participation [based on those with acute coronary syndrome (ACS) five years after an event].[12] As the lower employment participation rates in both the coronary heart disease and ACS studies were based on populations in developed countries, these rates were adjusted by the observed rates of reduced employment participation for those with disability in Europe and Latin America, as reported by the Organization for Economic Cooperation and Development (OECD).[13]

Forgone income due to premature death was based on mortality statistics for each condition and the otherwise expected life expectancy according to WHO life tables.[14] The anticipated number of years of life left to live by the deceased individual was multiplied first by employment rates and then by the average weekly wage for men and women respectively. The productivity discount rate for future earnings was 5.25% based on the difference between wage growth and inflation (using the annualized average for both over the past five years). The present value of future wages was based on the five-year average real growth rate.[15]

Informal care costs were identified for both HF and MI. For HF, each individual was provided an estimated 6.7 hours of informal care per week.[16] While there are a variety of sources

Table 1 – Number of people with the four heart conditions in Brazil, 2015

Condition	Number of people	Percentage of the adult population*
HF	2 845 722	2.0
MI	334 978	0.2
AF	1 202 151	0.8
HTN	44 526 201	31.2
Total conditions	48 909 052	34.3
Total persons with any condition (i.e. accounting for comorbidities)	45 658 048	32.0

*: *Percentage reflects the evidence from studies among populations aged 20 years and over. HF: heart failure; MI: myocardial infarction; AF: atrial fibrillation; HTN: hypertension.*

[a] The ILO reports the unemployment rate for Brazil at 6.8% in 2014 (the most recent year it was reported)

Table 2 – Financial cost of heart conditions in Brazil, 2015 (millions of reais)

Category	HF	MI	AF	HTN	Total (unadjusted)	Total (adjusted for comorbidities)^
Health system costs	14 469	16 119	3 697	1 098	35 382	35 382
	65%	72%	94%	14%	63%	63%
Productivity losses	7 663	6 257	225	6 927	21 071	20 858
	35%	28%	6%	86%	37%	37%
Income forgone by individuals*	3 528	4 540	156	2 063	10 287	10 196
	16%	20%	4%	26%	18%	18%
Income forgone by businesses*	333	403	31	4 378	5 145	5 050
	2%	2%	1%	55%	9%	9%
Opportunity cost of informal care by family/friends	2 404	196			2 600	2 596
	11%	1%			5%	5%
Tax revenue forgone by government**	1 399	1 117	37	486	3 039	3 016
	6%	5%	1%	6%	5%	5%
Total cost	22 132	22 375	3 921	8 025	56 454	56 241

*Results in millions of reais. *: The result from absenteeism, reduced employment participation, and premature mortality. **: Due to reduced income of individuals with heart conditions and their carers. ^: Comorbidity totals do not sum to the total of the individual conditions as one person can have more than one condition and the interaction between conditions causes the total estimate of the four conditions together to vary. HF: heart failure; MI: myocardial infarction; AF: atrial fibrillation; HTN: hypertension.*

for this parameter, the study chosen was the most robust methodologically and provided a similar estimate to what could be derived from a study in Latin America.[17] For MI, based on a study of coronary heart disease patients, informal care hours were estimated to be 279 hours per year per patient.[18]

Taxation revenue foregone was based on the average income tax rate for a single individual and the average indirect tax rate according to the OECD.[19,20] The estimated income tax liability was applied to the estimated total value of forgone earnings to determine the value of taxation lost. An adjustment was also applied for the number working in the 'informal economy' which is likely to reduce the taxation revenue collected. Exchange rates between USD and the local currency were based on the average of the daily exchange rates from the International Monetary Fund from January 2015 to November 2015.

Comorbidities

As multiple conditions could affect one person simultaneously, the total cost of the four conditions was estimated by reviewing literature[21-23] that identified the number of individuals with two, three or four concomitant conditions as outlined in Figure 1. Where literature did not outline the concomitant rates between each of the four conditions, the sources were extrapolated until all combinations were derived.

Cost-effectiveness analysis for HF

To undertake the analysis, a targeted literature review was carried out to identify either published cost-effectiveness studies which could be adapted to the Brazilian context, or literature which could inform the design of, and inputs to, a cost-effectiveness model. The review identified a relatively recent network meta-analysis and cost-effectiveness analysis of TM and STS programs after discharge in patients with HF, conducted by the National Institute for Health Research in 2013.[24] This study was therefore used as the basis for a cost-effectiveness analysis of STS and TM from the perspective of the Sistema Unico de Saude.

Model structure

A Markov model was constructed in TreeAge Pro©2015 to evaluate the cost-effectiveness of STS and TM compared with standard care (SC) for a hypothetical cohort of patients discharged in the last 28 days following HF-related hospitalizations. The model as shown in Figure 2 considered two different permanent health states, 'alive at home' and 'dead' as well as two temporary health states for 'hospitalized due to HF' and 'hospitalized for all other causes'. The model is based on monthly cycles with half-cycle corrections.

Time horizon, duration and discount rate

As HF is a life-long condition after onset, the model captured a lifetime horizon of 30 years with patients progressing through the model until they either died or reached the end of the 30-year time horizon. It was assumed that the interventions of STS, TM and SC were provided for the full duration of the time horizon, outside of hospitalization. Both health system costs and quality-adjusted life-years (QALYs) were discounted at an annual rate of 5%.

Data sources

Efficacy estimates

The monthly probability of death with SC following a non-fatal hospitalization was based on data from the CHARM study,[25] which followed 7,572 patients for a period of

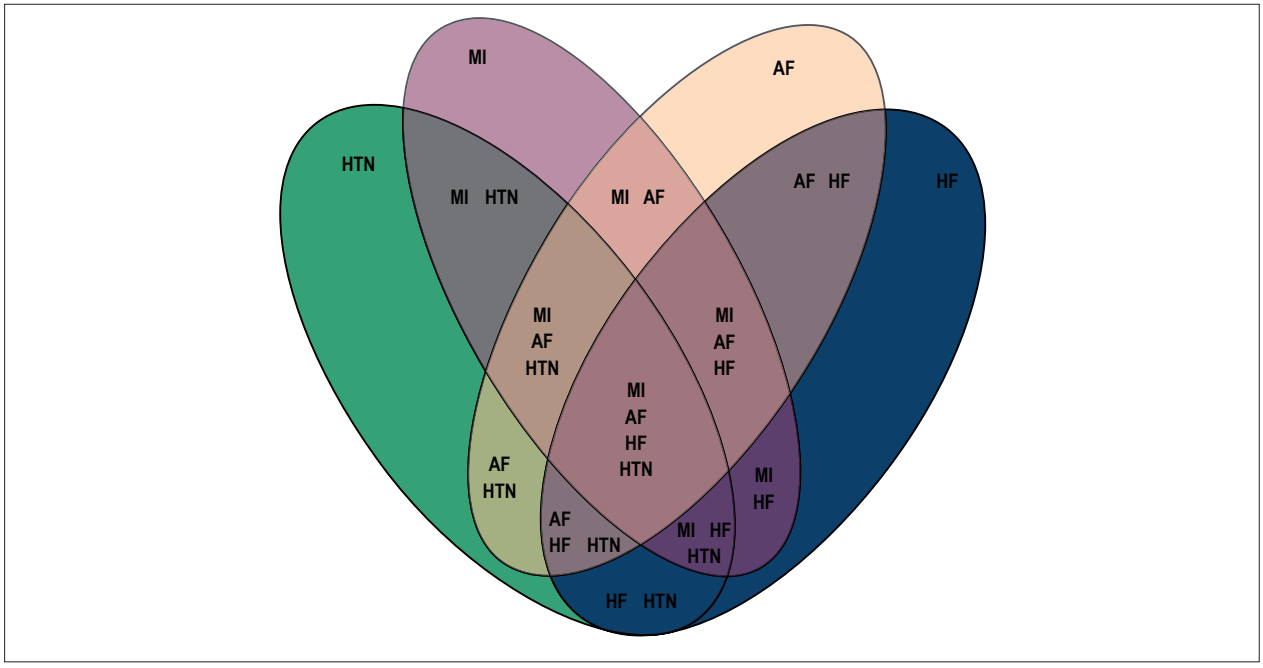

Figure 1 – *Potential comorbidity combinations accounted for. HF: heart failure; MI: myocardial infarction; AF: atrial fibrillation; HTN: hypertension.*

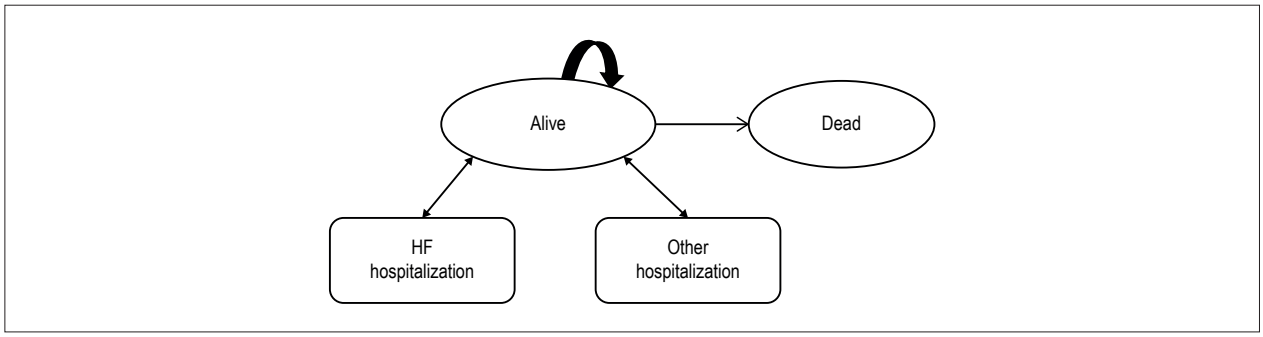

Figure 2 – *Markov model for recently discharged heart failure (HF) patients.*

38 months and showed the mortality risk to be the highest after hospital discharge, then decreasing over time. The mean number of HF-related and other (all cause) hospitalizations were based on a published meta-analysis[26] and estimated by the National Institute for Health Research.[24]

Effectiveness parameters relating to risks of death and hospitalization for STS and TM interventions were based on the hazard ratios for all-cause mortality, all-cause hospitalizations and HF-related hospitalizations during the treatment period. The hazard ratios were estimated from the network meta-analysis by the National Institute for Health Research.[24]

Health state utilities

Health state utilities for SC, STS and TM treatment approaches were based on the previous economic model of TM strategies conducted in a published meta-analysis,[26] which used utilities of 0.612 and 0.662 for SC and STS/TM groups, respectively. As with previous economic analyses, a negative adjustment of 0.1 was applied to account for the disutility associated with HF-related hospitalizations.[24]

Resource utilization and costs

STS and TM consist of three main units of healthcare resources:

- devices and equipment within the patient's home, which include the device hub, peripherals and communication costs;
- maintenance/monitoring in the STS or TM center; and
- medical care units to deal with events or alerts, such as GP or nurse visits, or hospital-based outpatient visits.

The units of resources making up the components of SC, STS and TM were based on the published literature, and unit costs were obtained from DATASUS, the Brazilian Ministry of Health's data department.

Results

Cost of illness for heart failure, myocardial infarction, atrial fibrillation and hypertension

The four heart conditions were estimated to affect approximately 45.7 million people in Brazil, 32.0% of the adult[b] population. After adjusting for comorbidities, heart conditions were conservatively estimated to result in a financial cost of 56.2 billion reais (17.3 billion USD) in 2015 in Brazil. Of this, approximately 62.9% was health system cost. In 2015, the burden of these four conditions comprised approximately 5.5% of total national healthcare expenditure.

Prevalence/incidence

HTN has the highest prevalence of the four conditions, followed by HF. As outlined in Table 1 there were 48.9 million conditions affecting 45.7 million people (some people have more than one condition).

Economic impact

MI imposes the greatest financial cost, followed by HF, HTN and, finally, AF. Table 2 outlines the cost per condition by bearer of cost, demonstrating that each condition impacts individuals, government and society differently. Health costs make up the majority of expenditure for HF, MI and AF, reflecting the nature of Brazil's health system.

Table 3 shows that HTN has the lowest cost per case and MI the highest. While the costs per case seem quite small for HTN, they reflect the total cost of the condition divided by the total number of people with the condition; whether they are receiving treatment or not. This per person cost should be considered in this 'average' context, rather than reflecting the actual health costs incurred for someone receiving treatment.

Loss of wellbeing

In addition, the heart conditions included impose a substantial wellbeing loss as outlined in Table 4. Of the 3.2 million disability adjusted life years (DALYs), adjusted for comorbidities, there are 1.9 million healthy years lost due to disability (YLD) and over 1.3 million years of life lost due to premature mortality (YLL).

Cost-effectiveness analysis for heart failure

Base case result

Over the 30-year time horizon, the estimated discounted cumulative costs for the TM and STS interventions were 50,098 and 44,038 reais higher than SC, respectively, but generated an additional 1.91 and 1.63 QALY, respectively. This resulted in an estimated incremental cost-effectiveness ratio (ICER) of 26,437–81,984 reais/QALY and 27,281 reais/QALY for TM and STS, respectively, compared to SC, noting a willingness to pay (WTP) threshold of 27,328 reais/QALY. The threshold was based on one to three times the GDP per capita of Brazil.[6c] The incremental net monetary benefit was 1,688 reais for TM vs SC and 77 reais for STS vs SC (Table 5).

Table 3 – Financial cost of heart conditions in Brazil per case, 2015 (reais)

	HF	MI	AF	HTN
Health system cost per case	5 085 (65%)	48 118 (72%)	3 075 (94%)	25 (14%)
Productivity cost per case	2 693 (35%)	18 678 (28%)	187 (6%)	156 (86%)
Total financial cost per case	7 777	66 797	3 262	180

HF: heart failure; MI: myocardial infarction; AF: atrial fibrillation; HTN: hypertension.

Table 4 – Loss of wellbeing of heart conditions in Brazil, 2015

Condition	YLDs	YLLs	DALYs
HF	270 806 (14%)	251 136 (18%)	521 941 (16%)
MI	2 128 (0.1%)	1 112 469 (80%)	1 114 597 (34%)
AF	269 014 (14%)	28 237 (2%)	297 251 (9%)
HTN	1 380 312 (72%)		1 380 312 (42%)
Total (unadjusted)	1 922 260	1 391 842	3 314 102
Total (adjusted for comorbidities)^	1 901 386	1 340 453	3 241 838

HF: heart failure, MI: myocardial infarction, AF: atrial fibrillation, HTN: hypertension. ^: Comorbidity totals do not sum to the total of the individual conditions as one person can have more than one condition and the interaction between conditions causes the total estimate of the four conditions together to vary. YLDs: years lost due to disability; YLLs: years of life lost due to premature mortality; DALYs: disability-adjusted life-years.

[b] Percentage reflects the evidence from studies among populations aged 20 years and over.

[c] As promoted by the WHO Choosing Interventions that are Cost-Effective project, an intervention that costs less than three times the national annual GDP/capita is considered cost-effective, whereas one that costs less than once the national annual GDP/capita is considered highly cost-effective.

Table 5 – Base case result

	SC	TM	STS
Total costs (reais)	5 832	55 930	49 870
Total QALYs	3.99	5.89	5.61
Net monetary benefit	103 306	104 994	103 382
Incremental costs (reais)		50 098	44 038
Incremental QALYs		1.89	1.61
Incremental cost (reais) per QALY		26 437	27 281
Incremental net monetary benefit		1 688	77

QALY: quality-adjusted life-year; SC: standard care; TM: telemedicine; STS: structured telephone support.

Multivariate sensitivity analysis

An alternative multivariate scenario analysis was carried out where the costs of TM and STS were varied as well as the health state utilities. In this scenario, the costs of the interventions were increased by 20% and the health state utilities for health states for the strategies were assumed to be the same as those for SC. The results of this scenario analysis are presented in Table 6, which shows that the ICER increases from 26,437 to 41,123 reais/QALY for TM vs SC, and increases from 27,281 to 40,309 reais/QALY for STC vs SC.

Assuming a WTP threshold of 27,328- 81,984 reais/QALY as above, the cost-effectiveness analysis suggests that TM and STS may be cost-effective treatment options for the management of patients with HF.

Discussion

Our analysis provides the inaugural estimate on the cost of the four conditions across Brazil. By analysing four conditions concurrently in a common framework, we were able to identify the total impact and the impacts of the conditions relative to each other. We have identified that, while MI has significant acute care costs, it does not have as significant informal care costs as HF or HTN. Conversely, HF, while not having as significant acute care costs as MI, has significant productivity losses. While HTN has a low health cost per person, it has a significant total cost due to the large number of people with the condition. Our analysis demonstrates that these conditions can have a large productivity and wellbeing impact beyond their health system costs, which is an important finding from a societal perspective. If policymakers focus only on health costs of a condition, or the relative cost of care per person, they may miss the broader impact that these conditions have across the economy, and the true cost once other fiscal impacts are taken into account.

While the study has focused on using administrative datasets for health costs, as they are more likely to be reflective of cost allocation by payers, the datasets themselves may not reflect real costs for each condition. For example, the coding and reporting of conditions is subject to clinicians' individual judgement in nominating the underlying cause, active condition, or chronic condition as the primary condition, and this choice can change the reporting of attributable impacts. A systematic review and meta-analysis of administrative databases for HF identified that datasets do not capture a quarter of cases,[27] while a systematic review of electronic medical data for AF identified that there was a disproportionate focus on inpatient data and additional research incorporating outpatient codes, and electrocardiogram data are required to correctly identify the presentations of AF.[28] Therefore, while the costs reported are reflective of current clinical judgement and administrative reporting, the cost allocation attributable to each condition can continue to be improved.

In attributing the relative severity of conditions, their treatment and the impact on related conditions should be considered. Treatment of one of these conditions could alleviate the future development of another costed condition, and the detailed relationships between conditions are still being established. For example, while HTN is understood to be a common risk factor for heart conditions, there is a growing body of evidence that suggests AF is associated with MI.[29] Therefore, addressing AF could alleviate future cases of MI and the corresponding cost attributed to MI.

The primary limitation in this study was comprehensive data availability. There are three key assumptions in the methodology that had to be made and could impact the results, which the reader should keep in mind. First, our health cost estimates are driven by reported hospital statistics for each of the conditions. This is likely to be more appropriate for conditions that have significant acute care management (e.g. MI), but it may under-represent the true cost of conditions that have a greater emphasis on primary care or pharmaceutical management, such as HTN. Second, common to all productivity estimates using a human capital approach, the unemployment rate for Brazil may or may not be sufficiently low to incur a permanent productivity loss. A loss in productivity due to heart conditions from a societal perspective will only equate to a loss in productivity to the economy under the condition that the economy is at the non-accelerating inflation rate of unemployment, so any reduction in hours worked due to illness cannot be replaced in the longer term by employing or increasing hours of other substitute workers. Thirdly, although TM and STS were found to provide beneficial effects in reducing all-cause mortality for recently discharged HF patients, in the original study,[24] these results were statistically inconclusive. While this uncertainty around estimates was assessed in the sensitivity analysis, these strategies will need to be re-examined as new evidence emerges.

Table 6 – Multivariate sensitivity analysis

	SC	TM	STS
Total costs (reais)	5,832	68 891	58 538
Total QALYs	3.99	5.45	5.30
Incremental costs (reais)		60 059	52 706
Incremental QALYs		1.46	1.31
Incremental cost (reais) per QALY		41 123	40 309

QALY: quality-adjusted life-year; SC: standard care; TM: telemedicine; STS: structured telephone support.

Conclusion

This study has found that heart conditions impose significant financial and wellbeing impacts across Brazil, with the four conditions costing $56.2 billion reais in 2015 alone. Prevention or better management of heart conditions could result in significant benefits both in improved wellbeing and economic savings. Telemedicine and structured telephone support are cost effective mechanisms for achieving improvements in the management of heart failure.

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The authors at Deloitte Access Economics designed the study, collected data, performed analysis and wrote the initial draft of the manuscript. All authors read, commented on, and approved the final manuscript. This research is part of a larger study of the Latin American region, with country specific results also identified for Mexico, Chile, Peru, Venezuela, Colombia, Ecuador, Panama and El Salvador. These results for Brazil were presented at ISPOR Vienna (November 2016) and the World Cardiovascular Congress (June 2016).

Author contributions

Conception and design of the research: Stevens B, Pezzullo L, Verdian L; Acquisition of data: Stevens B, Tomlinson J; Analysis and interpretation of the data: Stevens B, Pezzullo L, Verdian L, Tomlinson J; Statistical analysis: Stevens B, Tomlinson J; Obtaining financing: Pezzullo L; Writing of the manuscript: Stevens B, Verdian L, Tomlinson J, George A; Critical revision of the manuscript for intellectual content: Stevens B, Pezzullo L, Bacal F.

Potential Conflict of Interest

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

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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.

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Economic Burden of Cardiovascular Diseases in Brazil: Are Telemedicine and Structured Telephone Support the Solution?

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Short Editorial regarding the article: The Economic Burden of Heart Conditions in Brazil

The study by Stevens et al.[1] results from a project of Delloite Consulting, financed by Novartis and aimed at estimating the economic burden that heart failure, acute myocardial infarction, atrial fibrillation and systemic arterial hypertension (SAH) impose on Latin American countries, and at assessing the cost-effectiveness of telemedicine and structured telephone support as interventions that can relieve it.[1] The publication in this issue of the *Arquivos Brasileiros de Cardiologia* focused on presenting the results of the assessment in the Brazilian scenario.

This study provided us with the opportunity to reflect on important questions related to quality, interpretation and applicability of economic studies. Such studies have gained increasing relevance in the incorporation/disincorporation of technologies and the development of health policies and programs to improve healthcare quality. In addition, they are often used in other countries to support decision-making processes, although that is not a routine in Brazil.[2]

Several guidelines have been proposed in recent decades to improve the quality of the studies on economic assessment and their usefulness to healthcare systems. The *Consolidated Health Economic Evaluation Reporting Standards* (CHEERS)[3] is a collection of those recommendations, recently updated and published in JAMA,[2] which were only partially followed by Steven et al.

The measures used, for example, derived from sources not clearly indicated by the authors, who seem to have ignored any other related comorbidity besides the four conditions in question, such as stroke and chronic renal failure, as well as the presence or absence of other relevant comorbidities, such as diabetes, indicated by the NHS as one of the ten major causes of permanent disability and of high consumption of health resources currently.[4] In addition, the differences in the levels of severity and heterogeneity between the Brazilian geographic regions seem not to have been considered. The incidence of sequelae and the rate of progression of those conditions resulting in morbidity, deaths and quality of life loss vary according to the intensity of the treatment provided, differing, thus, from region to region.[5-7]

The results reported by the studies in Venezuela[8] and Mexico[9] were neither cited nor discussed by the authors, although the cost-utility measures obtained were identical or very close in the three countries, suggesting that, at least partially, the data used were common to the three assessments.

The cost of primary attention seems to have been inferred from hospital expenditure data, assuming that the costs were equal. However, in at least one systematic review about the economic burden of heart failure, hospital expenditure was at least three times greater than outpatient clinic expenses, including the costs with procedures, tests and medicines.[10]

In addition, the prevalence estimates seem little accurate. According to Picon et al.,[11] the prevalence of SAH has been decreasing by 3.7% every decade in Brazil. In the 1990s, the prevalence of SAH was estimated at 32.9%, while from 2000 to 2010, it was estimated at 28.7%, which would result in an expected prevalence from 2010 to 2020 lower than that observed in the previous decades. The authors started from a prevalence of 31.2% without indicating exactly what was the source of that information.

In the cost-effectiveness analysis, the interventions were not clearly defined, with disagreement between what the study claimed to assess ("telemedicine") and the technology studied by the NHS report, on which the authors claimed to be based ("telemonitoring").[12] Especially for cost-effectiveness studies, depending on the intervention assessed, the results can be diametrically opposed, completely changing the recommendations.

In addition, according to the authors, the healthcare system costs attributable to those four conditions added up to 35 billion *reais* in 2015, which would represent one third of the total budget approved for health by the Brazilian Congress in that same year,[13] suggesting that the estimates presented are overestimated.

Therefore, despite the relevance of the topic, the study by Stevens et al. provides convincing information on neither the burden of the selected diseases nor the cost-effectiveness of telemedicine or structured telephone support for approaching those conditions. The study has important limitations that prevents a clear interpretation of its results, as well as its application in the national scenario in a comprehensive manner.

Keywords

Cardiovascular Diseases; Health Policy; Cost-Effectiveness-Evaluation; Quality Management; Telemedicine/trends; Telephone/trends.

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Adropin and Irisin in Patients with Cardiac Cachexia

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Abstract

Background: Cardiac cachexia is an important predictive factor of the reduction in survival of patients with heart failure with reduced ejection fraction.

Objectives: To evaluate adropin and irisin levels in cachectic and non-cachectic subjects and the relationships between the levels of these proteins and clinical and laboratory parameters in patients with HFrEF.

Methods: The clinical records of patients who were admitted to the cardiology outpatient clinic for heart failure with reduced ejection fraction were screened. Cachectic patients were identified and assigned to the study group (n = 44, mean age, 65.4 ± 11.2 y; 61.4% men). Heart failure with reduced ejection fraction patients without weight loss were enrolled as the control group (n = 42, mean age, 61.0 ± 16.5 y; 64.3% men). The serum adropin and irisin levels of all patients were measured. A p-value < 0.05 was considered significant.

Results: Serum adropin and irisin levels were significantly higher in the cachexia group than in the controls (Adropin (ng/L); 286.1 (231.3-404.0) vs 213.7 (203.1-251.3); p < 0.001, Irisin (μg/mL); 2.6 (2.2-4.4) vs 2.1 (1.8-2.4); p = 0.001). Serum adropin and irisin levels were positively correlated with brain natriuretic peptide (BNP) levels and New York Heart Association (NYHA) class and negatively correlated with body mass index (BMI) and serum albumin levels (all p values: < 0.001). In a multivariate analysis, adropin was the only independent predictor of cachexia in the heart failure with reduced ejection fraction patients (OR: 1.021; 95% CI: 1.004−1.038; p = 0.017).

Conclusions: The results suggest that adropin and irisin may be novel markers of cardiac cachexia in heart failure with reduced ejection fraction patients. Adropin and irisin are related with the severity of heart failure. (Arq Bras Cardiol. 2018; 111(1):39-47)

Keywords: Cachexia / complications; Heart Failure / physiopathology, Hypertrophy, Left Ventricular; Ventricular Function, Left; Adropin; Peptides; Hormones.

Introduction

Heart failure with reduced ejection fraction, which is a multifactorial and common disease, is considered a major public health problem worldwide.[1] Cardiac cachexia, which is characterized by loss of muscle, with or without loss of fat mass, is a serious and life-threatening complication of heart failure with reduced ejection fraction. Moreover, studies have demonstrated that it was an important independent prognostic factor for cardiovascular mortality after adjustment for age, left ventricular ejection fraction and functional capacity to perform physical activities.[2-4]

Adropin is a novel membrane-bound protein, which contains 76 amino acids and is encoded by the energy homeostasis-associated gene.[5] It is expressed predominantly in the liver, brain, coronary arteries, vascular endothelium and heart (all layers).[6] A recent study reported that elevated plasma levels of adropin in heart failure with reduced ejection fraction patients were positively correlated with disease severity, as classified by the New York Heart Association (NYHA).[7] Irisin is a thermogenic protein, which is expressed in adipose tissue, cardiac muscle, heart and other peripheral tissues. The main functions of irisin are energy expenditure by converting white adipose tissue to brown adipose tissue and regulation of carbohydrate metabolism, resulting in improved glucose homeostasis and insulin sensitivity and weight loss.[6-11]

Cardiac cachexia in heart failure with reduced ejection fraction is associated with impaired energy homeostasis due to anabolic and catabolic imbalance, and serum adropin and irisin levels play important roles in energy balance and metabolism. Based on the aforementioned, we hypothesized that both serum adropin and irisin levels would differ in cachectic heart failure with reduced ejection fraction patients and non-cachectic individuals.

The aims of the present study were: 1) to investigate serum adropin and irisin levels in cardiac cachectic and non-

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cachectic patients with heart failure with reduced ejection fraction, and 2) to investigate the relationship between adropin and irisin levels and clinical and laboratory parameters in patients with heart failure with reduced ejection fraction.

Methods

Patient selection and study protocol

To identify cachectic patients, the clinical records of patients admitted to the cardiology outpatient clinic of a training and research hospital either for the diagnosis or treatment of heart failure with reduced ejection fraction were screened. Subsequently, the patients were contacted by phone and asked to attend the clinic. Heart failure with reduced ejection fraction patients without weight loss were enrolled as a control group.

The inclusion criteria were a diagnosis of heart failure with reduced ejection fraction according to the '2012 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure' and treatment for heart failure with reduced ejection fraction for at least 6 months before enrolment in the study.[12] The following were exclusion criteria: acute decompensated heart failure, heart failure with preserved ejection fraction, hospitalization for acute coronary syndromes, primary valvular heart disease, chronic obstructive pulmonary disease, peripheral vascular disease, musculoskeletal disease, acute/chronic inflammatory or infectious diseases, connective tissue diseases, neoplastic diseases, congenital heart diseases, hepatic failure, acute or chronic end-stage kidney failure, recent trauma or major surgery and pregnancy.

Demographic, clinical and laboratory data and the medical therapies administered to each patient during their index hospitalization were recorded by a systematic review of the patient files. To determine left ventricle ejection fraction values, all individuals underwent a transthoracic echocardiographic examination (Vivid S5; General Electric, Wisconsin, USA), which was performed by an experienced operator. The left ventricle ejection fraction was determined using Simpson's method of discs and two-dimensional echocardiography.

All patients were older than 18 years and able to provide written informed consent, which was a prerequisite for enrolment. The study complied with the Declaration of Helsinki, and the trial protocol was approved by the Local Ethical Committee.

Laboratory measurements

Blood samples were drawn by venipuncture into tubes containing anticoagulant ethylenediaminetetraacetic acid (EDTA). The samples were collected after a 12-hour overnight fast from the antecubital vein, with the patient in a sitting position. The serum was obtained by centrifugation at 4000 rpm at 4°C for 20 min. The obtained sera were stored at -80°C until used in the analysis. All routine biochemical and hematological parameters were measured on the same day as the blood sampling. Biochemical parameters, including fasting blood glucose, creatinine, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides (TG), were measured using an Abbott Diagnostics C8000i (Abbott, Germany) auto-analyzer with commercial kits. The LDL cholesterol was assayed by applying Friedewald's formula to samples with TG ≤ 400 mg/dL. Hematological parameters were obtained using a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland, Inc., Mervue, Galway, Ireland). Serum brain-natriuretic peptide (BNP) levels (pg/ml) were measured using commercially available kits (Phoenix Pharmaceuticals, Inc., Burlingame, CA, USA).

Serum adropin levels were measured with a commercially available kit using an enzyme-linked immunosorbent assay (ELISA) method (Human adropin ELISA kit, catalogue n°. ck-e90267, Hangzhou Eastbiopharm Co., Blue Ocean International Times Mansion, China), with a low sensitivity limit of 2.49 ng/L. All samples were measured in duplicate in a single experiment. The intra- and inter-assay coefficients of variance of this kit were < 10% and < 12%, respectively. The detection range of adropin was 5-1000 ng/L. Serum irisin levels were detected with a commercially available kit, using the ELISA method (Human irisin ELISA kit, catalogue n°. CK-E90905, Hangzhou Eastbiopharm Co., Blue Ocean International Times Mansion, China). The sensitivity limit was 0.023 μg/mL, and the intra- and inter-assay coefficients of variance were < 10% and < 12%, respectively. The detection range of irisin was 0.05-15 μg/mL.

Definitions

Cardiac cachexia can be defined as underlying disease and involuntary non-edematous weight loss ≥ 6% within the previous 6-12 month.[12,13]

Hypertension was diagnosed if systolic arterial pressure exceeded 140 mm Hg, diastolic arterial pressure exceeded 90 mmHg, or the patient was taking antihypertensive drugs. Hyperlipidemia was defined as fasting total serum cholesterol > 200 mg/dL, LDL cholesterol > 130 mg/dL, serum TG > 180 mg/dL or the use of lipid-lowering drugs. Diabetes mellitus was defined as a previous history of the disease, the use of insulin or oral antidiabetic drugs, or a fasting venous blood glucose level ≥ 126 mg/dL on two occasions in previously untreated patients.[14] Anthropometric measurements were used to determine body mass index (BMI), triceps skinfold thickness (TST) and arm circumference (AC). The TST was measured using a Holtain skinfold caliper. The arm muscle area (AMA) was calculated by the formula (AC-TST × π) 2/4 × π and considered an indicator of body muscle mass.[15] The heights and weights of the study participants were measured, and the BMI was calculated as body weight in kilograms divided by the square of the height in meters (kg/m^2).

Statistical Analysis

Descriptive analyses are presented using means and standard deviations or the median and the interquartile range (IQR, range from the 25th to 75th percentile). The standard effect size of the current trial was determined 0.62 with power of 80% and error of 5% according to the equation reported by Pardo et al.[16] The sample size was established at a minimum of 41 volunteers per group to detect differences in irisin between cachectic and control patients.

The categorical variables are expressed as numbers and percentages. Visual (histograms and probability plots) and analytical methods (Kolmogorov–Smirnov) were used to determine whether the variables were normally distributed. The independent samples T-Test was used for the comparison of normally distributed continuous numerical variables, the Mann–Whitney *U*-test was used for non-normally distributed numerical variables, and the χ^2-test was used for comparing categorical variables between the two groups. Receiver operating characteristic curves were plotted for BNP, adropin and irisin. When a significant cut-off value was observed, the sensitivity, specificity, positive and negative predictive values were recorded. Spearman's correlation analysis was performed to determine the association of adropin and irisin levels with the examined variables. Multiple logistic regression analyses were performed to identify the independent risk factors associated with cachexia. Variables found to be statistically significant in the univariate analyses were entered into a multivariate logistic regression analysis. An overall 5% type-I error level was used to infer statistical significance, and a *p*-value less than 0.05 was considered significant. Statistical analyses were performed using the Statistical Package for Social Sciences (IBM SPSS 17 Statistics for Windows, Version 20.0. Armonk, NY, USA).

Results

The present study included 86 heart failure with reduced ejection fraction patients: 44 with cardiac cachexia (mean age, 65.4 ± 11.2 y; 61.4% men) and 42 with a normal body weight (mean age, 61 ± 16.5 y; 64.3% men). The weight difference between two groups is shown in Figure 1. The baseline demographic and clinical characteristics of the study groups are summarized in Table 1. As expected, BMI, TST and AMA were significantly lower in the cardiac cachexia group than the non-cachectic group. The NYHA class of the two groups was also significantly different, with more patients in the cardiac cachexia group classified as NYHA class III and IV, and more in the non-cachectic group classified as NYHA class I and II.

The baseline laboratory characteristics of the two groups are presented in Table 1. Hemoglobin, albumin and HDL cholesterol levels were significantly higher in the non-cachectic individuals compared to the cachectic patients. Furthermore, the serum BNP, adropin and irisin levels were significantly higher in the cachectic group than in the non-cachectic group [adropin (ng/L): 286.1 (231.3-404.0) vs 213.7 (203.1-251.3), $p < 0.001$; irisin (μg/mL): 2.6 (2.2-4.4) vs 2.1 (1.8-2.4), $p = 0.001$; BNP (pg/mL): 698.0 (340.0-1517.0) vs 1408.5 (725.0-4041.0), $p = 0.001$]. Analysis of the association between adropin and irisin levels and the clinical and laboratory parameters of the patients (Table 2) revealed that NYHA class and BNP levels were significantly positively correlated with both adropin and irisin levels. However, BMI, AMA, TST and serum albumin, which were significant indirect clinical and laboratory indicators of cardiac cachexia, were significantly inversely correlated with adropin and irisin levels. In addition, there was a direct correlation between adropin and irisin levels and heart failure with reduced ejection fraction. Creatinine levels were also positively correlated with irisin levels.

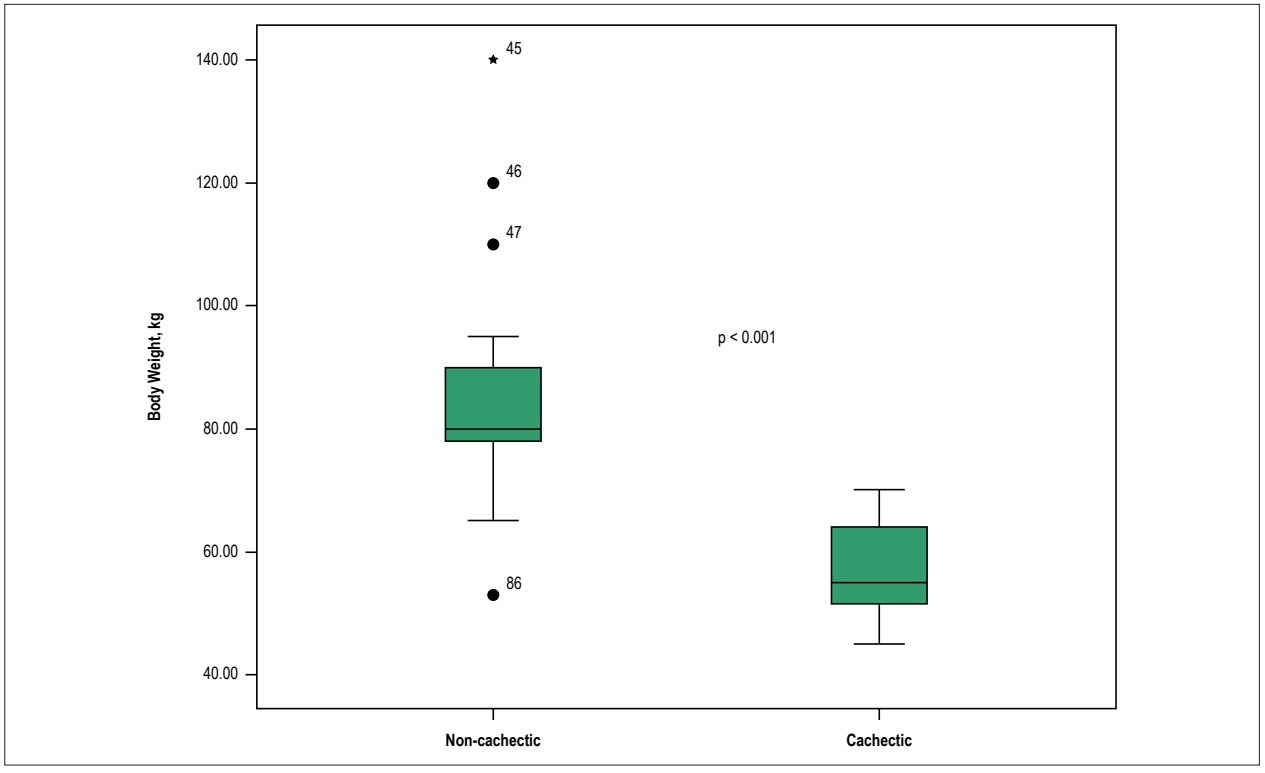

Figure 1 – *Body weight difference between cachectic and non-cachectic groups.*

Table 1 – Baseline demographic, clinical and laboratory characteristics of the study groups

	CHF without cachexia (n = 42)	CHF with cachexia (n = 44)	p value
Age, (years), mean (SD)	61.0 (16.47)	65.4 (11.18)	0.179
Male Gender, n (%)	27 (64.3)	27 (61.4)	0.779
NYHA, class I-II, n (%)	30 (60)	20 (40)	0.015
class III-IV, n (%)	12 (33.3)	24 (66.7)	
Ischemic Etiology, n (%)	28 (66.7)	26 (59.1)	0.468
LVEF, n (%)			
Anthropometric parameters	31.7 (7.89)	31.4 (6.71)	0.882
BMI (kg/m^2), mean (SD)	29.2 (4.25)	19.9 (1.12)	< 0.001
TST (mm), mean (SD)	17.9 (3)	13.4 (2.45)	< 0.001
AMA (cm^2), mean (SD)	35.9 (8.7)	24.4 (4.03)	< 0001
Comorbidities			
Hypertension, n (%)	27 (64.3)	26 (59)	0.620
Diabetes mellitus, n (%)	18 (42.9)	26 (59.1)	0.290
Chronic renal failure, n (%)	14 (33.3)	15 (34.1)	0.941
Chronic obstructive lung disease, n (%)	8 (19)	8 (18.2)	0.918
Laboratory parameters			
Glucose (mg/dL), mean (SD)	155.3 (78.5)	150.3 (48.3)	0.685
Creatinine (mg/dL), mean (SD)	1.15 (0.63)	1.19 (0.8)	0.997
Hemoglobine (%), mean (SD)	11.9 (1.38)	11.3 (1.34)	0.049
WBC (mg/L), mean (SD)	8.35 (4.2)	8.45 (3.98)	0.742
Adropin (ng/L) median (IQR)	213.7 (203.1-251.3)	286.1 (231.3-404.0)	< 0.001*
Irisin (µg/mL), median (IQR)	2.1 (1.8-2.4)	2.6 (2.2-4.4)	0.001*
BNP (pg/mL), median (IQR)	698.0 (340.0-1517.0)	1408.5 (725.0-4041.0)	0.001*
Albumin (mg/dL), mean (SD)	3.3 (0.46)	3.12 (0.36)	0.041
Sodium (mEq/L), mean (SD)	138.7 (10.1)	135.7 (9.7)	0.136
Total cholesterol (mg/dL), mean (SD)	164.5 (44.1)	153.2 (44.4)	0.240
LDL-cholesterol (mg/dL), mean (SD)	108.4 (40.5)	101.1 (32.7)	0.366
HDL-cholesterol (mg/dL), mean (SD)	36.2 (10.4)	31 (9.1)	0.015
Triglyceride (mg/dL), mean (SD)			
Drug therapy	134.2 (50)	122.3 (56)	0.302
Furosemide, n (%)	35 (83.3)	40 (90.9)	0.293
ACE-i/ARB, n (%)	20 (47.6) / 11 (26.2)	28 (63.6) / 11 (25.2)	0.136
Spironolactone, n (%)	26 (61.9)	30 (68.2)	0.542
Statin, n (%)	16 (38.1)	18 (40.9)	0.790
Beta-blocker, n (%)	33 (78.6)	39 (88.6)	0.206
Ivabradine, n (%)	15 (25)	11 (25)	0.289
CRT, n (%)	9 (21.4)	6 (13.6)	0.341

*n: number; SD: standard deviation; IQR: interquartile range; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; BMI: body mass index; TST: triceps skinfold thickness; AMA: arm muscle area; WBC: white blood cell; BNP: brain natriuretic peptide; LDL: low-density lipoprotein; HDL: high-density lipoprotein; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blocker; CRT: cardiac resynchronization therapy. *: mann-whitney u-test.*

Table 2 – The correlations of adropin and irisin with clinical and laboratory parameters of patients

		Age	BMI	AMA	TST	Albumin	BNP	NHYA	Irisin	LVEF	Creatinine
Adropin	r	0.077	-0.463	-0.386	-0.415	-0.250	0.676	0.762	0.669	-0.042	0.177
	p	0.480	< 0.001	< 0.001	< 0.001	0.02	< 0.001	< 0.001	< 0.001	0.704	0.104
Irisin	r	0.044	-0.384	-0.279	-0.374	-0.323	0.403	0.523		0.123	0.232
	p	0.687	< 0.001	< 0.001	< 0.001	0.002	< 0.001	< 0.001		0.259	0.031

BMI: body mass index; AMA: arm muscle area; TST: triceps skinfold thickness; BNP: brain natriuretic peptide; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction.

To investigate the discriminative value of serum BNP, adropin and irisin in cachectic and non-cachectic heart failure with reduced ejection fraction patients, a receiver operator characteristic curve was generated for sensitivity and specificity, using the respective areas under the curve (AUC) (Figure 2 and Table 3). The results indicated that adropin levels greater than 229.4 pg/mL had sensitivity of 77.3% and specificity of 64.3% for cardiac cachexia in heart failure with reduced ejection fraction patients [AUC: 0.770; 95% confidence interval (CI): 0.668-0.872; $p < 0.001$]. Moreover, the sensitivity of irisin levels of more than 2.2 pg/mL was 75.0%, whereas the specificity was 52.4% for cachexia (AUC: 0.705; 95% CI: 0.596-0.815; $p < 0.001$).

Variables found to be statistically significant in the univariate analyses were entered into a multivariate logistic regression analysis. In the multivariate analysis, adropin [odds ratio (OR) 1.021, 95% CI: 1.004-1.038; $p = 0.017$] was the only independent predictor of the presence of cachexia in patients with heart failure with reduced ejection fraction (Table 4).

Discussion

The main findings of the study were as follows: 1) serum adropin and irisin levels were significantly higher in the cachexia group than in the non-cachectic subjects; 2) NYHA class and BNP levels, which are validated indicators of heart failure with reduced ejection fraction severity, were significantly positively associated with both adropin and irisin levels; 3) there was a direct relation between adropin and irisin levels; 4) sensitivity of adropin and irisin were higher than their specificity for predicting cardiac cachexia. Both adropin and irisin sensitivity higher than BNPs sensitivity; and 5) adropin was the only independent predictor of the presence of cachexia in patients with heart failure with reduced ejection fraction.

The annual incidence of cardiac cachexia in patients with NYHA class III-IV was reported to be 10%, and the prevalence was reported to be 12-15% among those with NYHA class II-IV.[13] Several factors, including impaired food intake and absorption, immunological and neurohormonal activation, endothelial dysfunction, increased insulin resistance, triggered pro-inflammatory cytokine production and anabolic and catabolic imbalance, play a pivotal role in the complex process of cardiac cachexia.[13,17] This complex is associated with poor short- and long-term prognoses, unfavorable response to drug treatment and poor quality of life.[18] Previous studies reported elevated levels of some hormones and peptides, such as adiponectin, ghrelin, leptin and melanocortin, in cachectic heart failure with reduced ejection fraction patients.[17,19-20] However, there are no studies on the levels of adropin and irisin in this patient population in the literature. In the present study, the levels were significantly elevated in the cardiac cachexia group with heart failure with reduced ejection fraction compared to the non-cachectic group.

Sente et al.[21] have reported that cardiac and skeletal muscle energy deficiency played a major role in the pathophysiology of heart failure, which results in a hyperadrenergic state. Plasma free fatty acids increase under a hyperadrenergic state and inhibit glycolysis and glucose uptake by heart and skeletal muscle, with subsequent increases in plasma glucose. Multifactorial pancreatic damage, together with hyperglycemia, causes both systemic and myocardial insulin resistance.[22] The concept of metabolic failure in heart failure with reduced ejection fraction includes both catabolic over-reactivity (lipolysis) and anabolic deficiency, with catabolic over-reactivity activating glycolytic and lipolytic pathways and anabolic deficiency inducing loss of skeletal muscle mass and function.[18]

Adropin is a recently identified protein, which has been implicated in the maintenance of energy homeostasis.[5] A study of adropin-deficient mice suggested that this peptide hormone was required for maintaining insulin sensitivity and protecting against impaired glucose tolerance.[23] Thus, we hypothesized that adropin might increase as a consequence of insulin resistance in heart failure with reduced ejection fraction patients.

Kumar et al.[5] have reported that overexpression or systemic administration of adropin in diet-induced obese mice resulted in a marked improvement in insulin sensitivity and weight loss. Thus, weight loss in cachectic heart failure with reduced ejection fraction patients could contribute to the elevation of plasma adropin levels. The findings of the present study pointed to a metabolic association of increased serum adropin with muscle wasting and lipolysis in cachectic heart failure with reduced ejection fraction patients.

In addition to important metabolic effects of adropin, Lovren et al. have reported a potential endothelial protective role for this protein that was likely mediated by upregulation of endothelial nitric oxide synthase (eNOS) expression. They suggested that adropin might help protect against vascular diseases by markedly elevating eNOS expression of coronary artery endothelial cells.[24] Topuz et al.[9] have reported reduced adropin levels in type 2 diabetic patients with endothelial dysfunction. Wu et al.[8] have demonstrated an inverse and independent association between adropin

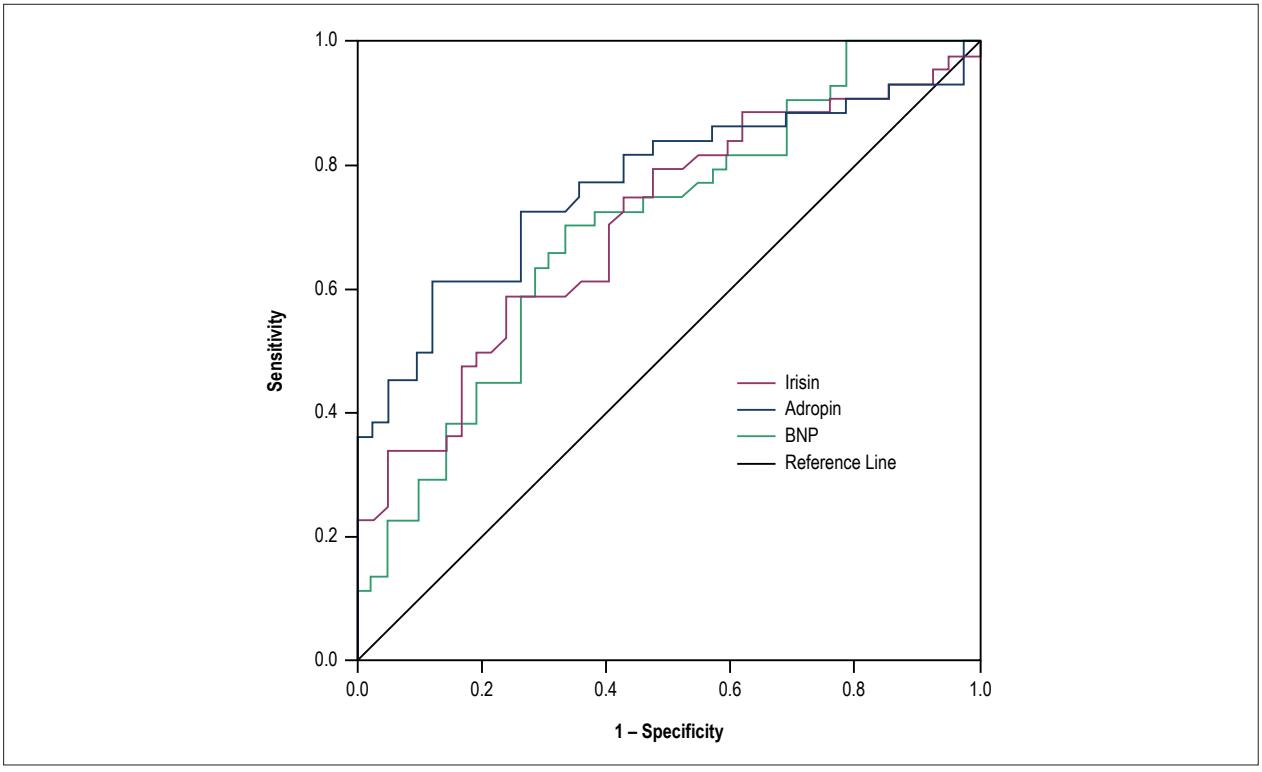

Figure 2 – *Receiver-operating characteristic curve for discriminative value of serum adropin, irisin and BNP levels in systolic heart failure with reduced ejection fraction patients with or without cachexia.*

Table 3 – Receiver-operating characteristic curve analysis of adropin, irisin and brain natriuretic peptide (BNP) for predicting cachexia

Variable	AUC	SE	CI (95%)	P value	Sensitivity	Specificity	PPV	NPV
Adropin	0.770	0.052	0.668-0.872	0.0001	%77.3	%64.3	%69.4	%73.0
Irisin	0.705	0.056	0.596-0.815	0.001	75.0	%52.4	%62.3	%66.7
BNP	0.700	0.056	0.590-0.811	0.001	%72.7	%61.9	66.7	%68.4

AUC: area under the curve; SE: standard error; PPV: positive predictive value; NPV: negative predictive value.

levels and the severity of coronary artery atherosclerosis in diabetic patients. Zhang et al.[25] have presented similar results for patients with stable coronary artery disease. In another study, they have reported an important association between decreased adropin levels, high SYNTHAX scores and the severity of stable coronary artery disease.[26] Yu et al.[27] have examined the role of adropin in acute myocardial infarction (MI) and have shown that serum adropin levels were reduced in cases of acute MI.

By elevating eNOS, adropin may have the potential to improve endothelial dysfunction, which has been widely reported in patients with heart failure with reduced ejection fraction, and decelerate left ventricular dysfunction in heart failure with reduced ejection fraction.[28] Lian et al.[7] have reported that an elevated level of adropin in heart failure with reduced ejection fraction was correlated with the severity of heart failure with reduced ejection fraction according to the NYHA class and BNP levels. The present study revealed similar findings and relations in cachectic patients with heart failure with reduced ejection fraction. Unlike the study by Lian et al., in which adropin levels and BMI were directly correlated with each other, there was an inverse relationship between adropin levels and BMI in cardiac cachexia in the present study, as expected.

Although irisin is predominantly expressed in muscle and is directly associated with muscle mass, it can be expressed in different tissues. Brown adipose tissue is known to dissipate energy in the form of heat via activation of uncoupling protein 1. This process increases energy expenditure, reduces body weight and improves metabolic parameters, such as insulin sensitivity. In white tissue, irisin stimulates BAT-like phenotype changes via a process known as browning. Based on the aforementioned properties, irisin has been proposed as a possible novel treatment for diabetes and obesity.[29] Although some studies have reported positive correlations between irisin and BMI, others have reported contradictory results.[6,29] The present study revealed an inverse correlation between irisin and BMI. In addition, AMA, TST

Table 4 – Logistic regression analyses to identify the independent risk factors associated with cardiac cachexia

	Univariate			Multivariate		
	p	OR	(95% CI)	p	OR	(95% CI)
Albumin	0.044	0.331	0.113-0.972	0.387	0.571	0.161-2.029
BNP	0.013	1.000	1.000-1.001	0.770	1.000	1.000-1.000
Age	0.151	1.023	0.992-1.056			
Gender	0.779	1.133	0.472-2.720			
Irisin	0.025	1.865	1.081-3.218	0.776	0.880	0.378-2.047
Adropin	0.002	1.016	1.006-1.026	0.017	1.021	1.004-1.038
Creatinine	0.760	1.098	0.604-1.994			
Glucose	0.720	0.999	0.992-1.005			
LVEF	0.880	0.996	0.939-1.056			
Total cholesterol	0.239	0.994	0.984-1.004			
Triglyceride	0.302	0.996	0.987-1.004			
LDL	0.363	0.995	0.983-1.006			
HDL	0.022	0.941	0.893-0.991	0.102	0.950	0.893-1.010
NYHA III - IV	0.016	3.000	1.226-7.339	0.463	0.550	0.111-2.717

BNP: Brain Natriuretic Peptide; LVEF: Left Ventricular Ejection Fraction; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; NYHA: New York Heart Association.

and serum albumin levels were inversely related with irisin. In patients with heart failure with reduced ejection fraction, muscle, fat and bone loss were reported to be associated with worse outcomes.[30] Moreover, a recent study reported a gradual decrease in irisin levels in patients with acute MI, suggesting that irisin may be a new diagnostic marker in this setting.[31] In a recently published study, Shen et al.32 have reported that serum irisin level was significantly higher in deceased acute heart failure (AHF) patients compared to that in survived AHF and predicted 1-year all-cause mortality in AHF patients. In that study irisin and NT-pro-BNP were determined by ROC curve analysis. NT-pro-BNP (AUC: 0.670) had only moderate prognostic values for AHF mortality risk compared to serum irisin level (AUC: 0.753).[32] The findings of that study are similar to ours. This increase may be the result of adipose tissue metabolism and insulin resistance. Studies are needed to determine whether irisin levels are the result of a reduced peripheral muscle mass in cachectic heart failure with reduced ejection fraction patients. In addition, in our study, adropin was found to be more predictive than irisin and BNP.

In our study, only adropin was found to be an independent predictor of cachexia in patients with heart failure. Although irisin predicted cardiac cachexia in univariate analysis, it did not predict in multivariate analysis. Irisin was found to be a predictive biomarker for 1-year all-cause mortality in the study by Shen et al.[32] This difference may be due to the fact that the adropin molecule was not used in multivariate analysis at this work. Further studies are highly needed to examine this relationship.

Similar to adropin, irisin was significantly positively correlated with BNP levels and NYHA class. Natriuretic peptides, such as BNPs, in addition to diuretic peptides and vasodilators, trigger lipolysis in the human body and play a role in fat metabolism.[7] Hence, we hypothesized that lipolysis by BNPs might be associated with adropin and irisin synthesis in cachectic heart failure with reduced ejection fraction patients. A further study will be necessary to elucidate the precise mechanism of adropin and irisin release in patients with cardiac cachexia.

Study Limitations

The present study had some limitations. Firstly, the study population was relatively small. However, the results pointed to an important relationship between adropin and irisin levels and cardiac cachexia in patients with heart failure with reduced ejection fraction. Secondly, a lack of follow-up data on future major adverse cardiovascular events, including mortality or hospitalization for heart failure with reduced ejection fraction, meant that the prognostic value of the levels of both proteins could not be evaluated.

Conclusions

The present study showed that serum adropin and irisin levels were significantly increased in the cachectic heart failure with reduced ejection fraction group and that these were significantly associated with previously validated markers of heart failure with reduced ejection fraction severity, such as the BNP level and NYHA class. The results suggest that adropin and irisin may be novel markers of cardiac cachexia in heart failure with reduced ejection fraction patients. Adropin and irisin are related with the severity of heart failure.

Author contributions

Conception and design of the research: Kalkan AK, Cakmak HA, Aydin S, Celik A; Acquisition of data: Kalkan AK, Uzun F, Tasbulak O, Diker VO; Analysis and interpretation of the data: Kalkan AK, Cakmak HA, Erturk M, Tasbulak O, Diker VO; Statistical analysis: Kalkan AK, Erturk M, Uzun F, Celik A; Obtaining financing: Kalkan AK, Aydin S, Celik A; Writing of the manuscript: Kalkan AK, Erturk M, Kalkan KE, Aydin S, Celik A; Critical revision of the manuscript for intellectual content: Kalkan AK, Kalkan KE.

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 Mehmet Akif Ersoy Thoracic and Cardiovascular Disease Education and Training Hospital under the protocol number 2015-23. 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.

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Adropin and Irisin in Patients with Cardiac Cachexia

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Short Editorial regarding the article: Adropin and Irisin in Patients with Cardiac Cachexia

Cardiological clinical practice involves the care of patients with heart failure who lose weight, which not rarely culminates in cardiac cachexia. The differential diagnosis with other consumptive disorders can lead to an extensive diagnostic investigation.

That has been a theme of interest in the medical literature for decades,[1] and its importance remains recognized over time.[2-7] Physicians with decades of experience in cardiological clinical practice have noticed that individuals with heart failure due to heart valvular disease gain weight after well-succeeded surgical interventions that reverse heart failure. In other words, heart failure reversion also manifests as weight gain. A recent outpatient clinical observation [Correia GF & Lima NNC, unpublished data] of 36 patients for months has found body weight variation with the current pharmacological treatment for heart failure including betablockers (Figure 1).

Different metabolic mechanisms can mediate that clinical manifestation.[8,9]

In this issue of the *Arquivos Brasileiros de Cardiologia*, Kalkan et al.[10] have added to the studies in the area the results of the research on two proteins that act on the mechanisms of energetic homeostasis – adropin[11] and irisin.[12] Those authors have found that the concentration of those proteins differed in 44 patients with cachexia (body mass index 19.9; standard deviation 1.12) as compared to that of 42 patients without cachexia (body mass index 29.2; standard deviation 4.25). On multivariate logistic regression, adropin remained associated with cachexia, despite the low hazard ratio.

Some limitations of the study by Kalkan et al.[10] were the lack of information about the etiology of heart failure, the small sample size and the lack of log-term follow-up data. Therefore, the results presented, although initial and exploratory, are important, and further studies should be conducted to elucidate the metabolic mechanisms of weight loss in patients with heart failure.

Keywords

Heart Failure; Adropine; Cachexia; Prognosis; Weight Loss.

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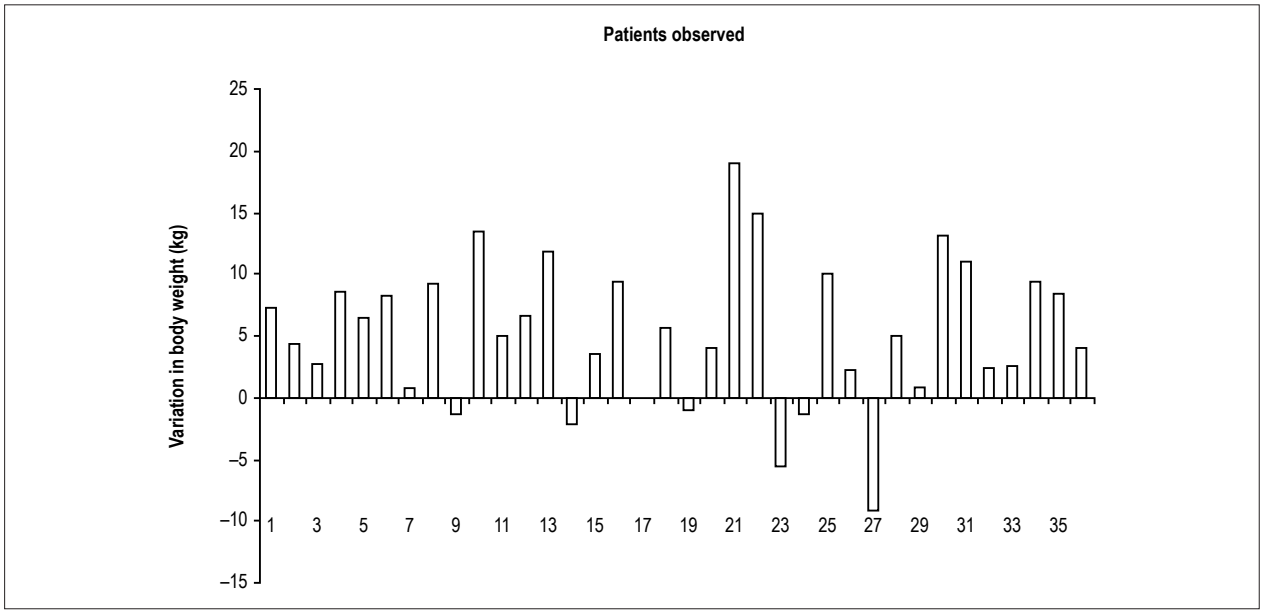

Figure 1 – *Body weight variation in 2 observations.*

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Genetic Risk Analysis of Coronary Artery Disease in a Population-based Study in Portugal, Using a Genetic Risk Score of 31 Variants

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Abstract

Background: **Genetic risk score can quantify individual's predisposition to coronary artery disease; however, its usefulness as an independent risk predictor remains inconclusive.**

Objective: **To evaluate the incremental predictive value of a genetic risk score to traditional risk factors associated with coronary disease.**

Methods: **Thirty-three genetic variants previously associated with coronary disease were analyzed in a case-control population with 2,888 individuals. A multiplicative genetic risk score was calculated and then divided into quartiles, with the 1st quartile as the reference class. Coronary risk was determined by logistic regression analysis. Then, a second logistic regression was performed with traditional risk factors and the last quartile of the genetic risk score. Based on this model, two ROC curves were constructed with and without the genetic score and compared by the Delong test. Statistical significance was considered when p values were less than 0.05.**

Results: **The last quartile of the multiplicative genetic risk score revealed a significant increase in coronary artery disease risk (OR = 2.588; 95% CI: 2.090-3.204; p < 0.0001). The ROC curve based on traditional risk factors estimated an AUC of 0.72, which increased to 0.74 when the genetic risk score was added, revealing a better fit of the model (p < 0.0001).**

Conclusions: **In conclusion, a multilocus genetic risk score was associated with an increased risk for coronary disease in our population. The usual model of traditional risk factors can be improved by incorporating genetic data. (Arq Bras Cardiol. 2018; 111(1):50-61)**

Keywords: **Coronary Artery Disease / history; Coronary Artery Disease / morbidity; Mortality; Polymorphism, Genetic; Epidemiology; Risk Factors.**

Introduction

Coronary artery disease (CAD) has become a major health problem worldwide, with increasing prevalence and high morbidity and mortality. Traditional risk factors (TRFs) are insufficient to identify asymptomatic high-risk individuals. Epidemiology and family studies have long documented that approximately 50% of the susceptibility for heart disease is genetic.[1] Knowledge of genetic predisposition to cardiac disease is crucial for its comprehensive prevention and treatment.

Although much of the genetic basis of coronary disease remains to be discovered, some progress has been made using both candidate gene and genome-wide association studies (GWAS).[2] In fact, a number of genetic variants have been previously identified at several genomic regions associated with CAD.[2]

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Until now, the risk attributable to any individual variant has been modest. However, discovering and combining multiple loci with modest effects into a global genetic risk score (GRS) could improve the identification of high-risk populations and improve individual risk assessment.

Therefore, the purpose of this work was to generate a multilocus GRS based on common variants previously shown to be associated with CAD, and evaluate whether it is independent of TRFs and improves the predictive ability of a model based only on TRFs.

Methods

Study Population

Study population was enrolled from GENEMACOR (GENEs in Madeira Island Population with CORonary artery disease), a population-based ongoing case-control registry of CAD with 2,888 participants, 1,566 cases (mean age 53.3 ± 8.0 years, 79.1% male) and 1322 controls (mean age 52.7 ± 7.8 years, 76.4% male). Cases were selected from patients discharged after being admitted for myocardial infarction/unstable angina diagnosed according to the previously described

criteria,[3] or with CAD confirmed by coronary angiography with ≥ 1 coronary lesions of ≥ 70% stenosis in ≥ 1 major coronary artery or its primary branches. Absent or non-flow limiting atheroma was excluded from the analysis. The control group consisted of healthy volunteers, without symptoms or history of CAD, selected from the same population. All controls underwent clinical assessment of conventional cardiovascular risk factors, an electrocardiogram (ECG), and, in doubtful cases, an exercise stress test, a stress echocardiography or computerized tomography for calcium scoring. Cases and controls were matched for gender and age.

Inclusion criteria comprised an age limit of 65 years and being a permanent resident to avoid genetic admixture. Principal Component Analysis (PCA)[4] was used for analysis of population stratification for possible genetic admixture and detection of significant genetic outliers (< 5%).[4]

The study was approved by the Hospital ethics committee according to the Declaration of Helsinki and all patients provided written informed consent.

Data collection

Data was collected from all subjects in a standardized file comprising demographic, clinical characteristics and TRFs traditional risk factors (gender, age, level of exercise, smoking status, arterial hypertension, dyslipidemia, diabetes, family history of CAD, body mass index (BMI), heart rate and pulse wave velocity (PWV).

"Smokers" referred to current smokers or subjects with less than 5 years of smoking cessation.[5]

Essential hypertension was considered when patients, at the entry into this study, were already diagnosed and/or had been on antihypertensive medication for more than 3 months or newly diagnosed hypertensives with systolic blood pressure (SBP)/diastolic blood pressure (DBP) ≥ 140/90 mmHg measured on at least 3 occasions.[6]

Dyslipidemia was defined for control population as low-density lipoprotein (LDL) > 140 mg/dL, high-density lipoprotein (HDL) < 45 mg/dL for women and < 40 mg/dL for men, Triglycerides > 150 mg/dL and apolipoprotein (Apo) B > 100 mg/dL. For patients (at high risk) dyslipidemia was considered when LDL > 100, HDL < 45 mg/dL for women and < 40 mg/dL for men, triglycerides > 150 mg/dL, Apo B > 100 mg/dL and non-HDL (total cholesterol-HDL) > 130 mg/dL.[7]

Subjects were classified as having diabetes if they were taking oral anti-diabetic medication or insulin or if their fasting plasma glucose was higher than 7.0 mmol/L or 126 mg/dL.[8]

Subjects were considered to have a family history of premature cardiovascular disease (CVD) if the father or brother had been diagnosed with CVD under the age of 55 or mother or sister under the age of 65.

The definition of other TRFs was based on the standard criteria, as previously reported.[9,10]

Biochemical analysis

Blood samples were extracted after 12 hours' fasting. Biochemical analyses were performed at the Central Laboratory of the Hospital, according to standard techniques. In order to determine total cholesterol, HDL, LDL, triglycerides and glucose, blood samples were placed in dry tubes, centrifuged half an hour later at 3,500 g and subsequently quantified by an enzymatic technique using an "AU 5400" (Beckman Coulter) autoanalyzer. Biochemical markers such as lipoprotein-a – Lp(a), (Apo B), and high-sensitivity C-reactive protein (hs-CRP) were quantified by immunoturbidimetry also using an "AU 5400" (Beckman Coulter) automatic system.

Single Nucleotide Polymorphisms (SNP) selection

Two parallel approaches were employed to identify SNPs for the GRS. In the first approach, we searched the National Human Genome Research Institute database, which included SNPs identified by means of GWAS and catalogued based on phenotype and/or trait. We searched for the keywords: "coronary artery disease", "coronary disease", "myocardial infarction" and "early myocardial infarction." The second approach included SNPs that were identified through candidate gene approaches, included in a published GRS for CAD.

Including criteria included genes described in previous studies with an Odds Ratio (OR) for CAD ≥ 1.1 and a minor allele frequency (MAF) > 5%. Genes with low Hardy-Weinberg equilibrium ($p < 0.002$) (after Bonferroni correction) were excluded.

In total, 33 SNPs were selected according to their possible CAD-related function: association with cell cycle, cellular migration and inflammation (rs1333049 (9p21.3), rs4977574 (CDKN2B), rs618675 (GJA4), rs17228212 (SMAD3), rs17465637 (MIA3), rs12190287 (TCF21), rs3825807 (ADAMTS7), rs11556924 (ZC3HC1), rs12526453 (PHACTR1)); genes involved in pro-oxidative status (rs1801133 (MTHFR 677), rs1801131 (MTHFR 1298), rs705379 (PON 1), rs662 (PON 192), rs854560 (PON 55), rs6922269 (MTHFD1L); genes associated with modifiable risk factors such as lipids metabolism, hypertension and diabetes/obesity (rs3798220 (LPA), rs2114580 (PCSK9), rs20455 (KIF6), rs7412/rs429358 (APOE), rs964184 (ZNF259), rs599839 (PSRC1), rs5186 (AT1R), rs699 (AGT), rs4340 (ACE), rs4402960 (IGF2BP2), rs1326634 (SLC30A8), rs266729 (ADIPOQ), rs7903146 (TCF7L2), rs17782313 (MC4R), rs1801282 (PPARG), rs1884613 (HNF4A), rs8050136 (FTO) and rs1376251 (TAS2R 50)) (Supplementary Table 1).

Genetic analyses

Genetic analyses were performed at the Human Genetics Lab of the University of Madeira. Genomic DNA was extracted from 80 μl of peripheral blood using a standard phenol-chloroform method. A TaqMan allelic discrimination assay for genotyping was performed using labelled probes and primers pre-established by the supplier (TaqMan SNP Genotyping Assays, Applied Biosystems).

All reactions were done on an Applied Biosystems 7300 Real Time PCR System and genotypes were determined using the 7300 System SDS Software (Applied Biosystems, Foster City, USA) without any prior knowledge of individual's clinical data. Quality of genotyping techniques was controlled by the

inclusion of one non-template control (NTC) in each plate of 96 wells. All SNPs TaqMan assays had blind duplicates accounting for 20% of all samples. Some SNP genotypes were randomly confirmed by conventional direct DNA sequencing, as 10-15% of all samples were re-amplified for sequencing. Call rates for SNPs in the GRS were 98%-100% and a minimum 95% call rate was set for quality control.

Computation of the GENETIC RISK SCORE

We have tested several models to construct the GRS using both non-weighted and weighted scores, taking into consideration each pattern of inheritance for each gene locus. An additive score (AGRS) was generated, i.e., for each one of the 31 variants a score of 0, 1, and 2 was defined as there were 0, 1 or 2 risk alleles, by calculating the accumulated sum of the risk alleles in these variants. Each individual could be assigned a GRS of 0-62. Additionally, a multiplicative GRS (MGRS) was calculated by multiplying the relative risk for each genotype.

Validation of the risk score calculation was performed in a random sample of 597 patients (20%).

Statistical analysis

Categorical variables were expressed by frequencies and percentages and compared by the Chi-squared test or Fisher's exact test. Continuous variables were expressed as mean ± standard deviation (SD) or median (1st quartile – 3rd quartile) and compared by Student's t-test (unpaired) or Mann-Whitney, as appropriate. The Kolmogorov-Smirnov test and the Levene´s test were used to test the assumption of normality and the homogeneity of the variables. All analyses were considered significant when p values were less than 0.05.

Binary logistic regression was used to determine the combined and separate effects of the variables on the risk for angiographic CAD. GRS was modeled using as a continuous variable and as quartiles, using the first quartile as the reference category. Multivariate analyses were used to adjust for 7 covariates also reported to be associated with CAD. We plotted receiver operating characteristic (ROC) curves and calculated the area under the curve (AUC) for logistic regression models including TRFs without and with GRS (quartiles). Pairwise comparison of ROC curves was performed using the Delong test.[11] The model calibration was tested with Hosmer-Lemeshow goodness-of-fit test. A P-value less than 0.05 was considered statistically significant. Collinearity between the variables was measured by assessment of tolerance and variance inflation factor (VIF).

Associations of SNPs with CAD were considered significant at $p < 0.05$ and in aggregate with GRS models at $p < 0.0015$ applying Bonferroni correction.

For MAF of 30%, the study had 70% power to detect an OR for CAD of 1.3 and > 90% for OR ≥ 1.35, for 2-sided alpha of < 0.05 for 2,000 cases and 1,000 controls. Power calculations used *G power Statistical Power Analyses*.

The potential of GRS to improve individual risk stratification then was measured using the net reclassification improvement (NRI) method,[12] defined as the percentage of subjects in each subgroup changing categories when the new model of GRS (in quartiles) was added. The integrated discrimination improvement (IDI), defined as the incremental improvement prognostic value of GRS, was compared between cases and controls. NRI was computed by categorical and non-categorical (continuous) variables using the PredictABEL package available in R software (version 3.2.0).

Statistical analyses were performed using SPSS version 19.0 (IBM), MedCalc version 13.3.3.0 and R software version 3.1.2.

Results

Baseline characteristics of the population

Table 1 shows the baseline characteristics of our population. As expected, cases and controls showed no significant differences concerning gender and age, since this was a selection criterion. Higher frequency of dyslipidemia, diabetes, hypertension, physical inactivity, smoking habit, alcohol consumption, and family history of premature cardiovascular disease was found in CAD patients when compared to the controls ($p < 0.0001$). Also, PWV, BMI and waist-to-height ratio were higher in cases than in controls, with statistical significance ($p < 0.05$) (Table 1). The other biochemical variables analyzed such as hemoglobin, leucocytes, fibrinogen, homocysteine and hs-CRP > 3 showed significantly higher levels in the coronary patients group when compared to the controls ($p < 0.05$) (Table 1).

Computation and analysis of Genetic Risk Score

Deviation from Hardy-Weinberg equilibrium for the 33 genotypes at individual loci were assessed using the Chi-squared test and $p < 0.002$ with Bonferroni correction for all SNPs included. LPA gene variant was excluded for further analyses due to its low Hardy-Weinberg p-value ($p < 0.002$). Linkage disequilibrium for the mutually adjusted SNPs within the genes was studied. CDKN2B gene was excluded because of the strong linkage disequilibrium with another selected SNP, rs1333049, which resides in the 9p21 region. The remaining 31 SNPs were included for further analysis (Supplementary Table 1).

In this study, the MGRS had the highest AUC value for assessing the risk for CAD disease with a specificity of 62.3% and sensitivity of 54% (data not shown) and therefore this model was computed in the subsequent analyzes (Supplementary Table 2).

The MGRS of 31 SNPs was significantly higher in CAD cases than in controls (0.67 ± 0.73 vs 0.48 ± 0.53; $p < 0.0001$), even by quartile and gender discrimination (Table 2).

A normal distribution of risk alleles in the total sample set including cases and controls is shown in Figure 1. While CAD patients exhibited lower GRS values, risk alleles were more prevalent in this group than in controls. In CAD patients, a mean of 27 risk alleles was seen in 52% of the individuals, and a mean of 26 risk alleles was found in 53% of controls (Figure 1).

When analyzed in deciles, GRS showed that the increase in the number of risk alleles was significantly associated with CAD

Table 1 – Baseline characteristics of our study population

Variables	Cases (n = 1566)	Controls (n = 1322)	p value
Age, years	53.3 ± 8.0	52.7 ± 7.8	0.053
Male Gender, n (%)	1238 (79.1%)	1010 (76.4%)	0.087
Dyslipidemia†, n (%)	1398 (89.3)	1103 (83.4)	0.0001
Total Cholesterol, mg/dl	180.0 (154.0 – 213.0)	205.0 (181.0 – 234.0)	< 0.0001
LDL, mg/dl	104.6 (82.8 – 128.7)	127.2 (104.7 – 152.3)	< 0.0001
HDL, mg/dl	41.0 (35.0 – 49.0)	48.0 (41.0 – 57.0)	< 0.0001
Triglycerides, mg/dl	141.0 (102.0 – 210.0)	121.0 (89.0 – 174.0)	< 0.0001
Apolipoprotein B, mg/dl	93.9 (75.5 – 113.3)	92.5 (43.0 – 115.8)	< 0.0001
Lipoprotein (a), mg/dl	20.4 (9.2 – 62.0)	12.8 (8.8 – 29.3)	< 0.0001
Diabetes, n (%)	533 (34.0)	175 (13.2)	< 0.0001
Fasting glucose, mg/dl	106.0 (96.0 – 129.0)	99.0 (91.0 – 109.0)	< 0.0001
Hypertension, n (%)	1114 (71.1)	700 (53.0)	< 0.0001
SBP, mmHg	137.9 ± 20.8	136.2 ± 18.1	0.024
DBP, mmHg	82.6 ± 11.8	83.9 ± 11.1	0.002
Heart rate, bpm	68.8 ± 12.5	72.3 ± 11.5	< 0.0001
PWV, m/s	8.6 ± 1.9	8.3 ± 1.7	< 0.0001
Smoking status*, n (%)	730 (46.6)	309 (23.4)	< 0.0001
Level of exercise*, n (%)	573 (36.6)	761 (57.6)	< 0.0001
Alcohol, g/day	24.7 ± 49.7	18.2 ± 28.2	< 0.0001
BMI, kg/m^2	28.6 ± 4.2	28.1 ± 4.5	0.007
Waist/Height	0.61 ± 0.06	0.59 ± 0.07	< 0.0001
Family history, n (%)	373 (23.8)	167 (12.6)	< 0.0001
Hemoglobin, g/dl	14.6 (13.8 – 15.4)	14.7 (14 – 15.4)	0.001
Leucocytes, 103/µl	7.1 (6 – 8.3)	6.6 (5.6 – 7.8)	< 0.0001
Fibrinogen, mg/dl	387 (337 – 444)	361 (315 – 409)	< 0.0001
Homocysteine, µmol/L	12.2 (10 – 14.9)	11.4 (9.7 – 13.6)	< 0.0001
Hs-CRP, mg/L > 3, n (%)	648 (41.4)	496 (37.5)	0.035

*† Controls: LDL > 140 mg/dL, HDL < 40 mg/dL for men and < 45 mg/dLfor women; triglycerides > 150mg/dL, APO B > 100 mg/dL. Cases: LDL > 100 mg/dL; triglycerides > 150 mg/dL, HDL < 40 mg/dL for men and < 45 mg/dL for women; APO B > 100 mg/dL, non HDL > 130 mg/dL; *More than 40 min/week; *Current smokers or < 5 years of cessation; HDL: high density lipoprotein; LDL: low density lipoprotein; SBP: systolic blood pressure; DBP: diastolic blood pressure; PWV: pulse wave velocity; BMI: body mass index; Hs-CRP: high sensitivity C-reactive protein. Categorical variables compared by the Chi-square test. Continuous variables expressed as mean ± standard deviation (using Student's t-test) and biochemical variables as median (1st quartile – 3rd quartile) (using Mann-Whitney's test). Statistical significance: p < 0.05.*

as shown by inter-deciles p values (1st decile: OR = 0.612 (0.439 – 0.853), p = 0.004; 9th decile: OR =0.957 (01.400 – 2.734), p < 0.0001 and last decile: OR = 2.472 (1.755 – 3.482), p < 0.0001) (Figure 2).

A logistic regression analysis was performed with GRS quartiles, using the first as the reference category. Results showed an increase in CAD risk with statistical significance across the 2nd, 3rd and 4th quartiles with respective ORs and CIs of 1.372 (1.114 – 1.689), 1.878 (1.522 – 2.317) and 2.588 (2.090 – 3.204), respectively (data not shown).

A multivariable predictive model for CAD incorporating GRS quartiles and TRFs is presented in Table 3. The 4th GRS quartile has intermediate contribution to CAD phenotype – OR = 2.727 (2.162 – 3.439), greater than dyslipidemia – OR = 1.298 (1.023 – 1.646) and hypertension – OR = 2.067 (1.744 – 2.450). The reduced contribution of dyslipidemia on CAD risk may be due to standard use of statins in CAD patients. Extended adjustment for cofounding variables (gender, age, heart rate, PWV, low exercise level, BMI and family history of CAD) revealed modest increases in the OR for TRFs and the 2nd and 3rd quartiles of GRS.

We used VIF to test for multi-collinearity among the variables included in our GRS adjusted logistic regression model. Tolerance and VIF were respectively > 0.1 and < 10 attesting for no significant collinearity between variables included in the adjustment model.

Table 2 – Distribution of multiplicative genetic risk score (MGRS) for cases and controls by quartiles and gender

Variables	Cases (n = 1566)	Controls (n = 1322)	p value
MGRS	0.67 ± 0.73	0.48 ± 0.53	< 0.0001
1st Quartile	0.18 ± 0.05	0.17 ± 0.05	
2nd Quartile	0.33 ± 0.05	0.33 ± 0.05	< 0.0001
3th Quartile	0.52 ± 0.07	0.52 ± 0.07	
4 th Quartile	1.35 ± 1.02	1.18 ± 0.88	
MGRS male	0.67 ± 0.77	0.48 ± 0.44	< 0.0001
MGRS female	0.65 ± 0.58	0.51 ± 0.74	0.006

MGRS was expressed as mean ± standard deviation (SD) (using Student's t-test). Statistical significance: p < 0.05.

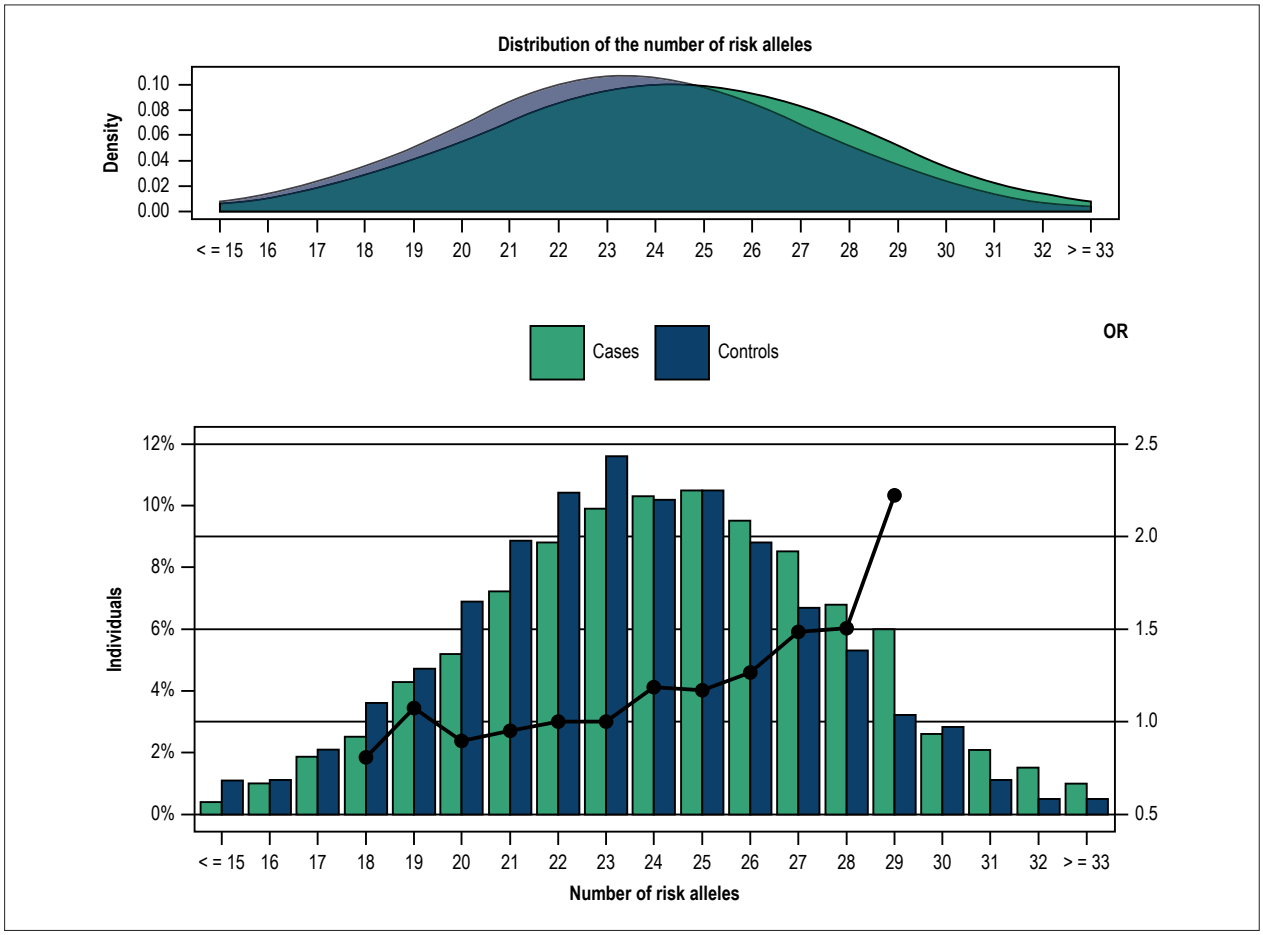

Figure 1 – *Distribution of the number of risk alleles by cases and controls. A logistic regression model was used to determine the coronary artery disease risk by the number of risk alleles compared to the number of reference alleles (23 alleles, in relation to the median value of the controls). Dots: regression analysis odds ratio for coronary artery disease.*

Two ROC curves were plotted based on the TRFs without and with the GRS (Figure 3). The first ROC curve estimated an AUC of 0.72, which increased to 0.74 when the GRS was added, revealing a better fit of the model ($p < 0.0001$) (Figure 3).

The NRI and its *p* value were used to make conclusions about improvements in prediction performance gained by adding a set of biomarkers to an existing risk prediction model. The addition of GRS quartiles to TRF improved the risk classification of the models (Table 4). This new marker provided a continuous NRI of 31% (95% CI: 23.8-38.3%; $p < 0.0001$) with 14.6% reclassification of CAD patients and 16.4% of healthy control population (Table 4).

Table 3 – Multivariate analysis performed with the multiplicative genetic risk score (MGRS) (quartiles) and traditional risk factors

Variables	OR* (95% CI)	p value	OR+ (95% CI)	p value
MGRS (Quartiles)	------	------	------	< 0.0001
2nd	1.355 (1.082 – 1.698)	0.008	1.406 (1.107 – 1.786)	0.005
3rd	1.934 (1.539 – 2.429)	< 0.0001	2.006 (1.575 – 2.554)	< 0.0001
4th	2.727 (2.162 – 3.439)	< 0.0001	2.657 (2.083 – 3.389)	< 0.0001
Smoking	3.440 (2.887 – 4.100)	< 0.0001	3.651 (3.030 – 4.401)	< 0.0001
Diabetes	3.138 (2.559 – 3.847)	< 0.0001	3.436 (2.763 – 4.273)	< 0.0001
Hypertension	2.067 (1.744 – 2.450)	< 0.0001	2.187 (1.816 – 2.633)	<0.0001
Dyslipidemia	1.298 (1.023 – 1.646)	0.032	1.344 (1.044 – 1.731)	0.022
Constant	0.186	< 0.0001		

Using forward Wald method (SPSS vs. 19.0); Dyslipidemia. Controls: LDL > 140 mg/dL, HDL < 40 mg/dL for men and < 45 mg/dLfor women; triglycerides> 150 mg/dL, APO B > 100 mg/dL. Cases: LDL > 100 mg/dL; triglycerides > 150 mg/dL, HDL < 40 mg/dL for men and < 45 mg/dL for women; APO B > 100 mg/dL, non HDL > 130 mg/dL; OR: odds ratio adjusted for age and gender; OR+: odds ratio adjusted for gender, age, heart rate, pulse wave velocity, sedentary life style, alcohol, body mass index and family history; CI: confidence interval; Statistically significant for p < 0.05.*

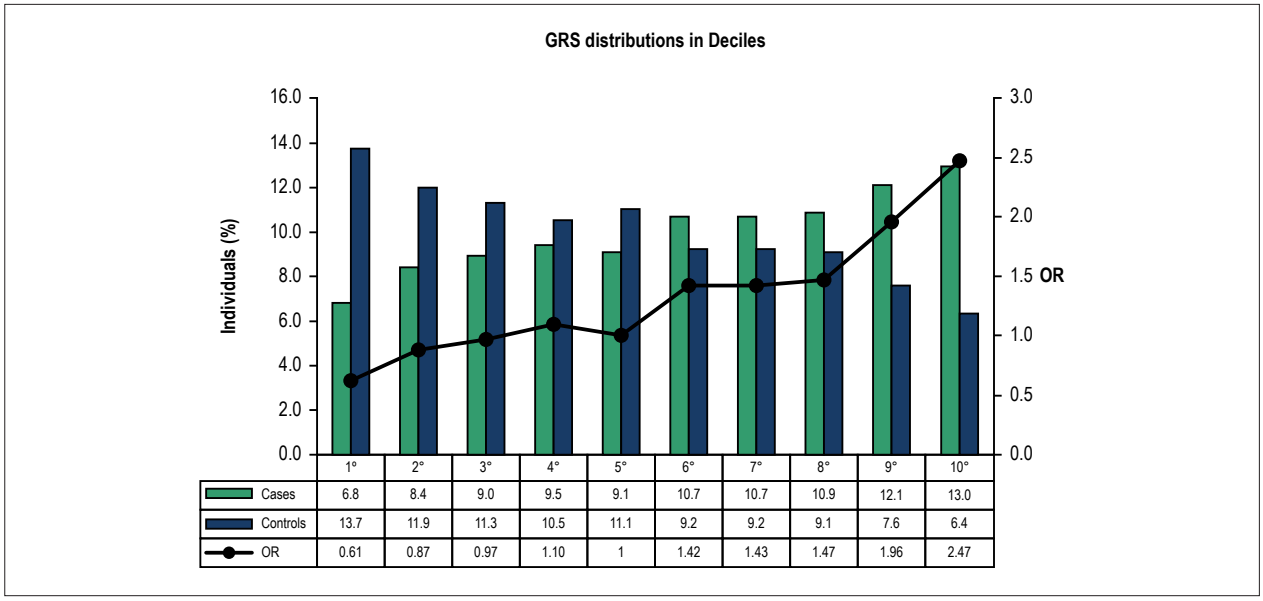

Figure 2 – *Distribution of genetic risk score in deciles by cases and controls. A logistic regression model was used with the 5th decile of the controls as the reference class.*

NRI was also computed using categorical variables and applied to this case-control study and was defined as the percentage of subjects changing categories in each subgroup when adding the new marker (CAD quartile score). Movement towards a better category (higher in patients than in controls) was calculated to address a potential impact for clinical use. NRI showed higher improvement capacity in reclassifying 19.5% of patients from the 50-75% category to the highest risk (75-100%) category. Likewise, 14.1% of healthy controls were moved down into a lower risk category, from 25-50% risk category to < 25% one (Table 5).

Furthermore, the inclusion of GRS quartiles to TRF also provided an IDI of 2.5% (95%CI: 1.9-3.1%; p < 0.0001) (data not shown).

Discussion

Several years ago, polymorphisms involved in specific biological pathways, relevant to coronary atherosclerosis, were genotyped to determine their association with CAD. This candidate gene approach revealed about 30 high-confidence SNPs loci with significant effects on atherosclerosis.[13] However, following traditional candidate gene approach has generated many conflicting results or with weak associations; replication studies are necessary for consistent validation of these results.

In 2004, Mendonça et al. first genotyped *angiotensin*-converting enzyme (ACE) I/D polymorphisms in a Portuguese population yielding similar reports as described in literature.[14]

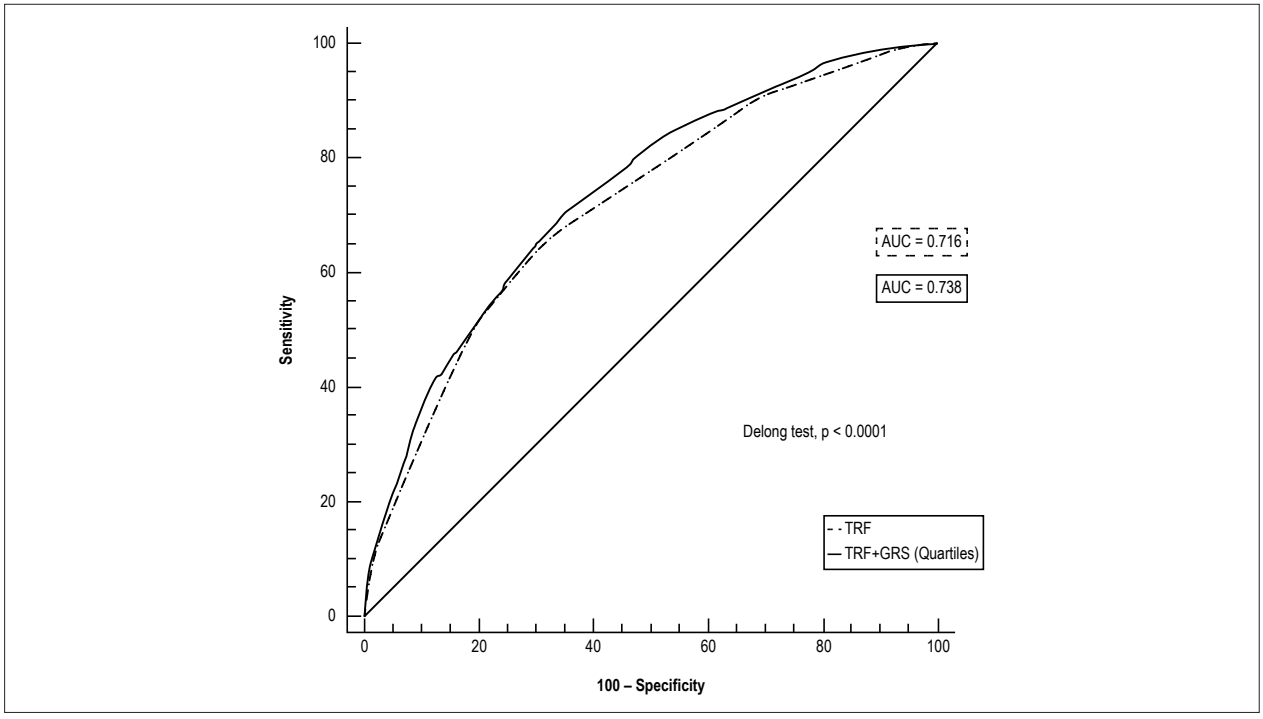

Figure 3 – *ROC curves based on the baseline model (traditional risk factors, TRFs) and after adding the genetic risk score (GRS) (quartiles) in predicting the risk for coronary artery disease. The two curves are based on logistic regression models incorporating conventional risk factors (diabetes, dyslipidemia, smoking and hypertension) with and without the GRS. AUC indicates area under curve. The Delong test compares the difference between the two AUCs (p < 0.0001).*

Table 4 – The category-free net reclassification index (cfNRI) after addition of the GRS quartiles

Group	n	Higher risk n (%)	Lower risk n (%)	p (cfNRI)	cfNRI (%)	cfNRI (95% CI)
CAD patients	1566	897 (57.3%)	669 (42.7%)	< 0.0001	14.6%	(9.7-19.5%)
Healthy controls	1322	553 (41.8%)	769 (58.2%)	< 0.0001	16.4%	(11.2-21.8%)
Total	2888	---	---	< 0.0001	31%	(23.8-38.3%)

GRS: genetic Risk Score; CAD: coronary Artery Disease; CI: confidence Interval; cfNRI: category-free net reclassification index. This analysis uses the function "improveProb" from R software package "Hmisc".

After the development of high capacity arrays in 2008,[15] GWAS examined millions of polymorphisms simultaneously in several ethnical subpopulations with a case-control design. The standardized minimum significance level set at $1x10^{-5}$ added reliability to cardiovascular genetics and put it into perspective.[16]

In 2007, Samani et al.[17] first identified chromosomal loci that were strongly associated with CAD in the Wellcome Trust Case Control Consortium (WTCCC) study (which involved 1,926 case subjects with CAD and 2938 controls) and looked for replication in the German MI (Myocardial Infarction) Family Study.[17]

In the following years, a surprisingly large number of gene variants were consistently reported to be associated with CAD. The 9p21 variant was the most frequently gene variant reported across populations. The huge consortium of Wellcome Trust and three other European research groups joined for the CARDIOGRAM project that confirmed, in a very large sample (> 22,000 cases) of individuals of European ancestry, a 29% increase in risk for MI per copy of the rs1333049 9p21 variant ($p = 2\times10^{-20}$).[18]

Our research group replicated this 9p21 variant analysis in the Portuguese population and found a CC genotype prevalence of 35.7% in CAD patients, with an adjusted OR of 1.34, p = 0.010. The adjusted OR for TRF of CC genotype was 1.7 (p = 0.018) and CG genotype of OR = 1.5, p = 0.048. The authors concluded that although the mechanism underlying the risk is still unknown, the robustness of this risk allele in risk stratification for CAD has been consistent, even in very different populations. The presence of the CC or CG genotype may thus prove to be useful for predicting the risk of developing CAD in the Portuguese population.[19]

The most recent meta-analysis of GWAS for (CAD) identified 46 genome-wide loci with significant association and 104 genome-wide loci potentially associated with increased risk.[20,21]

Table 5 – Reclassification table comparing predicted coronary artery disease (CAD) risk with and without genetic risk score (GRS) quartiles

Predicted risk (without GRS)	Reclassified predicted risk (with GRS)				% Increase	%/ Decrease
CAD patients (n = 1,566)	< 25%	25-50%	50-75%	75-100%		
< 25%	6	11	0	0	0,7%	0%
25-50%	44	335	123	0	7,9%	2.8%
50-75%	0	59	471	305	19,5%	3.8%
75-100%	0	0	9	203	0%	0.6%
NRI CAD patients			20.9%			
Healthy controls (n = 1,322)						
< 25%	65	36	0	0	2,7%	0%
25-50%	186	504	88	0	6,7%	14.1%
50-75%	0	60	268	79	6%	4.5%
75-100%	0	0	1	35	0%	0.1%
NRI controls			3.3%			
NRI total			24.2%			

NRI: net reclassification improvement (categorical NRI); CAD: coronary artery disease.

In our study, we found a gradual and continual increase in CAD risk with increasing number of CAD risk alleles carried. Individuals in the bottom decile are naturally protected and subjects in top decile of the GRS had a CAD risk of 2.472 (1.755 – 3.482). Even though the score distribution overlaps between cases and controls, the GRS is significantly associated with CAD risk and can be used to identify subjects at highest risk in terms of lifestyle or therapeutic interventions.

Our results are similar to others reports in Caucasians populations where GRS with 13, 29 or 109 SNPs[22-24] were independent and marginally increased the predictive power of TRF conferred either by AUC increases, C-index changes or more modern discriminative statistical methods like reclassification measures or improved discrimination.

We report a higher OR for the 4th quartile of GRS (2.59) compared to 1.66 reported by Ripatti et al. in the highest quintile.[22] When comparing the relative weight of the GRS in the multivariate logistic analysis we found slightly lower OR than smoking, hypertension, and dyslipidemia. In Ripatti´s[22] cohort, a weighted GRS was also an independent predictor even after adjusting for age, sex and TRFs in a Northern European population-based trial. The relative risk of the GRS based on 13-SNP was also lower than that of dyslipidemia and comparable to the effects of hypertension.[22]

An increased power to TRFs definition has been given in this study. For instance, we have used a broad dyslipidemia term including Apo B levels as indicated by 2016 lipid guidelines.[7] Moreover, we have not considered ex-smokers until 5 years of cessation to account for the risk for CV disease events decrease be comparable to a nonsmoker.[5]

Thanassoulis et al.[24] demonstrated that adding to a 13 SNP-based GRS, 89 SNPs associated with modifiable risk factors did not increase the power of the GRS reporting a HR of 1.01 (95% CI 0.99 –1.03; p = 0.48). This revealed that the weak association of polymorphisms with CAD risk factors in GRS analysis could be masked by the relative stronger effect of other polymorphisms. Considering the lack of a significant association of lipid profiles with CAD risk, Jansen et al. reported in 2015 that several SNPs associated with type 2 diabetes mellitus were related with CAD risk.[25] Recently, Webb et al. identified 6 new loci associated with CAD at genome-wide significance. The study confirmed a pleiotropy between lipid traits, blood pressure phenotypes, body mass index, diabetes, and smoking behavior.[26] Our GRS is an assembly of risk factors and non-risk factors-related SNP, reinforcing the genotype-phenotype interactions.

Limitations of this study

The main clinical utility of the GRS in our population is a modest improvement in risk stratification. GRS seems to be a better indicator of patients at a higher than average risk for DAC as compared with TRF stratification. The number and type of SNPs included is limited in our study and a larger number of GWAS hit SNPs should be included in further studies. Nevertheless, the increasing capability of analyzing multiple SNPs in GRS so far have not been translated into increasing ability of risk prediction.

Finally, this study did not include a gene-gene (G-G) and gene-environment (G-E) analysis. It is expected that, as better statistical significance arises from those interplays, the G-G and G-E incorporation in GRS plus TRF will increase our ability to accurately and individually predict risk.

Conclusions

We conclude that a multilocus GRS based on multiple variants of genetic risk was associated to an increased cardiovascular risk in a Portuguese population. We found that a GRS calculated with the 31 studied SNPs was significantly associated to CAD and that 25% of individuals who carry the greatest risk alleles have, approximately,

2.5 times increased CAD risk when compared to those in the lowest quartile. This GRS has provided a slight improvement of the predictive ability compared to the initial model and can enhance individual risk stratification. These results highlight the potential value of including genetic information in the usual models.

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Author contributions

Conception and design of the research and Writing of the manuscript: Pereira A; Acquisition of data: Pereira A, Freitas AI, Sousa AC, Brehm A; Analysis and interpretation of the data and Statistical analysis: Pereira A, Freitas S, Henriques E, Rodrigues M; Critical revision of the manuscript for intellectual content: Pereira A, Mendonça MI, Borges S, Brehm A, Reis RP.

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of Doctoral submitted by Andreia Pereira, from Universidade Nova de Lisboa.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the SESARAM, EPE under the protocol number 50/2012. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Supplementary Table 1 – List of the 33 genetic variants previously associated with coronary artery disease risk, used for the development of the genetic risk score in the study population

SNP ID	Nearest gene	Chr	Position	Genotypic OR (95%CI)	p value	Allelic OR (95%CI)	p value	MAF (%)	Potential Mechanism of Action
rs1333049	9p21.3	9	22125504	1.147 (1.036-1.270)+	0.008	1.155 (1.041-1.282)	0.007	45.8	Cellular
rs4977574	CDKN2B	9	22098575	1.161 (1.049-1.286)+	0.004	1.172 (1.056-1.302)	0.003	42.0	Cellular
rs618675	GJA4	1	34922761	1.143 (0.792-1.649)*	0.475	1.046 (0.918-1.191)	0.502	19.6	Cellular
rs17228212	SMAD3	15	65245693	1.202 (0.888-1.629)*	0.234	1.025 (0.910-1.155)	0.684	25.3	Cellular
rs17465637	MIA3	1	222650187	1.088 (0.971-1.220)+	0.148	1.088 (0.971-1.220)	0.147	28.6	Cellular
rs12190287	TCF21	6	134256218	1.230 (1.100-1.375)+	< 0.0001	1.226 (1.098-1.368)	0.0003	32.7	Cellular
rs3825807	ADAMTS7	15	76876166	1.073- (0.967-1.191)+	0.185	1.074 (0.967-1.194)	0.181	41.2	Cellular
rs11556924	ZC3HC1	7	130023656	1.227 (1.058-1.423)*	0.007	1.157 (1.037-1.290)	0.009	34.3	Cellular
rs1332844	PHACTR1	6	12927312	1.113 (1.003-1.235)+	0.044	1.113 (1.003-1.236)	0.043	44.3	Cellular
rs2114580	PCSK9	1	55167236	1.079 (0.821-1.417)*	0.587	0.974 (0.866-1.096)	0.665	26.3	Lipids
rs3798220	LPA	6	160540105	1.484 (1.212-1.816)+	< 0.0001	2.167 (1.452-3.235)	< 0.0001	2.1	Lipids
rs20455	KIF6	6	39357302	1.129 (0.896-1.424)*	0.306	1.060 (0.949-1.184)	0.302	32.8	Lipids
rs7412/ rs429358[1]	APOE[1]	19	44908822/ 44908684	1.261 (1.062-1.497)#	0.008	1.231 (1.056-1.435)	0.008	13.4	Lipids
rs964184	ZNF259	11	116778201	1.131 (0.986-1.298)+	0.078	1.130 (0.986-1.295)	0.079	17.7	Lipids
rs599839	PSRC1	1	109279544	1.059 (0.933-1.203)+	0.375	1.058 (0.933-1.201)	0.379	21.4	Lipids
rs1801133	MTHFR 677	1	11796321	1.178 (1.017-1.365)#	0.029	1.114 (0.998-1.243)	0.055	33.5	Oxidation
rs1801131	MTHFR 1298	1	11794419	0.944 (0.816-1.093)#	0.443	0.958 (0.854-1.075)	0.465	28.0	Oxidation
rs705379	PON -108	7	96324583	1.135 (0.950-1.355)#	0.163	1.068 (0.962-1.184)	0.217	46.4	Oxidation
rs662	PON 192	7	95308134	0.836 (0.652-1.072)*	0.157	0.927 (0.828-1.037)	0.186	30.1	Oxidation
rs854560	PON 55	7	95316772	1.161 (1.044-1.290)+	0.006	1.161 (1.044-1.290)	0.006	40.4	Oxidation
rs6922269	MTHFD1L	6	150931849	1.067 (0.804-1.416)*	0.653	0.996 (0.887-1.118)	0.943	27.3	Oxidation
rs5186	AT1R	3	148742201	1.245 (0.906-1.710)*	0.177	1.062 (0.942-1.198)	0.323	24.7	RAS
rs699	AGT	1	230710048	0.932 (0.798-1.090)#	0.380	0.969 (0.873-1.076)	0.552	42.9	RAS
rs4340	ACE	17	61565892	1.165 (1.001-1.355)*	0.048	1.083 (0.973-1.205)	0.143	38.1	RAS
rs4402960	IGF2BP2	3	185793899	1.124 (0.876-1.443)*	0.358	1.020 (0.911-1.141)	0.736	30.8	Diab/Obes
rs1326634	SLC30A8	8	117172544	1.213 (0.914-1.609)#	0.181	1.081 (0.961-1.217)	0.195	25.8	Diab/Obes
rs266729	ADIPOQ	3	186841685	1.209 (1.041-1.403)#	0.013	1.165 (1.030-1.318)	0.015	23.3	Diab/Obes
rs7903146	TCF7L2	10	112998590	0.961 (0.862-1.072)+	0.480	0.962 (0.863-1.072)	0.482	35.3	Diab/Obes
rs17782313	MC4R	18	60183864	1.314 (0.931-1.855)*	0.120	1.016 (0.896-1.152)	0.806	21.6	Diab/Obes
rs1801282	PPARG	3	12351626	1.427 (0.717-2.843)#	0.309	1.164 (0.970-1.396)	0.102	8.8	Diab/Obes
rs1884613	HNF4A	20	44351775	1.159 (0.987-1.360)#	0.072	1.106 (0.960-1.273)	0.163	16.2	Diab/Obes
rs8050136	FTO	16	53782363	1.194 (1.026-1.390)#	0.022	1.129 (1.016-1.255)	0.025	39.7	Diab/Obes
rs1376251	TAS2R 50	12	11030119	1.556 (0.767-3.155)*	0.217	1.080 (0.920-1.267)	0.349	11.9	Diab/Obes

*SNP: Single Nucleotide Polymorphism; Chr: Chromosome; OR: Odds Ratio; CI: Confidence Interval; MAF: Minor Allele Frequency; RAS: Renin-Angiotensin System; Diab/Obes: Diabetes/Obesity; +Additive model;*Recessive model; #Dominant model; [1]Resulting from a Haplotype; Table shows susceptibility loci for coronary artery disease, genotypic and allelic ORs and p values for the lead SNP within each locus reported in genome-wide association studies and candidate gene studies. Genotypic ORs are given for additive, recessive and dominant models. Potential mechanism of action is on the basis of what is already known about the function of the nearby genes. It includes "Cellular" (genes associated to cell cycle, cellular migration and inflammation); "Oxidation" (genes involved in pro-oxidative status) and associated with modifiable risk factors such as "Lipids" metabolism, hypertension ("RAS") and Diabetes/Obesity.*

Supplementary Table 2 – Logistic regression with respective ORs and ROC curves with respective AUCs of the GRS models

GRS models	OR (95% CI)	P value[1]	AUC (95% CI)	Sensitivity (%)	Specificity (%)	P value[2]
Multiplicative	1.78 (1.52 – 2.10)	< 0.0001	0.61 (0.59 – 0.62)	54.0	62.3	< 0.0001
Additive	1.06 (1.04 – 1.09)	< 0.0001	0.56 (0.54 – 0.58)	58.7	50.5	< 0.0001
Weighted (Best model OR)	1.02 (0.94 – 1.10)	0.660	0.57 (0.55 – 0.59)	41.0	70.3	< 0.0001
Weighted (Beta)	2.23 (1.88 – 2.65)	< 0.0001	0.60 (0.58 – 0.61)	43.0	71.5	< 0.0001
Weighted (Literature OR)	1.35 (1.12 – 1.62)	0.001	0.54 (0.52 – 0.55)	53.4	54.1	0.008
Classic weighted	3.01 (2.32 – 3.89)	< 0.0001	0.59 (0.57 – 0.61)	59.4	54.4	< 0.0001

OR: Odds ratio; ROC: Receiver Operating Characteristic; AUC: Area under curve; GRS: Genetic Risk Score; CI: Confidence interval; P value[1]: Obtained by logistic regression to evaluate the significance of the odds ratio; P value[2]: Obtained by the ROC Curve to verify the significance of the area under the curve; Statistically significant for p < 0.05.

Genetic Risk in Coronary Artery Disease

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Short Editorial regarding the article: Genetic Risk Analysis of Coronary Artery Disease in a Population-based Study in Portugal, Using a Genetic Risk Score of 31 Variants

Coronary artery disease (CAD) is a leading cause of death worldwide. It is most commonly caused by atherosclerosis in coronary arteries. Coronary artery disease has a complex etiology, mainly a combination of traditional risk factors and genetic predisposition. Traditional risk factors include type 2 diabetes, dyslipidemia, arterial hypertension, and cigarette smoking.[1] However, these are not sufficient to identify high risk asymptomatic individuals and do not explain all cases of CAD. In fact, hereditary influence on CAD susceptibility accounts for between 40% and 50% of cases.[2]

Polymorphisms are common genetic variations, defined as being present in more than 1% of the population.[3] A polymorphism is a nucleotide substitution that does not alter the primary amino acid structure of the resulting protein.[3] A single-nucleotide polymorphism (SNP) is a variation in DNA in a single nucleotide that occurs at a specific position in the genome. An SNP may be a marker of disease susceptibility.[3] Populations of healthy and affected individuals can be evaluated by genotyping SNP within a gene and its regulatory sequences.[4] Genome-wide association studies (GWAS) have been used to create genetic risk scores to improve CAD risk prediction.[4-6] However, their value as an independent risk predictor for CAD is not clear.

In this issue of *Arquivos Brasileiros de Cardiologia*, Pereira et al.[7] provide us with an interesting study on generating a multilocus genetic risk score based on common variants already associated with CAD. They then evaluated whether genetic risk score is independent of the traditional risk factors and improves CAD risk prediction in relation to a traditional risk factor only model.

By searching data from the National Human Genome Research Institute, the authors analyzed 33 genetic variants previously associated with CAD. The study population was selected from GENEMACOR (*GENEs in a population from the Portuguese island of MAdeira with CORonary artery disease*), a developing case-control population study with 1,566 cases and 1,322 controls. Coronary risk was determined by logistic regression analysis. Two ROC curves were constructed, one with and one without genetic risk score; these were compared by use of the DeLong test. The estimated area under the traditional risk factor ROC curve was 0.72, which statistically increased to 0.74 when the genetic risk score was added, thus revealing a better fit of the model. The study strength comes from assessing a large sample size and a homogenous population as only permanent Madeira residents were included.

Genetic risk scores have undergone extensive study and major progress has been made to better understand the role of genetic influence on CAD and the function of each novel locus.[4,8-13] However, the role of most genetic variants in disease processes remains unknown.[10] Furthermore, the presence or lack of a traditional risk factor may determine whether or not a genetic factor will contribute to disease.[5]

Although in the study by Pereira et al.[7] the addition of genetic risk score gave a statistically superior score in identifying high risk patients, the difference between the two risk factor curves was small. Therefore, considering that traditional risk factors have been poorly controlled in the general population and the high financial cost of determining genetic risk scores, it is important to remain focused on preventing and controlling traditional risk factors until the role of genetic risk scores is better understood.

Keywords

Coronary Artery Disease/genetics; Polymorphism, Genetic; Genome-Wide Association Study.

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Effects of Coexistence Hypertension and Type II Diabetes on Heart Rate Variability and Cardiorespiratory Fitness

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Abstract

Background: Type 2 diabetes Mellitus (T2DM) is associated with cardiac autonomic dysfunction, which is an independent predictor of mortality in chronic diseases. However, whether the coexistence of systemic arterial hypertension (HTN) with DMT2 alters cardiac autonomic modulation remains unknown.

Objective: To evaluate the influence of HTN on cardiac autonomic modulation and cardiorespiratory fitness in subjects with DMT2.

Methods: 60 patients of both genders were evaluated and allocated to two groups: DMT2 patients (n = 32; 51 ± 7.5 years old) and DMT2 + HTN patients (n = 28; 51 ± 6.9 years old). RR intervals were obtained during rest in supine position. Linear and nonlinear indices of heart rate variability (HRV) were computed using Kubios HRV software. Pulmonary gas exchange was measured breath-by-breath, using a portable telemetric system during maximal incremental exercise testing on a cycle ergometer. Statistical analysis included Shapiro-Wilk test followed by Student's t Test, Pearson correlation and linear regression.

Results: We found that patients in the DMT2+HTN group showed lower values of mean RR intervals (801.1 *vs* 871.5 ms), Shannon entropy (3 *vs* 3.2) and fractal dimension SD 1 (9.5 vs 14.5), when contrasted with patients in the DMT2 group. Negative correlations were found between some HRV nonlinear indices and exercise capacity indices.

Conclusion: HTN negatively affects the cardiac autonomic function in diabetic patients, who are already prone to develop autonomic dysfunction. Strategies are need to improve cardiac autonomic functionality in this population. (Arq Bras Cardiol. 2018; 111(1):64-72)

Keywords: Hypertension/prevalence; Diabetes Mellitus,Type 2; Cardiovascular Diseases; Risk Factors; Autonomic Nervous System; Heart Rate.

Introduction

The prevalence of hypertension in patients with type 2 diabetes mellitus (T2DM) is up to three times higher than in patients without T2DM.[1] The coexistence of hypertension and diabetes significantly increases the probability of developing cardiovascular disease (CVD).[2]

The harmful association of these two conditions may cause deleterious effects on the cardiovascular system, accelerating the atherosclerosis process involved in both T2DM and hypertension.[3] In addition, it is well known that cardiac autonomic neuropathy (CAN), resulting from damage to the autonomic nerve fibers that innervate the heart and blood vessels, is a serious complication of T2DM[4] and systemic arterial hypertension (HTN).[5]

The autonomic nervous system plays a significant role in the circulatory system and in blood pressure regulation.[6] Damage to the nerve fibers that innervate the heart and blood vessels leads to abnormalities in heart rate (HR) control and vascular dynamics.[7] Heart rate variability (HRV) analysis is a widely used tool to assess the cardiac autonomic regulation.[8] HRV is commonly analyzed using linear models, such as time domain and spectral analysis; however, non-linear methodologies have been recently proposed as novel tools to investigate the complexity of HR dynamics.[9]

It has been widely documented that reduced HRV is associated with various pathological conditions, including CVDs, such as hypertension[10] and diabetes.[11] However, despite the evidence that HRV is reduced in the presence of one of these conditions, it remains unknown whether HRV is altered in the coexistence of T2DM and HTN.

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Additionally, it is well established that exercise capacity, which is a strong predictor of cardiovascular and overall mortality,[12] is reduced in patients with T2DM compared with non-diabetic subjects [13] as well as hypertensive patients.[14] Although the causes of reduced exercise capacity in these populations are unknown, cardiac autonomic dysfunction may play an important role in the development of heart disease in diabetic patients leading to impaired exercise capacity.[15]

Recently, new variables derived from the cardiopulmonary exercise test (CPET), such as circulatory power (CP) and ventilatory power (VP) have been used for the clinical evaluation of heart failure patients as important markers of exercise limitation[16]. These indices could provide a potentially valuable measure of cardiopulmonary function in the coexistence of TM2DM and HTN.

Considering this knowledge gap, the primary objective of the present study was to assess the cardiac autonomic modulation in T2DM patients with and without HTN. The secondary objective was to verify if HRV indices are correlated with exercise capacity in these patients.

We hypothesized that patients affected by DMT2 and HTN would have an altered cardiac autonomic control when compared with diabetics and that there would be a correlation between HRV indexes and exercise capacity.

Methods

Design

The present investigation is a cross sectional study.

Participants

A total of 60 patients (mean age ± SD = 51 ± 7 years; 42 male and 18 female) diagnosed with T2DM, followed at the cardiovascular outpatient clinic of the Federal University of Sao Carlos (UFSCar), agreed to participate in the study. Patients were divided into two groups according to the presence or not of HTN: 1) DMT2 (n = 32; 20 males and 12 female) and 2) T2DM + HTN (n = 28; 20 males and 8 female). Duration of DMT2 and HTN was recorded, based on the date of diagnosis self-reported by patients. The experimental procedures were performed in the UFSCar Cardiopulmonary Physiotherapy Laboratory.

Inclusion criteria for both groups consisted of age between 40 and 60 years and clinically diagnosed DMT2 – based on fast glycemia and hemoglobin A1c (HbA1c) values, according to current guidelines – currently under hypoglycemics and clinically stable for at least 6 months. All patients were sedentary (self-reported). In the DMT2 + HTN group, diabetic subjects had clinical diagnosis of HTN and were under hypoglycemic and antihypertensive therapy. Exclusion criteria consisted of a history consistent with coronary heart disease or other concomitant respiratory diseases.

RR interval recording

The RR intervals were recorded continuously using a Polar S810i telemetry system (Polar Electro Oy, Kempele, Finland) at a sampling rate of 500Hz, and these data were used to derive the HRV indices. Each subject rested for 10 minutes before the initiation of data collection to ensure HR stabilization. The RR interval signal was continuously recorded for 10 minutes, while the patient rested in supine position, breathing spontaneously. Participants were instructed not to speak unnecessarily during the evaluation to avoid HR signal interference.

HRV analysis

The RR interval signals were transferred to a microcomputer and reviewed by visual inspection by an independent examiner to verify the quality of the signals and detect any abnormalities. Segments which presented any abnormalities were discarded. The data were transferred to Kubios HRV analysis software (MATLAB, version 2 beta, Kuopio, Finland) and a stable and free of artifacts series of 256 sequential RR intervals was selected and analyzed. To analyze the tachograms, a multivariate approach was followed, which allows for a comprehensive assessment of the cardiac autonomic function.

The nonlinear dynamic properties of HRV were analyzed by calculating approximate entropy (ApEn),[17] correlation dimension (CD)[18] and Poincaré plots[19]. ApEn quantifies the regularity of a time series and represents a simple index of the overall complexity and predictability of the signal. High ApEn values indicate high irregularity, while smaller values indicate a more regular signal. Thus, higher ApEn values reflect better health and function.[17] The CD index represents a measure of the dimensionality of the space occupied by the state vectors or the number of the degrees of freedom of a time series, also referred to as fractal dimension. A higher CD reflects more degrees of freedom of the cardiac sinoatrial node and, therefore, a greater range of possible adaptive responses to internal or external stimuli in an ever-changing environment.[20]

Poincaré plots were built for each RR interval series and the following two descriptors were computed: (i) SD1 – the standard deviation measuring the dispersion of points perpendicular to the line-of-identity. This parameter is usually interpreted as a measure of short-term HRV, which is mainly influenced by respiratory sinus arrhythmia (parasympathetic modulation); and (ii) SD2 – the standard deviation measuring the dispersion of points along the identity line, which is interpreted as a measure of both short- and long-term overall HRV. Shannon entropy (SE) was computed to quantify the degree of complexity of the distribution of the signals samples.[21]

A set of time domain HRV parameters were calculated, including: (i) mean and standard deviation of RR intervals (SD RR), in ms; (ii) square root of the mean squared differences of successive RR intervals (RMSSD), in ms; and (iii) geometrical parameters, including the integral of the RR interval histogram divided by the height of the histogram (RR tri index) and the baseline width of the histogram (TINN), in ms. A spectral analysis was performed on the tachograms, in order to calculate the signal spectral power in the frequency band between 0.03 Hz and 0.14 Hz (low-frequency [LF] band) and in the frequency band between 0.15 Hz and 0.4 Hz (high-frequency [HF] band), both expressed in

normalized units.[22] STD RR represents a global index of HRV and reflects all the cyclic components responsible for variability in the recording period; RMSSD reflects alterations in autonomic tone that are predominantly vagally mediated; the geometrical HRV indices are an estimate of the overall HRV.[23] However, reference values for these parameters, available in the literature, were obtained in healthy subjects aged from 40 to 60 years –rMSSD from 33.39 to 28.77 (ms) for male and from 30 to 25.80 (ms) for female; HFnu from 22.85 to 24.51 for male and from 27.74 to 27.94 female; LFnu from 77.07 to 75.49 for male and from 72.26 to 72.06 for female; LF/HF from 3.36 to 3.08 for male and from 2.60 to 2.58 female. Reference values for nonlinear variables are also available only for the same age – SD1 from 24.01 to 20.56 for male and from 21.55 to 18.44 (ms) for female and SD2 from 198.61 to 185.20 for male and from 176.15 to 165.41 (ms) for female.[24]

Laboratorial exams

Blood samples were obtained after an overnight fast. HbA1c was measured in a central laboratory by anion-exchange high-performance liquid chromatography (Variant II, Bio Rad, Berkeley, California), coupled with a fluorescence detector method certified by the National Glycohemoglobin Standardization Program.[25]

Insulin resistance was evaluated by HOMA–IR using the following formula: (fasting plasma glucose [mg/dL] x fasting plasma insulin [μU/mL] / 22.5).[25] Fasting plasma glucose was measured by an enzymatic method using an AU 680® (Beckman Couter, Suarlée, Namur, Belgium) and fasting plasma insulin was measured by a chemiluminescent assay (UniCel® DxI 800, Pasadena, California, USA). Total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides were measured by an enzymatic method using the AU 680® (Beckman Couter, Suarlée, Namur, Belgium). The Brazilian Society of Diabetes criteria for metabolic control were used as reference values – HbA1c 7% or 53 mmol/mol and fasting plasma glucose < 110 mg/dL.[26]

Cardiopulmonary exercise testing (CPET)

A symptom-limited incremental exercise test was performed on a cycle ergometer (Recumbent Corival of MedGraphics - Minnesota, USA.). Gas exchange and ventilatory variables were recorded during the test using a calibrated computer-based exercise system (Metabolic analyzer System Greenhouse telemetry module for field studies Oxycon-Mobile, Jaeger, Hoechberg, Germany).

The day before the CPET, subjects were taken to the experimental room for familiarization with the procedures and equipment to be used.

All subjects were evaluated in the morning to avoid circadian influences on their physiological responses. All subjects were instructed to: (i) avoid caffeinated and alcoholic beverages or any other stimulants (drinks, foods or medications) the night before and the day of data collection; and (ii) not to perform activities requiring moderate-to-heavy physical exertion on the day before data collection. The tests were carried out under controlled relative air humidity and temperature conditions. Before the CPET, the exercise protocol was described to each subject by a member of our group.[27]

Peak VO_2 was defined as the highest VO_2 value during the last 15 seconds of exercise.[28] Fifteen second averaged ventilation (V_E) and carbon dioxide production (VCO_2) data, obtained from the initiation of exercise to exercise peak, were input into Microsoft Excel, Microsoft Corp., Bellevue, WA, USA).

Outcome measures

Primary outcome: The primary outcome measures were the HRV indices, able to detect abnormalities in the cardiac autonomic system regulation.

Secondary outcome: As a secondary outcome measure, the exercise capacity was assessed by CP and VP, both of which have been showed to serve as a surrogate predictor of mortality and prognosis.[16]

Statistical analysis

Data are reported as mean ± SD. All data were verified for the assumptions of normality, and comparisons between groups (T2DM *vs* T2DM+HTN) were performed using unpaired t tests. The categorical variables were presented in percentage (absolute number) and the comparisons between the groups of these variables were performed by means of the chi-square test. Statistical analyses were performed using Statistica 5.5 (StatSoft Inc., Tulsa, USA).

Pearson's product moment correlation coefficient was used to examine the relationship between linear and nonlinear indices and cardiorespiratory variables. The magnitude of the correlations was determined considering the following classification scheme for r-values ≤ 0.35 low or weak; $r = 0.36 \leq 0.67$ moderate; $r \geq 0.68$ strong or high; $r \geq 0.9$ very high; $r = 1$ perfect.[29] The probability of a type I error was set at 5% for all tests ($\alpha = 0.05$).

Results

Subject characteristics

A total of 60 patients were evaluated over a 1-year period. Table 1 shows demographic, anthropometric and clinical characteristics of subjects in the two groups (DMT2 and DMT2+HTN).

There were no significant differences between groups in baseline characteristics (age, height, and duration of T2DM). However, BMI was higher in the group of patients with both diseases ($p = 0.03$). However, no other body composition measurements were performed in order to better characterize the body status. There were no significant differences regarding other risk factors for CVD and oral hypoglycemic medications. Additionally, insulin and HOMA-IR were significantly higher in T2DM + HTN when compared to T2DM, indicating higher insulin resistance. There were no significant differences for fasting plasma glucose, total-C, LDL-C, HDL-C and HbA1c. The HRV indices are presented in Table 2. Mean values of RR intervals and the nonlinear indices SD1, Shannon entropy and ApEn were significantly lower in T2DM +HTN when compared to T2DM.

Table 1 – Patients demographic, anthropometric and clinical characteristics

Variables	DMT2 (n = 32)	DMT2+HTN (n = 28)	p value
Gender (males/females)	20/12	20/8	0.464
Age (years)	51 ± 7.5	51 ± 6.9	0.660
Weight (kg)	79.3 ± 9.6	86.2 ± 14*	0.033
Height (m)	1.7 ± 0.1	1.7 ± 0.1	0.450
BMI (kg/m^2)	28.5 ± 4.4	31 ± 3.8*	0.031
Duration DMT2 (years)	5.7 ± 5.3	6.6 ± 6.4	0.334
Duration HTN (years)	-	3 ± 2.6	-
SBP (mmHg)	129 ± 16	140 ± 20	0.021
DBP (mmHg)	87 ±7	94 ± 12	0.011
Medications			
Antiglycemics - % (n)			
Biguanides	87.5 (28)	75 (21)	0.312
Sulfonylureas	50 (16)	57.1 (16)	0.613
DPP-4 inhibitors	6.2 (2)	-	-
Antihypertensive- % (n)			
ARBII	-	50 (14)	-
Diuretics	-	25 (7)	-
ACE I inhibitors	-	21.4 (6)	-
Renin Inhibitors	-	10.7 (3)	-
β-blocker	-	7.1 (2)	-
Risk factors - % (n)			
Smoking	-	-	-
CAD family history	21.88 (7)	25 (7)	1.000
Sedentarism	100 (32)	100 (28)	1.000
Dyslipidemia	43.75 (14)	46.43 (13)	1.000
Laboratory exams			
HbA1c (%)	8 ± 2.14	8.7 ± 1.6	0.394
Insulin (μU/mL)	12 ± 8	19.1 ± 12.5*	0.010
Fasting glucose (mg/dL)	160 ± 69.4	164.6 ± 50.7	0.774
QUICKI	0.34 ± 0.07	0.29 ± 0.02*	0.011
HOMA-IR	4 ± 4	8 ± 6.6*	0.020

*Data are expressed as mean ± standard deviation. DMT2: type 2 diabetes Mellitus HTN: arterial hypertension; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure (reference values according to the Brazilian Society of Diabetes criteria; DPP4: dipeptidyl peptidase-4; ARBII: angiotensin II receptor antagonists; ACE I: angiotensin converting enzyme I inhibitor; CAD: coronary artery disease; HbA1c: glycated hemoglobin; QUICKI: quantitative insulin sensitivity check index; HOMA-IR: homeostatic model assessment insulin resistance. * p<0.05, unpaired Student's t-test or chi-square test.*

Cardiopulmonary exercise test

Table 3 shows the comparison between groups in relation to peak variables obtained during the CPET. Compared with the T2DM group, T2DM+HTN had significantly higher values of systolic blood pressure (SBP) and diastolic blood pressure (DBP) at rest ($p = 0.02$).

Considering only the DMT2 group, we found that ApEn influenced the slope ($R^2 = -0.40$, $p < 0.05$) and the VP ($R^2 = -0.48$, $p < 0.02$) (Figure 1). Finally, when we considered both T2DM and T2DM + HTN groups, we found that the nonlinear indices influenced the VP ($R^2 = -0.10$, $p < 0.03$) and the V_E/VCO_2 slope ($R^2 = -0.08$, $p < 0.05$) (Figure 2).

Maximum workload was no different between groups, as well as VO_2, VCO_2, respiratory exchange ratio (RER), slope, CP and VP. Stepwise regression analysis was performed to determine the possible influence of HRV indices on CPET variables of interest, which was observed with three of the variables, affected by risk factors – slope was influenced by SD1 (interaction effects: $R^2 = -0.28$, $p < 0.005$) and VP ($R^2 = -0.32$, $p < 0.03$), when both groups considered together.

Table 2 – Linear and non-linear HRV indices for both groups in resting conditions

Variables	DMT2 (n = 32)	DMT2+HTN (n = 28)	p value
Linear			
Mean RR intervals (ms)	871.5 ± 105.8	801.1 ± 89.0*	0.010
RMSSD (ms)	17.9 ± 11.1	21.2 ± 15.2	0.358
STD RR	29.3 ± 21.5	31.5 ± 23.2	0.718
LF (nu)	66.3 ± 19.8	59.7 ± 22.9	0.247
HF (nu)	33.7 ± 19.8	40.3 ± 22.9	0.241
TINN	110.5 ± 59.8	121.3 ± 67.5	0.523
RR Tri	5.5 ± 2.6	7.1 ± 4.5	0.082
Nonlinear			
SD1	14.5 ± 8.2	9.5 ± 4.4*	0.021
SD2	40.4 ± 20.0	43.0 ± 23.1	0.662
SE	3.2 ± 0.3	3.0 ± 0.3*	0.012
ApEn	14.5 ± 8.2	9.5 ± 4.4*	0.021
SampEn	1.4 ± 0.3	1.5 ± 0.3	0.601
CD	1.2 ± 1.3	1.6 ± 1.6	0.271

*Data are expressed as Mean ± SD. HRV: heart rate variability; RMSSD: square root of the mean squared differences of successive RR intervals; STD RR: standard deviation of RR; LF nu: normalized unit in the low frequency band; HF nu: normalized unit in the high frequency band; TINN: baseline width of the RR intervals histogram; RR tri: integral of the RR interval histogram divided by the height of the histogram; SD: standard deviation of instantaneous RR interval variability, SE: Shannon Entropy; ApEn: approximate entropy; SampEn: sample entropy, CD: correlation dimension. * p < 0.05, unpaired Student's t-test.*

Table 3 – Cardiopulmonary exercise testing responses

Variables	T2DM (n = 32)	T2DM+HTN (n = 28)	p value
VO_2 ($ml.Kg^{-1}.min^{-1}$)	22.6 ± 7.5	20.4 ± 3.5	0.18
VCO_2 ($mL.min^{-1}$)	2126.7 ± 673.5	2186.8 ± 510.3	0.72
V_E ($L.min^{-1}$)	63.9 ± 19.7	69.5 ± 15.7	0.26
RER	1.2 ± 0.1	1.2 ± 0.1	0.59
V_E/VCO_2 slope	28.4 ± 4.6	29.9 ± 4.6	0.27
CP ($mmHg.ml.kg^{-1}\ min^{-1}$)	4902.7 ± 2004.9	4642.3 ± 1157.1	0.58
VP (mmHg)	1.4 ± 0.5	1.5 ± 0.4	0.26
SBP rest (mmHg)	130.03 ± 16.08	137.6 ± 17.4	0.10
DBP rest (mmHg)	86.7 ± 7.6	92.7 ± 11.2‡	0.02
SBP peak (mmHg)	209 ± 32.1	225.4 ± 24.6‡	0.04
DBP peak (mmHg)	100.38 ± 16.35	104.1 ± 16.4	0.41
Workload (watts)	125.4 ± 37.4	126.5 ± 36.5	0.92

Data are expressed as Mean ± SD. ‡ Unpaired Student's t-test. T2DM: type 2 diabetes mellitus; HTN: hypertension; VO_2: oxygen uptake; VCO_2: carbon dioxide production; RER: respiratory exchange ratio; VE/VCO_2 slope: minute ventilation/carbon dioxide output relationship from the beginning of exercise to peak exercise; CP: circulatory power; VP: ventilator power; SBP: systolic blood pressure, DBP: diastolic blood pressure.

Discussion

Summary of findings

The main findings of the present study are: (i) individuals with DMT2 associated with HTN, even when controlled, presented with a greater impairment in linear and nonlinear HR dynamics compared to those with only DMT2; (ii) novel CPET derived parameters, confirming our hypothesis. To our knowledge, this is the first study to address nonlinear HR dynamics in this specific population. The findings of the present study stress the clinical importance of early evaluation of the cardiac nervous system functionality, once the association between T2DM and HTN alters the cardiac autonomic modulation.

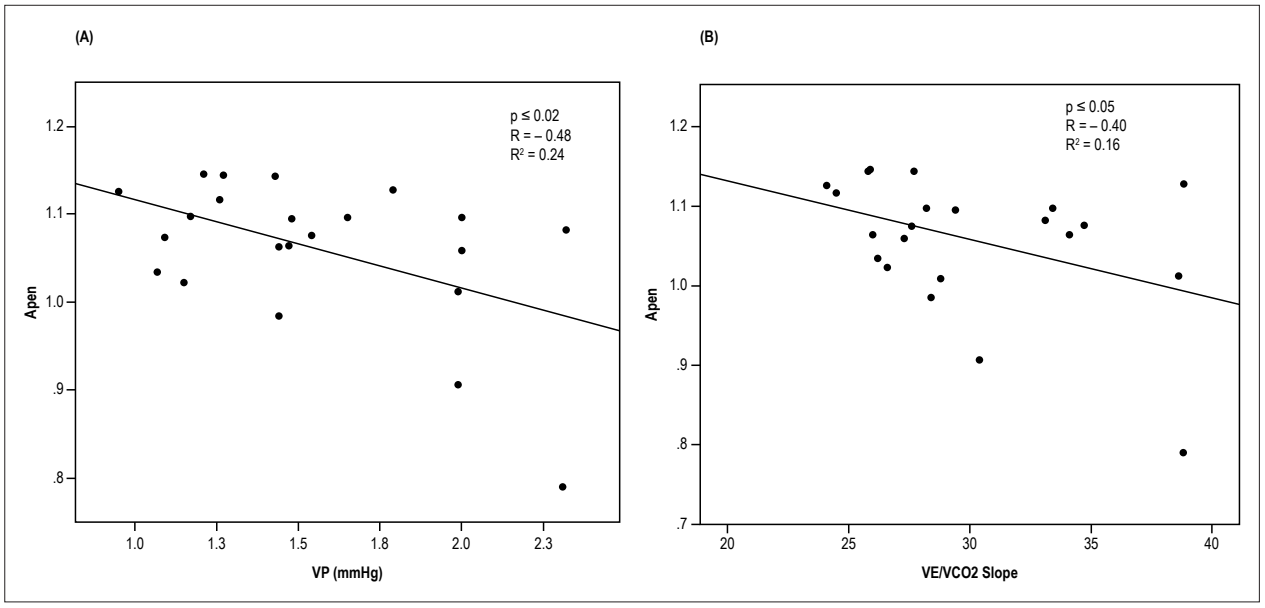

Figure 1 – *Significant and inverse relationship of approximate entropy (ApEn) with ventilatory power (VP) (A) and minute ventilation/carbon dioxide production ratio (V_E/VCO_2) slope (B) in response to peak intensity exercise in patients with type 2 diabetes.*

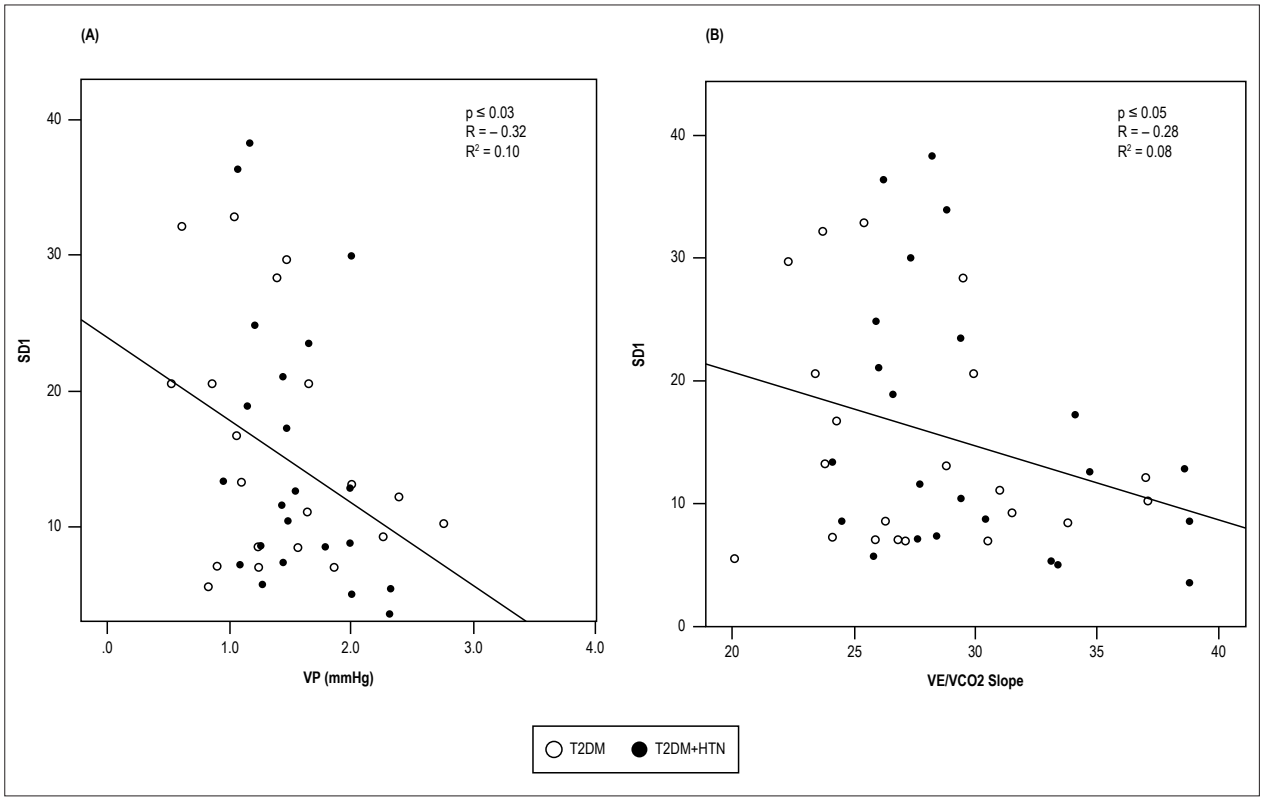

Figure 2 – *Significant and inverse relationship between SD1 and (A) VP (A) and between SD1 and (B) V_E/VCO_2 slope in response to peak intensity exercise in patients with diabetes mellitus type 2 and hypertension (TD2DM+HTN) (●) and in patients with type 2 diabetes mellitus (TD2DM) (°).*

Relevance of the present study

This is the first study, to our knowledge, to assess linear and nonlinear HRV dynamics in the coexistence of HTN and T2DM. Previous studies have reported cardiac autonomic dysfunction in diabetic subjects and in hypertensive subjects;[30] this study is relevant, as it showed that there is a simultaneous influence of HTN and DMT2 on nonlinear HRV indexes and on novel CPET derived parameters. In addition, VP and CP, indices that combine parameters of CPET with systemic hemodynamics during exercise represent important

physiologic measurements related to the ability to respond to aerobic exertion synergistically. In the present study these indices were shown as important markers of cardiocirculatory limitation to exercise in DMT2 and HTN.

Effects of the coexistence of DMT2 and HTN on linear and nonlinear HRV dynamics

HRV is reduced in patients with DMT2[31] as well as in patients with HTN[32] and its reduction is associated with poor cardiovascular prognosis.[33] Autonomic imbalance may be a final common pathway to increased morbidity and mortality in the presence of various conditions, including CVD.[34]

Although time and frequency-domain HRV parameters have been shown to be more sensitive in a previous study,[35] in the present study we did not find significant alterations in these parameters. Roy and Ghatak[36] in their study with diabetic type 1 patients diagnosed ≥ 5 years earlier, showed that HRV spectral indices were better indicators of the prevalence of CAN than cardiovascular reflex tests.[36] Meanwhile, the use of HRV spectral analysis only to diagnose CAN should be carefully considered, since previous studies[30,37] showed low reproducibility of HRV assessment by spectral analysis. The presence of CAN is closely associated with macrovascular complications, mortality due to fatal cardiac arrhythmia, severe hypoglycemia, and sudden death.[38]

However, nonlinear indices have been shown to be better than conventional methods for identifying subtle changes in cardiac autonomic modulation in various pathological conditions such as cardiovascular artery disease.[39] Nonlinear analysis has provided new insight into the HRV dynamics in various physiological and pathophysiological conditions, providing additional prognostic and analytical information to conventional approaches.[40] In the currently study, nonlinear indices were found to be reduced in the DMT2+HTN group when compared to the DMT2 group. Additionally, we observed that nonlinear indices of HRV were more sensitive in detecting differences in the autonomic impairment between patients with diabetes and patients with diabetes associated to HTN. ApEn and SE indicated changes that suggest that the coexistence of both diseases is associated to reduced complexity.[41] In the same way, Roy and Ghatak[36] showed that nonlinear analytical methods were effective to find differences in HRV patterns between diabetic patients and healthy matched controls. Recently, our group verified that patients with DMT2 with poor glycemic control are more susceptible to poor autonomic nervous control of HR, demonstrated by linear and nonlinear indices.[31] However, the present study is the first to analyze the coexistence of HTN and DMT2 by means of linear and nonlinear HRV analysis.

The Diabetes Control and Complications Trial (DCCT) showed that glycemic control can reduce the incidence of CAN.[42] Previous studies evidenced that a reduction around 11% in the HbA1c improved HRV in patients with type 1 diabetes.[43]

Additionally, Vinik et al.,[4] showed that the CAN prevalence and mortality rates were higher among individuals with DMT2, probably because of the longer duration of glycemic abnormalities before diagnosis. Our findings showed that, even after a short period from the DMT2 diagnosis, both groups demonstrate poor glycemic control, which might negatively affect HRV and, consequently, increase the patients' cardiovascular risk.

Effects of the coexistence of HTN and DMT2 on CPET

CPET represents an easy and non-invasive way to obtain information on the impairment of exercise capacity and of cardiopulmonary fitness.[44] Ugur-Altun et al.[45] demonstrated a negative correlation between insulin resistance and peak exercise capacity in diabetic patients. Interestingly, in our study we could not find any differences between groups in peak exercise capacity, maybe because both groups had poor glycemic control, as showed by HbA1c, even though the DMT2+HTN group has shown higher insulin resistance than the DMT2 group.

CP, which is related to the cardiac output and the mean arterial blood pressure at peak exercise, is considered a more powerful predictor of mortality than peak oxygen consumption.[46] In our study, we have not found differences in CP and VP between groups; however, negative correlations were shown of CP and VP with nonlinear indices of HRV. Castello-Simões et al.[16] studied patients with CVD (without heart failure) and demonstrated that both CP and VP might hold value as screening tools in assessing not only functional significance but also exercise tolerance, as the impairment of autonomic nervous modulation is related to reduced CP and VP.

The present study has some limitations that need to be stated. First, some relevant information, including DMT2 and HTN diagnostic date and physical activity status were self-reported by the patients and this could introduce a recall bias. Moreover, only the BMI was used to characterize the patients' body type. However, in order to provide a complete description, other body composition measurements should be considered. Secondly, in the present study a control group comprised of individuals without diabetes mellitus or arterial hypertension could be better clarify the potential influence of these risk factors on HRV indices.

Conclusion

In summary, cardiac autonomic alteration in the coexistence of DMT2 and HTN was observed when compared to matched DMT2 patients. In addition, the alteration of nonlinear HRV dynamics observed in resting conditions may have negative consequences on these patients' cardiopulmonary and cardiocirculatory responses.

Author contributions

Conception and design of the research: Bassi D, Cabiddu R, Mendes RG, Arakelian VM, Caruso FCR, Borghi-Silva A; Acquisition of data: Bassi D, Mendes RG, Arakelian VM, Caruso FCR, Bonjorno Júnior JC, Borghi-Silva A; Analysis and interpretation of the data: Bassi D, Mendes RG, Tossini N, Arakelian VM, Arena R, Borghi-Silva A; Statistical analysis: Bassi D, Mendes RG, Arakelian VM, Arena R, Borghi-Silva A; Obtaining financing: Bassi D, Borghi-Silva A; Writing of the manuscript: Bassi D, Cabiddu R, Mendes RG, Tossini N, Arakelian VM, Caruso FCR, Bonjorno Júnior JC,

Borghi-Silva A; Critical revision of the manuscript for intellectual content: Bassi D, Cabiddu R, Mendes RG, Caruso FCR, Bonjorno Júnior JC, Arena R, Borghi-Silva A.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Centro Universitário de Araraquara under the protocol number 1318/1. 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.

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Heart Rate Variability in Coexisting Diabetes and Hypertension

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Short Editorial regarding the article: Effects of Coexistence Hypertension and Type II Diabetes on Heart Rate Variability and Cardiorespiratory Fitness

The autonomic nervous system regulates heart rate through sympathetic and parasympathetic response to different stimuli. The resultant fluctuation between intervals of consecutive heart beats, called heart rate variability (HRV), is a valuable tool to assess autonomic nervous system activity.[1] A decrease in HRV is a marker of reduced parasympathetic and increased sympathetic tone and has long been considered to negatively impact the prognosis in cardiovascular disease.[2]

In 1996, the European Society of Cardiology and the North American Society of Pacing and Electrophysiology suggested standards for evaluation, physiological interpretation, and clinical use for time- and frequency-domain HRV analysis in short- and long-term recordings.[3] Some nonlinear measures have been suggested to work better than traditional measures in predicting future adverse events in several patient groups. More recently, newer computational tools have been derived from nonlinear dynamics and complex systems.[4] Although the physiological background of nonlinear measures of HRV is less understood than the conventional measures, it is speculated that nonlinear dynamics could provide better understanding on nonlinear behavior commonly occurring within human systems due to their complex dynamic nature.[5,6] In accordance, a good agreement between some non-linear HRV measures and the Framingham cardiovascular risk score was observed, suggesting that they could be used for screening cardiovascular risk.[7] In 2015, the e-Cardiology Working Group of the European Society of Cardiology and the European Heart Rhythm Association launched a critical review of new methodologies for analyzing HRV, including entropy rate, fractal scaling and *Poincaré* plot, and their application in different physiological and clinical studies.[8]

Keywords

Hypertension; Diabetes Mellitus; Chronic Disease; Heart Rate; Autonomic Nervous System.

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Alterations in HRV time and frequency domain indices have been frequently observed in chronic diseases, such as diabetes and hypertension, and associated with cardiac autonomic dysfunction.[9,10] Since co-existence of diabetes mellitus and systemic arterial hypertension is very common, some studies have compared HRV between type 2 diabetic patients with and without hypertension, and found contradictory results using time-and frequency-domain HRV analysis.[11-13] However, non-linear dynamics for HRV analysis in type 2 diabetes and hypertension co-existence is still to be explored.

In this issue of the *Arquivos Brasileiros de Cardiologia*, Bassi et al.[14] published a study evaluating the influence of systemic arterial hypertension on cardiac autonomic modulation and cardiopulmonary capacity in type 2 diabetic patients. Diabetes subjects were assigned to a normotensive (n = 32, age = 51 ± 7.5 years) or a hypertensive group (n = 28, age = 51 ± 6.9 years). Both groups had a poor glycemic control (normotensive group: glycated hemoglobin = 8.00 ± 2.14%; hypertensive group: glycated hemoglobin = 8.70 ± 1.60%; p = 0.39) and the hypertensive group had a higher insulin resistance (normotensive group: insulin resistance index (HOMA-IR) = diabetes 4.0 ± 4.0; hypertensive group: HOMA-IR = 8.0 ± 6.6; p = 0.02). The authors found that hypertensive and diabetic subjects had lower SD1 (derived from *Poincaré* plot) and Shannon entropy, both non-linear measures of HRV, in comparison to non-hypertensive diabetic patients. In addition, SD2 (derived from *Poincaré* plot) and approximate entropy correlated negatively with exercise capacity variables.

Although a healthy control group was not evaluated, the results suggest that systemic arterial hypertension further impairs HRV in diabetic patients. These data reinforce epidemiological findings showing that the combination of diabetes mellitus and hypertension induces greater cardiac remodeling than either condition alone.[15] Furthermore, heart failure is more prevalent in patients with both diseases. Additional studies are needed to establish the role of autonomic nerve dysfunction as a predictor of poor prognosis in patients with co-existing diabetes and hypertension.

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Early Assessment of Right Ventricular Function in Systemic Lupus Erythematosus Patients using Strain and Strain Rate Imaging

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Abstract

Background: **Right ventricular function is a crucial factor of the prognosis of systemic lupus erythematosus (SLE).**

Objectives: **To evaluate the right ventricular function in SLE patients with different degrees of pulmonary hypertension (PH) by strain and strain rate imaging.**

Methods: **A total of 102 SLE patients and 30 healthy volunteers were studied between October 2015 and May 2016. Patients were divided into three groups according to pulmonary artery systolic pressure (PASP) estimated by echocardiography: group control (A); PASP ≤ 30 mmHg (group B, n = 37); PASP 30-50 mmHg (mild PH; group C, n = 34); and PASP ≥ 50 mmHg (moderate-to-severe PH; group D, n = 31). Longitudinal peak systolic strain (ε) and strain rate (SR), including systolic strain rate (SRs), early diastolic strain rate (SRe) and late diastolic strain rate (SRa) were measured in the basal, middle and apical segments of the right ventricular free wall in participants by two-dimensional speckle tracking echocardiography (2D-STE) from the apical four-chamber view. A $p < 0.05$ was set for statistical significance.**

Results: **The parameters of ε, SRs, SRe, and SRa were significantly decreased in groups C and D compared with groups A and B. The ε of each segments was significantly lower in group D than in group C, while there were no differences in SRs, SRe and SRa between groups C and D.**

Conclusions: **Strain and strain rate imaging could early detect the right ventricular dysfunction in SLE patients with PH, and provide important value for clinical therapy and prognosis of these patients. (Arq Bras Cardiol. 2018; 111(1):75-81)**

Keywords: **Ventricular Function, Right / physiology; Lupus Erythematosus, Systemic; Hypertension, Pulmonary; Echocardiography.**

Introduction

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disorder involving multiple organs and systems, such as lung, muscle, skin, joint and heart, especially the right ventricle. Moreover, right ventricular (RV) function is a crucial factor for the prognosis of SLE patients.[1] Pulmonary hypertension (PH) is a common, severe, and devastating complication of SLE, and its prevalence varies between 0.5 and 43%.[2] It is an independent factor for SLE, with a 3-year survival rate of 44.9%.[3] SLE combined with PH can cause RV dysfunction, and its mortality is closely related to the RV function.[4] Thereby, early detection of subclinical RV dysfunction is important for the establishment of treatment strategy and improvement of prognosis in SLE patients with PH.

Although cardiac magnetic resonance and radionuclide angiography are considered gold standards for the assessment of RV systolic function, echocardiography is still widely used for its simplicity, low price, and non-invasiveness.[5] However, assessment of the right ventricle is limited due to its thin wall and complex anatomy – a triangular shape from the lateral view, and a crescent shape from section view.[6] It has been documented that two-dimensional speckle tracking echocardiography (2D-STE) derived strain and strain rate imaging, a novel technique with less dependence on the angle and intra/inter-observer variability, could reliably and qualitatively detect early subclinical RV dysfunction.[7-9] In this study, strain refers in particular to the longitudinal peak systolic strain (ε), and represents the degree of myocardial deformation. Strain rate (SR) is the shortening velocity of the myocardium, *i.e.*, it represents the change in deformation over time.[10] SR includes systolic SR (SRs), early diastolic SR (SRe) and late diastolic strain rate (SRa), which reflect cardiac contraction during systole and diastole, respectively.[11]

In this study, we aimed to assess the RV function through strain and SR by 2D-STE in SLE patients with PH estimated by echocardiography.

Methods

Study Subjects

A total of 102 SLE patients (M:F = 11:91; aged 20-52 years, mean age: 43.2 ± 9.3 years) and 30 age-matched healthy

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volunteers as control group (Group A) (M:F = 3:27, aged 23-51 years, mean age: 42.1 ± 10.5 years, mean pulmonary artery systolic pressure – PASP 22.54 ± 4.31 mmHg) were eligible to participate in this study. The study was conducted between October 2015 and May 2016 in our hospital. The eligibility criteria of SLE diagnosis met the 2012 Systemic Lupus International Collaborating Clinics (SLICC) standard criteria.[12] Exclusion criteria included left ventricular heart failure, congenital heart diseases, coronary heart disease, cardiomyopathy and valvular heart disease, pericardial effusion, use of cardiotoxic drugs, history of hypertension, infectious myocarditis and pulmonary obstructive diseases. Eight patients with poor-quality echocardiographic imaging and ten patients unwilling to participate in the study were excluded.

The selected patients were divided into three groups according to the PASP estimated by echocardiography: Group B included 37 patients with PASP ≤ 30 mmHg, which was considered as a non-PH group (M:F = 4:33, aged 21-51 years, mean age 45.3 ± 8.4 years, mean PASP 23.61 ± 3.11 mmHg); Group C included 34 patients with 30 < PASP < 50 mmHg, considered as mild PH group, (M:F = 4:30, aged 20-52 years, mean age: 41.3 ± 9.6 years, mean PASP 45.11 ± 5.50 mmHg); and Group D included 31 patients with PASP ≥ 50 mmHg, which was considered as moderate to severe PH group (M:F = 3:28, aged 23-51 years, mean age: 43.3 ± 7.5 years, mean PASP: 72.95 ± 7.92 mmHg).

All subjects gave their written informed consent after receiving a detailed explanation of the study protocol. The design proposal, methods of data collection, and analysis of this study were approved by the ethics committee of the hospital.

Image acquisition and analysis

Two-dimensional echocardiographic examinations were carried out with a GE Vingmed Vivid 7 (GE Vingmed Ultrasound, Horten, Norway) scanner equipped with a 1.7-3.4 MHz transducer (M3S probe). After a 15-minute rest in the supine position in a quiet room at 23°C, blood pressure (BP) and heart rate (HR) of all patients were measured three times and the mean values were calculated. An electrocardiogram (ECG) was also recorded simultaneously. The measurements and calculated formulas of the parameters in our study followed the 2015 American Society of Echocardiography and the European Association of Cardiovascular Imaging (ASE-EACVI) recommendations for chamber quantification.[13] During ECG recording at a stable frame rate in the left lateral position, the RV end-diastolic diameter (RVED) was obtained in the middle third of RV inflow, approximately halfway between the maximal basal diameter and the apex, at the level of papillary muscles at end-diastole in the RV-focused apical four-chamber view with left ventricle (LV) apex at the center of the scanning sector; the RV anterior wall thickness (RVAW) was obtained below the tricuspid annulus, at a distance approximating the length of the anterior tricuspid leaflet in its fully open position and parallel to the RV free wall as seen from a subcostal four-chamber view. Both parameters were measured by a conventional, two-dimensional grayscale echocardiography.[13] Tricuspid annulus plane systolic excursion (TAPSE) and peak systolic velocity of tricuspid annulus (S wave) were measured through the lateral portion of the tricuspid annulus by M-mode echocardiography and pulsed-wave tissue Doppler imaging (TDI) in the apical four-chamber view, respectively. RV fractional area change (RV FAC) was measured and calculated in the RV-focused apex four-chamber view: RV FAC (%) = 100 × (end-diastolic area [EDA] - end-systolic area [ESA]) / EDA.[13] Three-dimensional echocardiographic RV ejection fraction (3D RV EF) was also measured: 3D RV EF (%) = 100 × (end-diastolic volume [EDV] - end-systolic volume [ESV]) / EDV.[13] Left ventricular ejection fraction (LVEF) was measured by Simpson's biplane method. PASP was estimated according to the simplified Bernoulli equation: PASP = $4 \times V^2$ (V = peak velocity of tricuspid regurgitation) + right atrial pressure (RAP). RAP was estimated through echocardiography based on the diameter and respiratory variation in diameter of the inferior vena cava (IVC). A diameter of IVC < 2.1 cm that collapses > 50% with a sniff suggests there is a normal RA pressure of 3 mmHg; while an IVC diameter > 2.1 cm that collapses < 50% with a sniff or < 20% on quiet inspiration suggests a high RAP of 15 mmHg; if the IVC diameter and collapse do not fit this paradigm, an intermediate value of 8 mmHg would be used.[14]

All images were digitally recorded in hard disks on offline analysis (EchoPAC version 8, GE Vingmed Ultrasound). Two-dimensional dynamic images were recorded for the subsequent analyses. A frame rate of 40-80 frames/s acquisition was used. All 2D-STE data were measured by averaging data of three heartbeats. We selected the most stable cardiac cycle for generation of the strain curve. After manually tracing the RV endocardium on apical four-chamber view, a region of interest (ROI) divided into six segments was automatically generated. Only RV free wall segmental strain was analyzed. Using a single frame from end-systole, the RV free wall segments were manually mapped by marking the endocardial border and the width of the myocardium. The parameters of ε and SRs, SRe and SRa were measured in RV free wall for basal, middle and apical segments, respectively, from the apical four-chamber view.

Statistical analysis

The data were analyzed with SPSS 17.0 for Windows (SPSS, Chicago, IL, USA). Unpaired Student's T-test was performed for continuous variables, which were all normally distributed. Numeric variables are presented as the mean ± standard deviation (SD). One-way analysis of variance (ANOVA) was performed to test for statistically significant differences among the four groups. Continuous data were compared between individual groups using the Student-Newman-Keuls post-test to test for statistically significant differences. All statistical tests were two-sided, and $p < 0.05$ was set for statistical significance.

Results

Patient characteristics

Between the four groups, there were no significant differences in age, sex, body mass index (BMI), body surface area (BSA), systolic blood pressure (SBP), and diastolic blood pressure (DBP). Nevertheless, the HR in group D was significantly higher than that in the other three groups (Seen in Table 1).

Table 1 – Comparison of physiological parameters between systemic lupus erythematosus patients (groups B, C and D) and control group (Group A) ($\bar{x} \pm s$)

Parameters	Group A (n = 30)	Group B (n = 37)	Group C (n = 34)	Group D (n = 31)
Mean age, years	42.1 ± 10.50	45.3 ± 8.40	41.3 ± 9.60	43.3 ± 7.50
DBP, mm Hg	80.32 ± 3.66	79.92 ± 3.19	79.78 ± 4.97	82.52 ± 3.89
SBP, mm Hg	130.95 ± 5.27	128.4 ± 5.94	125.85 ± 9.07	128.39 ± 8.58
HR, beats/min	69.92 ± 9.57	73.13 ± 10.87	74.09 ± 8.61	89.52 ± 12.01$^{\$\#}$
BSA, m^2	1.59 ± 0.26	1.67 ± 0.25	1.79 ± 0.38	1.66 ± 0.37
BMI, kg/ m^2	26.38 ± 2.28	25.26 ± 2.94	25.56 ± 3.81	26.22 ± 1.46

DBP: diastolic blood pressure; SBP: systolic blood pressure; HR: heart rate; BSA: body surface area; BMI: body mass index. $^{\$}$: p < 0.05 vs. group A; *: p < 0.05 vs. group B; $^{\#}$: p<0.05 vs. group C.

Conventional echocardiographic parameters

There were no statistical differences in LVEF between the four groups. The RVAW and RVED were significantly higher in group D than in the other three groups, while TAPSE, RV FAC, pulsed Doppler S wave, and RV 3D EF were all significantly decreased in group D compared with the other groups. However, there were no significant differences in RVAW, RVED, TAPSE, RV FAC, pulsed Doppler S wave, and RV 3D EF between groups A, B and C (Seen in table 2).

2D-STE parameters

The average of the longitudinal strain and SR of each segment in the basal, middle, and apical regions of the RV free wall was calculated in each group (Seen in table 3; Figure 1).

We found that there were no significant differences in all the parameters between groups A and B. On the other hand, in groups C and D, ε, SRs, SRe and SRa of each segment were significantly decreased compared with groups A and B. The parameter ε of each segment in group D was also significantly lower than that in group C, although there were no significant differences in SRs, SRe and SRa of each segment between groups C and D.

Discussion

It has been previously demonstrated that RV function is a decisive factor for the severity and prognosis of SLE patients with PH,[15] and that 2D-STE-derived strain and strain rate imaging could precisely reflect deformation of RV myocardium, and detect the subclinical RV dysfunction.[16] Thereby, evaluation of RV function in SLE patients with PH is important for establishing treatment strategy, prevent clinical RV dysfunction and RV failure, and increase the survival rate of SLE patients with PH. To our knowledge, this has not been studied before.

In the present study, we found that there were no significant differences in age, sex, BMI, BSA, SBP, and DBP between the four groups. Nevertheless, the HR in group D was significantly higher than that in the other three groups. It has been reported that HR could affect ε, and the increased HR was related to reduced ε, which represents the degree of deformation.[17-20] It also indicates that the degree of deformation of group D was decreased.

The function of the RV is to maintain the normal blood flow of pulmonary circulation, which mainly depends on three factors: preload, contraction, and afterload.[21] PH is a common and devastating complication of SLE characterized by progressively increased pulmonary vascular resistance (PVR) and PASP.[22] Its mechanism is very complex and closely related to inflammation and the immune system.[23,24]

In this study, we found that RVAW and RVED were significantly higher in group D than those in the other three groups, while TAPSE, RV FAC, pulsed Doppler S wave, and RV 3D EF were all significantly decreased in group D compared with the other groups. However, there were no significant differences in RVAW, RVED, TAPSE, RV FAC, pulsed Doppler S wave, and RV 3D EF between groups A, B and C. It demonstrates that the structure of the RV was remodeled in group D, and the RV myocardial systolic function was also impaired. We argue that long-standing increases in PASP in SLE patients with PH cause increased RV afterload, decreased pulmonary vascular compliance, and compensatory increases in RV contractility. Structurally, these results in expansion of the right ventricle and increased RV wall thickness for maintenance of RV function.[18,22,25] As PASP further increases, the impaired RV myocardium undergoes hypoxia, which causes enlarged RV volume, tricuspid valve insufficiency, and increased RV preload. This progresses to increased right atrial diameter and exacerbated myocardial impairment, leading to RV remodeling and decompensation, reduced RV contraction, and finally clinical RV dysfunction.[22,26] Based on conventional data, group D experienced clinical RV dysfunction. Decreased TAPSE, RV FAC and pulsed Doppler S wave also implied a bad prognosis, and decreased RV 3D EF even triggered the RV failure of patients in group D, while the RV function in group C was still normal.

In this prospective study, based on the 2D-STE data, we found that ε, SRs, SRe and SRa of each segment were significantly decreased in groups C and D compared with groups A and B, while there were no significant differences in these parameters between groups A and B. The parameter ε of each segment in group D was also significantly lower than that in group C, although there were no significant differences in SRs, SRe and SRa of each segment between groups C and D. As mentioned before, ε represents the degree of deformation,

Table 2 – Comparison of conventional parameters between systemic lupus erythematosus patients (groups B, C and D) and control group (Group A) ($\bar{x} \pm s$)

Parameters	Group A (n = 30)	Group B (n = 37)	Group C (n = 34)	Group D (n = 31)	Reference normal value@
LVEF, %	64.51 ± 3.11	63.69 ± 6.61	62.11 ± 4.87	63.01 ± 4.86	≥ 50
RVAW, cm	0.36 ± 0.05	0.40 ± 0.03	0.43 ± 0.06	0.69 ± 0.09$^{\$*\#}$	0.1-0.5
RVED, cm	2.98 ± 0.43	3.11 ± 0.45	3.22 ± 0.39	3.65 ± 0.36$^{\$*\#}$	1.9-3.5
TAPSE, cm	2.24 ± 0.21	2.21 ± 0.19	1.76 ± 0.22	1.2 ± 0.18$^{\$*\#}$	> 1.7
RV FAC, %	50.45 ± 4.67	49.24 ± 4.81	42.69 ± 5.07	34.43 ± 3.95$^{\$*\#}$	> 35
Pulsed Doppler S wave, cm/s	13.35 ± 2.14	12.92 ± 1.90	11.48 ± 2.06	9.33 ± 1.81$*#	> 9.5
RV 3D EF, %	46.18 ± 2.28	45.80 ± 2.21	44.34 ± 2.14	31.19 ± 4.36$*#	≥ 40

*LVEF: left ventricular ejection fraction; RVAW: right ventricular anterior wall thickness; RVED: right ventricular end-diastolic diameter; TAPSE: tricuspid annulus peak systolic excursion; RV FAC: right ventricular fractional area curve; Pulsed Doppler S wave: peak systolic velocity of tricuspid annulus by pulsed-wave tissue Doppler imaging; RV 3D EF: three-dimensional echocardiographic right ventricular ejection fraction. $: p < 0.05 vs. group A. *: p < 0.05 vs. group B. #: p < 0.05 vs. group C. Chinese guidelines provide different reference normal values as compared with international guidelines.*

Table 3 – Comparison parameters of strain rate and strain of the SLE patients with the control group ($\bar{x} \pm s$)

strain	Group A (n = 30)	Group B (n = 37)	Group C (n = 34)	Group D (n = 31)
ε, %				
Basal	-33.87 ± 5.89	-32.19 ± 7.38	-25.77 ± 7.67†*	-19.55 ± 4.89$^{\$*\#}$
Middle	-31.67 ± 7.00	-29.09 ± 7.30	-22.89 ± 8.05†*	-17.67 ± 6.83$^{\$*\#}$
Apical	-25.45 ± 6.99	-27.51 ± 2.47	-19.64 ± 8.65†*	-15.91 ± 6.33$^{\$*\#}$
SRs, s^{-1}				
Basal	-2.33 ± 0.34	-2.43 ± 0.44	-1.84 ± 0.41†*	-1.73 ± 0.47$^{\$*}$
Middle	-1.78 ± 0.34	-1.67 ± 0.56	-1.59 ± 0.37†*	-1.36 ± 0.31$^{\$*}$
Apical	-1.53 ± 0.54	-1.54 ± 0.55	-1.33 ± 0.38†*	-1.16 ± 0.36$^{\$*}$
SRe, s^{-1}				
Basal	2.44 ± 0.74	2.43 ± 0.69	1.95 ± 0.49†*	1.85 ± 0.52$^{\$*}$
Middle	2.04 ± 0.58	2.06 ± 0.49	1.73 ± 0.54†*	1.66 ± 0.46$^{\$*}$
Apical	1.84 ± 0.69	1.83 ± 0.67	1.33 ± 0.65†*	1.29 ± 0.55$^{\$*}$
SRa, s^{-1}				
Basal	1.66 ± 0.64	1.63 ± 0.66	1.44 ± 0.56†*	1.42 ± 0.55$^{\$*}$
Middle	1.55 ± 0.70	1.56 ± 0.65	1.28 ± 0.41†*	1.21 ± 0.52$^{\$*}$
Apical	1.88 ± 0.49	1.85 ± 0.67	1.60 ± 0.56†*	1.54 ± 0.54$^{\$*}$

*SRs: systolic strain rate; SRe: early diastolic strain rate; SRa: late diastolic strain rate $: p <0.05 vs. group A. *: p < 0.05 vs. group B. #: p < 0.05 vs. group C.*

and SR represents ventricular contractility.[27] This means that the degrees of RV deformation in groups C and D were significantly lower compared with groups A and B, and significantly lower in group D than in group C. This implies that the RV function of both groups C and D was impaired, and this was more severe in group D. This is in accordance with the findings of Pirat et al.,[28] The discrepancy of ε and SR between groups C and D in this study might be related to the significant differences in HR and PASP in these groups. While SR has been shown to be independent of load, HR and other factors, an increased HR and altered load changes have been associated with reduced ε.[17-20] The impaired RV function of group C (mild PH group) was detected early by 2D-STE-derived strain and SR imaging compared with the conventional echocardiography.

Study limitations

There were several limitations of this study. First, PH was not determined via right heart catheterization, but estimated by echocardiography. Second, RV was not assessed by cardiac magnetic resonance for the sake of comparison. However, these might not be a limitation of this study, because it aimed to evaluate and compare the RV function of SLE patients with different degrees of PH estimated by 2D-STE-derived strain and SR imaging. Third, clinical data of SLE patients, such as antiphospholipid antibodies were not collected. Also, estimation of PH by 2D-STE may be influenced by factors, such as patient's breathing pattern. Finally, some participants such as obese patients may not be able to use this method, because it requires high-resolution image quality.

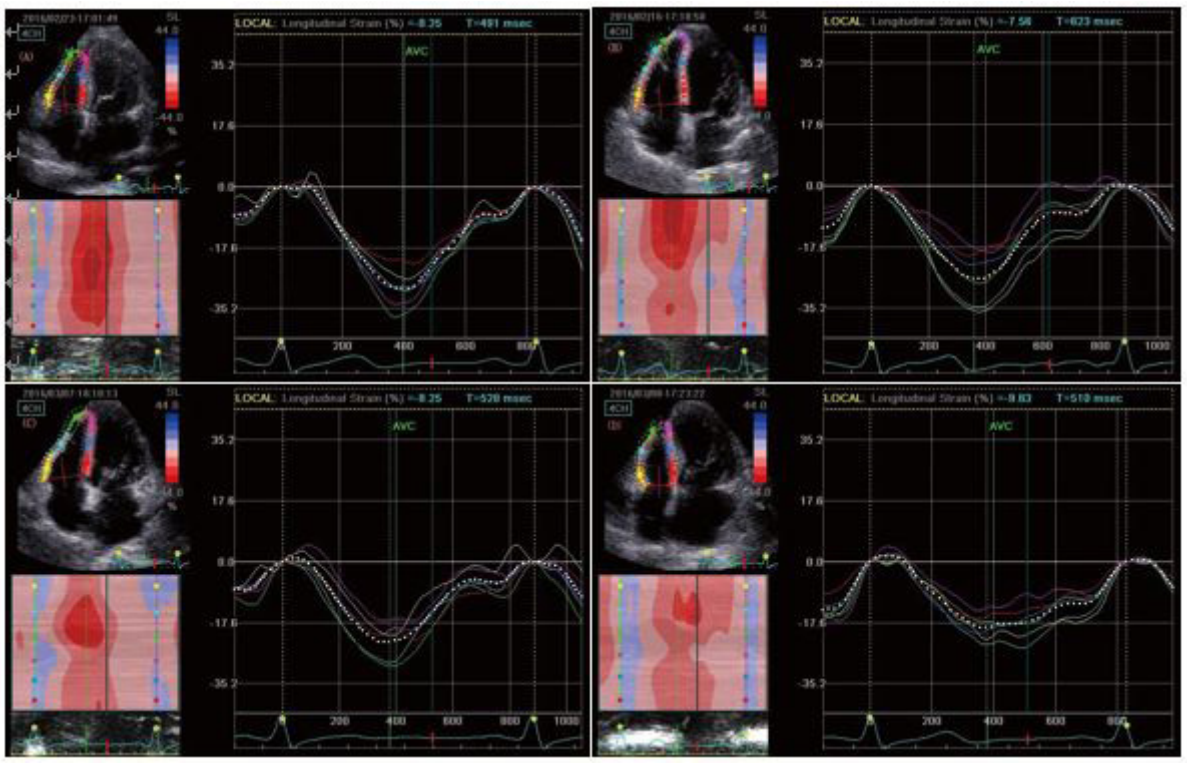

Figure 1 – *Longitudinal peak systolic strain (ε) curve was obtained in right ventricular free wall for basal, middle and apical segment by 2D-STE from the apical four-chamber view. (A) group A; (B) group B (systemic lupus erythematosus – SLE, without pulmonary hypertension); (C) group C (SLE with mild pulmonary hypertension); (D) group D (SLE with moderate-to-severe pulmonary hypertension).*

Conclusion

In conclusion, 2D-STE-derived strain and SR imaging could early detect the RV dysfunction in SLE patients with PH, especially in those with mild PH. This has an important value in guiding early therapy in clinical settings, improving the prognosis, and increasing the quality of life of SLE patients with PH.

Potential Conflict of Interest

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

Sources of Funding

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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 of Dalian Medical University under the protocol number 2015-3. 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.

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Original Article

Right Ventricular Dysfunction in Lupus Patients With Pulmonary Hypertension

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Short Editorial regarding the article: "Early Assessment of Right Ventricular Function in Systemic Lupus Erythematosus Patients using Strain and Strain Rate Imaging"

The importance of the right ventricle in cardiovascular physiology has been underestimated for decades. Previously considered a mere conduit, the right ventricle is currently known to play a major role in maintaining global cardiac function intact. In parallel, right ventricular (RV) systolic function has been shown to be an essential determinant of clinical outcomes in several scenarios,[1] and should thus be considered in the individualized management of patients. The need to diagnose RV dysfunction is evident. Because of its wide availability, echocardiography is the most frequently used imaging test in clinical practice to assess RV size and function. That assessment can be hindered by the complex RV anatomy; thus, important international societies of cardiovascular imaging have recommended the routine and systematic addition of several echocardiographic measurements and techniques.[2,3] That approach includes conventional parameters, such as RV basal diameter (normal ≤ 41 mm) and tricuspid annular plane systolic excursion (TAPSE - normal ≥ 17 mm), as well as advanced parameters, such as the *s* wave of the RV free wall on tissue Doppler (normal ≥ 9.5 cm/s), ejection fraction on 3D echocardiography (normal ≥ 45%) and longitudinal strain of the RV free wall (normal ≥ -20%).

In this scenario, strain (systolic shortening percentage) and strain rate (shortening rate), calculated by speckle tracking on two-dimensional echocardiography (2D speckle tracking or 2D-STE), emerge as alternatives in the RV systolic function analysis. The longitudinal strain of the RV free wall, excluding the ventricular septum, showed prognostic value in patients with signs and symptoms of cardiopulmonary disease, such as heart failure, myocardial infarction, pulmonary hypertension, congenital heart diseases, RV arrhythmogenic cardiomyopathy and amyloidosis.[1] Right ventricular longitudinal strain is a parameter less dependent on the angle, with less intra- and interobserver variability, that can apparently detect early RV dysfunction. Its drawbacks include the high dependence on image quality and the variability of the software of the equipment available in the market.[3] Recently an international consensus has been reached to standardize the use of 2D-STE to obtain RV strain.[4] The specific use of right-ventricle-focused apical 4-chamber view is recommended for correct strain measurement. Extreme care should be taken to define the region of interest (ROI) of the endocardial border (suggested ROI: 5 mm), because of the RV shape and thin walls. The pericardium should be excluded from the analysis, because of the risk of strain underestimation.

The study by Luo et al.,[5] published in this issue of the *Arquivos Brasileiros de Cardiologia*, shows that the assessment of strain and strain rate by use of 2D-STE can detect early RV dysfunction in individuals with systemic lupus erythematosus (SLE) associated with mild and subclinical pulmonary hypertension [PH: systolic pulmonary artery pressure (SPAP) between 30 and 50 mmHg]. It is worth noting that, considering the other conventional and nonconventional parameters of RV size and systolic function, RV dysfunction was only diagnosed in individuals with moderate to severe PH (SPAP ≥ 50 mmHg). It is necessary to acknowledge the little methodological limitation in estimating right atrial pressure, to which only two values were attributed (8 or 15 mmHg) in the dynamic analysis of the inferior vena cava. This might have overestimated the SPAP in some patients, but that bias does not invalidate the results of that study. Another study has reported that the survival rates of patients with SLE who develop PH seem lower than those of individuals with primary PH.[6] The findings of the study by Luo et al.[5] allow us to speculate that RV dysfunction is the mediator of the high mortality risk in that group of individuals. Those findings suggest that the use of strain to analyze RV systolic function in SLE can select patients in a subclinical phase who require careful surveillance and early therapy to prevent the development of RV failure and cardiovascular complications. Further studies are necessary to deepen the pathophysiological knowledge of RV dysfunction in the clinical context of SLE and to assess the role of intervention strategies to reduce mortality.

Keywords

Ventricular Dysfunction, Right; Lupus Erythematosus; Cardiovascular Diseases; Lung Diseases; Hypertension, Pulmonary; Echocardiography; Strain; Strain Rate.

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Carotid Sinus Massage in Syncope Evaluation: A Nonspecific and Dubious Diagnostic Method

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Abstract

Background: Carotid sinus hypersensitivity (CSH) is a frequent finding in the evaluation of syncope. However, its significance in the clinical setting is still dubious. A new criterion was proposed by Solari et al. with a symptomatic systolic blood pressure (SBP) cut-off value of ≤ 85 mmHg to refine the vasodepressor (VD) response diagnosis.

Objective: To determine and compare the response to carotid sinus massage (CSM) in patients with and without syncope according to standard and proposed criteria.

Methods: CSM was performed in 99 patients with and 66 patients without syncope. CSH was defined as cardioinhibitory (CI) for asystole ≥ 3 seconds, or as VD for SBP decrease ≥ 50 mmHg.

Results: No differences in the hemodynamic responses were observed during CSM between the groups, with 24.2% and 25.8% CI, and 8.1% and 13.6% VD in the symptomatic and asymptomatic groups, respectively (p = 0.466). A p value < 0.050 was considered statistically significant. During the maneuvers, 45 (45.45%) and 34 (51.5%) patients in the symptomatic and asymptomatic groups achieved SBP below ≤ 85 mmHg. Symptoms were reported especially in those patients in whom CSM caused a SBP decrease to below 90 mmHg and/or asystole > 2.5 seconds, regardless of the pattern of response or the presence of previous syncope.

Conclusion: The response to CSM in patients with and without syncope was similar; therefore, CSH may be an unspecific condition. Clinical correlation and other methods of evaluation, such as long-lasting ECG monitoring, may be necessary to confirm CSH as the cause of syncope. (Arq Bras Cardiol. 2018; 111(1):84-91)

Keywords: Syncope; Carotid Sinus / physiopathology; Accidental Falls; Aged; Hypotension.

Introduction

Carotid sinus hypersensitivity (CSH), an age-related phenomenon, is rarely diagnosed in patients under the age of 50 years.[1] It has been accepted as a cause of syncope and unexplained falls in the elderly, with prevalence as high as 45% in some reports.[2]

The clinical relevance of a positive response to carotid sinus massage (CSM) in patients with syncope is still controversial, in spite of the previous publications. Although the reported prevalence of CSH in patients with syncope is 23% to 41%,[3-8] it has been described in 17% of normal subjects, in 20% of patients with cardiovascular disease, and in 38% of patients with severe carotid artery disease.[9-11] Recently, some reports have proposed a modification of the diagnostic criterion according to hemodynamic findings during CSM,[12,13] with a cut-off value of symptomatic systolic blood pressure (SBP) of ≤ 85 mmHg to determine a vasodepressor (VD) form, instead of the current definition of 50 mmHg SBP fall. To clarify the practical implications of CSM and CSH in syncope evaluation, this study was aimed at determining CSH prevalence and analyzing the patterns of the hemodynamic responses to CSM and symptoms in patients older than 50 years with and without symptoms of syncope or presyncope seen in a tertiary referral unit.

Methods

The scientific and ethics committees of our institution approved this study. Written informed consent was obtained from each participant.

Patients aged 50 years or older with at least two episodes of syncope or presyncope in the previous year, referred to the Arrhythmia and Syncope Unit of the Instituto do Coração (InCor) – University of São Paulo Medical School Hospital were selected as the symptomatic group. The number of patients was determined by convenience sampling. Patients presenting with structural heart disease, such as dilated cardiomyopathy with a left ventricular ejection fraction ≤ 50%, moderate or significant valvular disease, myocardial infarction in the previous 6 months, unstable angina, stroke, carotid bruit or previously diagnosed carotid artery stenosis were excluded. Patients on chronic

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use of beta-blockers, digitalis, calcium channel blockers or alpha-methyldopa, who could not discontinue them, as well as patients with an artificial pacemaker, were also excluded.

For the asymptomatic group, 66 patients with no history of syncope or presyncope were selected from the geriatric outpatient clinic of the same institution. The exclusion criteria for the group were the same as those applied to the symptomatic group.

Carotid sinus massage

Carotid sinus massage was performed from 1:00 pm to 5:00 pm. Cardiac medications, such as beta-blockers, calcium channel blockers (diltiazem and verapamil), digoxin and alpha-methyldopa, were discontinued 3 days before the procedure. All CSM were performed by the same physician. Continuous electrocardiogram and noninvasive, beat-to-beat blood pressure were recorded by digital photoplethysmography (Finapres Monitor® Ohmeda, USA)[14] or a vascular unloading device (Task Force Monitor ® CNSystems Medizintechnik GmbH, Graz, Austria).[15-17]

Blood pressure was monitored in the first 3 minutes with the patient in the 70° upright position on a footplate-assisted tilt table to evaluate the presence of orthostatic hypotension (OH), which was defined as a postural drop in SBP of at least 20 mmHg or a drop in diastolic blood pressure (DBP) of at least 10 mmHg within the first 3 minutes of standing.[18]

Carotid sinus massage was performed for 5 seconds, in the 70° upright position after 5 minutes of standing, following the stabilization of blood pressure and heart rate, and at the point with the maximal carotid pulse on the anterior margin of the sternocleidomastoid muscle. Blood pressure and heart rate were monitored throughout. Right-sided CSM was followed by left-sided CSM (or vice versa) after at least 1 minute or as long as the heart rate and blood pressure values returned to baseline. The CSM was performed twice in each side to evaluate the reproducibility of the method. The sequence was completed even in the event of positivity of 1 massage. After each episode of CSM, patients were questioned about symptoms related to the maneuver. Cardioinhibitory (CI) CSH was defined as asystole of 3 seconds or more, and VD CSH was defined as a drop of 50 mmHg or more in SBP.[19]

Blood pressure was recorded continuously immediately before each CSM until it reached the lowest value recorded during or shortly after the maneuver. The magnitude of the blood pressure response was obtained by the difference between the baseline SBP and the minimum SBP during CSM (ΔSBP). Likewise, RR intervals were recorded, and the magnitude of heart rate response was given by the difference between the RR interval before CSM and the maximum RR interval during CSM (ΔRR).

Statistical analysis

The data were analyzed by using Excel 2003 and SPSS software for Windows, version 15.0. The nominal measures are presented in absolute (n) and relative (%) frequencies, and numerical measurements are described as mean, standard deviation, median, minimum and maximum values. The clinical characteristics and responses to CSM (the order, result and symptoms associated with CSM) were compared between groups by using the chi-square test and the likelihood ratio test. The numerical measurements between the groups were summarized by descriptive statistics and compared by using Student *t* test, chi-square test for categorical data, and Mann-Whitney test for continuous data. Nonparametric tests were used in the absence of normally distributed data assumption (Kolmogorov-Smirnov test). The intraclass correlation coefficient was used to analyze the reproducibility of the CSM response. A p value of < 0.050 was considered statistically significant.

Results

In the symptomatic group, almost all patients (93.9%) had syncope, with an average of 5.4 episodes (median - 3) in the year prior to evaluation. The baseline clinical characteristics of the 99 patients in the symptomatic group and the 66 patients in the asymptomatic group are shown in Table 1.

Patients in the symptomatic group had the most significant decreases in blood pressure after being tilted to 70°. The mean SBP and DBP changes after orthostatic stimulus are shown in Figure 1. The symptomatic group had more occurrences of OH (29 patients, 29.2%), of whom, 19 patients met the diagnostic criterion of a SBP decrease ≥ 20 mmHg, and 10 additional patients met the criterion of a DBP decrease ≥ 10 mmHg. Only 8 patients (12.1%) in the asymptomatic group had a diagnosis of OH, which was due to decreased SBP in 7 of them (p = 0.014).

Carotid sinus massage

There was no difference between the groups in the responses obtained during CSM (p = 0.466) (Figure 2). The response to CSM was considered normal in 64.8% of patients in the entire sample, 67.7% in the symptomatic

Table 1 – Clinical characteristics of the symptomatic and asymptomatic groups.

Variable	Symptomatic (n = 99)	Asymptomatic (n = 66)	p
Age, mean ± sd (median) (minimum – maximum)	69.67 ± 10.26 (70) (50–93)	73.01 ± 9.68 (74) (52–92)	0.037
Male, n (%)	41 (41.4%)	23 (34.8)	0.396
Hypertension	73 (73.7%)	54 (81.8%)	0.227
Diabetes	13 (13.1)	20 (30.3)	0.007
Coronary artery disease	5 (5.1)	11(16.7)	0.014

chi-square test; sd: standard deviation.

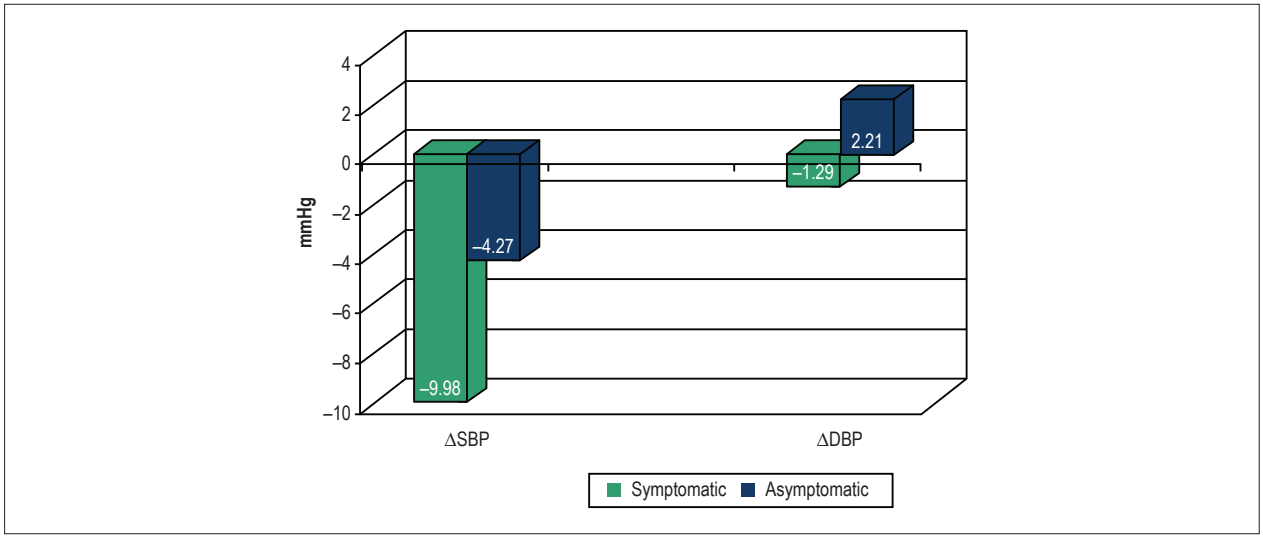

Figure 1 – *Magnitudes of the responses of systolic and diastolic blood pressure to a 70° tilt in the symptomatic and asymptomatic groups. Note there is significant fall in the systolic blood pressure (p < 0,001) and diastolic blood pressure (p = 0,001) in the symptomatic group compared with asymptomatic group.*

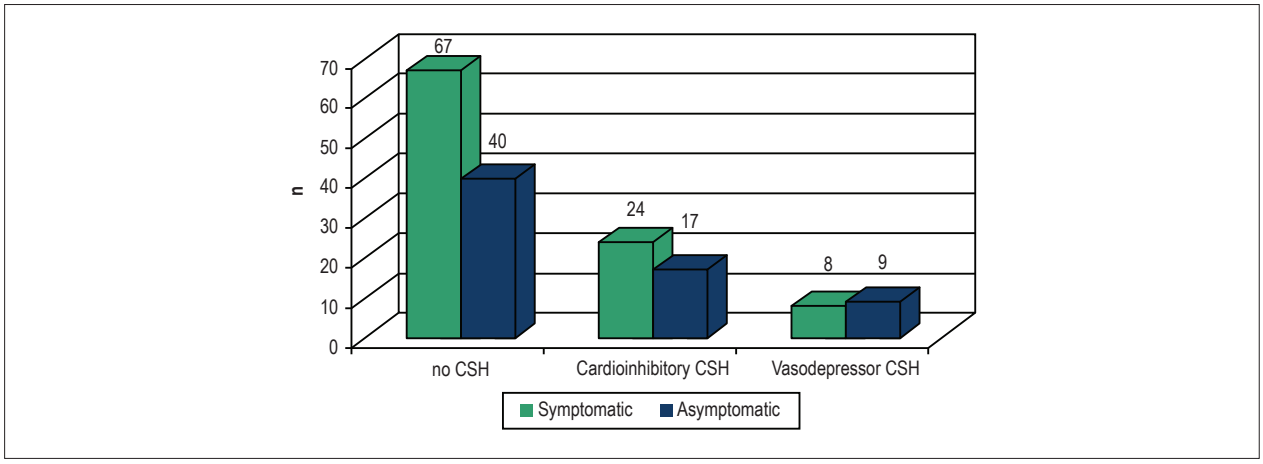

Figure 2 – *Results of carotid sinus massage according to the type of response obtained in the symptomatic and asymptomatic groups. CSH: carotid sinus hypersensitivity.*

group and 60.6% in the asymptomatic group. Over 32% of the patients in both groups had an abnormal response to CSM, with predominance of CI responses.

Men had more abnormal responses to CSM compared to women (53.8% vs. 23.0%, p < 0.001). A predominance of CI response was also observed in men compared to women (43.1% vs. 13.0%). There was no significant difference in responses to CSM related to age. Likewise, no association was observed between CSH and underlying diseases, such as hypertension, diabetes and coronary artery disease (Table 2).

There was no difference (Figure 3) in the response to CSM when comparing the decrease in SBP (ΔSBP) and heart rate (ΔRR) between the symptomatic and asymptomatic groups. All patients were in sinus rhythm except for 2 individuals from the symptomatic group, who had atrial fibrillation (AF). One patient had persistent AF, and the other had paroxysmal AF.

During the maneuvers, 45 (45.45%) symptomatic patients and 34 (51.5%) asymptomatic patients dropped their SBP to values ≤ 85 mmHg. The proportions of patients who achieved SBP ≤ 85 mmHg in the series of CSM are shown in Table 3. The VD reflex increased from 8.0% to 31.3% in the symptomatic group and from 13.6% to 28.7% in the asymptomatic group, when applying the cut-off value of SBP ≤ 85 mmHg for the diagnosis of CSH, compared to the classical blood pressure criteria with a fall in SBP ≥ 50 mmHg. Therefore, the change in the cut-off value increased the diagnosis of CSH by 21.2% (or total 53.5%) and 15.2% (total 54.5%) in the symptomatic and asymptomatic groups, respectively.

Although abnormal responses were similar in both groups, symptomatic patients reported more symptoms during CSM (41.4% vs. 27.3%, p = 0.063). The reported symptoms ranged from mild discomfort to syncope. In the symptomatic group, 20 patients reported presyncope, 16 patients reported dizziness, and 3 patients reported nonspecific symptoms.

Table 2 – Distribution of responses to carotid sinus massage by age, sex, and underlying diseases, such as hypertension, diabetes and coronary artery disease.

Variable	Response to CSM						TOTAL	p
	No CSH		Cardioinhibitory		Vasodepressor			
	n	%	n	%	n	%	n	
Age								**0.356#**
50–59	22	78.5	5	17.9	1	3.5	28	
60–69	30	69.7	9	20.9	4	9.3	43	
70–79	31	56.3	15	27.3	9	16.3	55	
≥ 80	24	61.5	12	30.8	3	7.6	39	
Sex								**< 0.001***
Male	30	46.1	28	43.1	6	9.2	65	
Female	77	77.0	13	13.0	11	11.0	100	
Hypertension								**0.849#**
-	25	65.7	10	26.3	3	7.8	38	
+	82	64.5	31	24.4	14	11.0	127	
Diabetes								**0.095#**
-	90	68.1	28	21.2	14	10.6	132	
+	17	51.5	13	39.4	3	9.0	33	
Coronary artery disease								**0.401#**
-	99	66.4	35	23.5	15	10.0	149	
+	8	50.0	6	37.5	2	12.5	16	
Total	103	62	41	25	21	13	165	

*CSM: carotid sinus massage; CSH: carotid sinus hypersensitivity; # likelihood ratio test; * chi-square test*

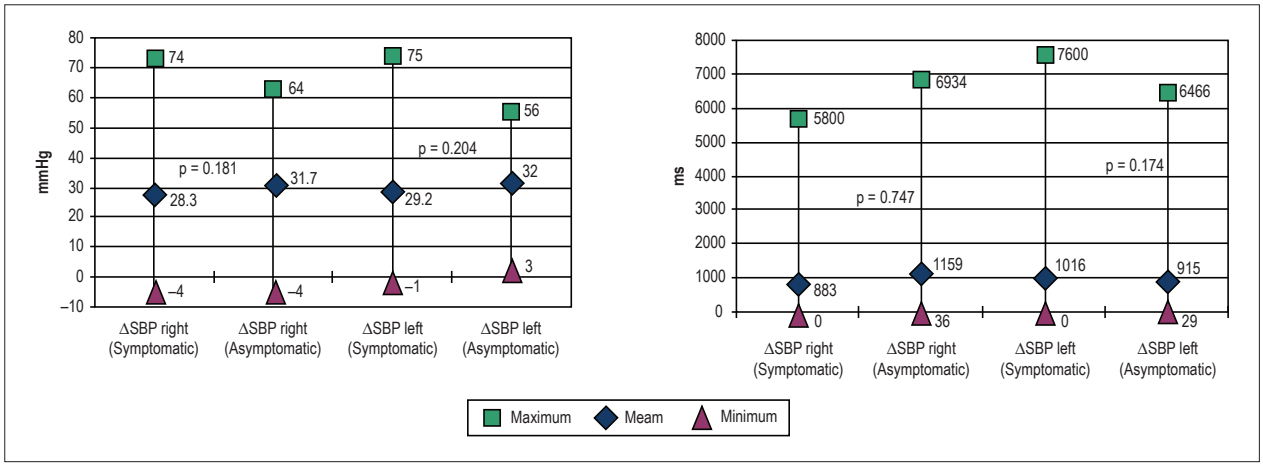

Figure 3 – *Magnitudes of systolic blood pressure response (ΔSBP) (above) and heart rate response (ΔRR) (below) in the symptomatic and asymptomatic groups during carotid sinus massage.*

In the asymptomatic group, 5 patients reported presyncope, 10 patients, dizziness, and 2 patients, nonspecific symptoms. Only 2 patients in the symptomatic group had syncope, which occurred with ventricular pauses of 8.2 and 8.1 seconds. Symptoms reported with normal or abnormal responses made up 17.8% of normal, 78% of CI, and 47.1% of VD responders. Likewise, many asymptomatic patients showed a positive response without related symptoms, especially VD response (82.2% of normal, 22% of CI, and 52.9% of VD). Symptoms resulting from the CSM occurred mainly when the SBP dropped below 90 mmHg and/or the RR intervals extended longer than 2500 ms (Table 4).

Table 3 – Proportions of patients with systolic blood pressure (SBP) ≤ 85 mmHg in the series of carotid sinus massage (CSM).

	Minimum SBP ≤ 85 mmHg during CSM				
	Right CSM 1 n (%)	Right CSM 2 n (%)	Left CSM 1 n (%)	Left CSM 2 n (%)	Total n (%)
Asymptomatic	24 (36.3)	24 (36.3)	20 (30.3)	16 (30.3)	66 (100)
Symptomatic	33 (33.3)	34 (34.3)	26 (26.2)	29 (29.2)	99 (100)

Table 4 – Correlation between occurrence of symptoms during carotid sinus massage and the value of minimum systolic blood pressure (SBP) and maximum RR interval obtained during the massage

	Symptoms	Mean ± SD	Median	Minimum	Maximum	n	p
Minimum right SBP (mmHg)	asymptomatic	102.5 ± 12.9	101	59	180	106	< 0.001*
	symptomatic	86.4 ± 23.6	85	42	151	59	
	Total	96.7 ± 23.7	96	42	180	165	
Minimum left SBP (mmHg)	asymptomatic	101.8 ± 20.7	98	64	185	106	< 0.001*
	symptomatic	89.0 ± 20.3	87,5	51	178	58	
	Total	97.3 ± 21.4	95	51	185	164	
Maximum right RR interval (ms)	asymptomatic	1326 ± 768	1154	625	5455	106	< 0.000#
	symptomatic	2639 ± 1762	1800	880	7500	59	
	Total	1795 ± 1369	1225	625	7500	165	
Maximum left RR interval (ms)	asymptomatic	1238 ± 564	1111	6326	4520	106	< 0.000#
	symptomatic	2772 ± 1891	1840	811	8160	59	
	Total	1786 ± 1419	1200	632	8160	165	

*SD:standard deviation; * Student's t Test; # Mann-Whitney test.*

The immediate reproducibility of the CSM response was evaluated by repeating the CSM during the same procedure. The heart rate response reproducibility was slightly superior as compared to the blood pressure response, with intraclass correlation coefficients of 0.68 for the right ΔSBP, 0.71 for the left ΔSBP, 0.83 for the right ΔRR, and 0.81 for the left ΔRR. The heart rate data demonstrate acceptable levels of conformity (above 0.75). Reproducibility of the abnormal blood pressure response (VD CSH) was observed in 40.8% (20/49 cases), and the abnormal heart rate response (CI CSH) in 48.5% (50/103 cases).

Discussion

The diagnosis and management of syncope are still a challenging task in medical practice. In elderly patients, identifying the underlying diagnosis may be more complex due to multiple comorbidities, atypical presentations, amnesia from loss of consciousness, and difficulties in remembering and characterizing the episode.

The occurrence of OH is an important risk factor for falls and syncope, especially in the elderly, with 18.2% of prevalence.[20-23] In this study, we observed more than twice the prevalence (29.2% vs. 12.1%) of OH in the symptomatic patients compared to the asymptomatic patients. This finding confirms the importance of investigating OH in aged patients with syncope, reinforcing OH as one of the most frequent causes of syncope in the elderly.

Differently from the results observed in the search of OH, similar responses were obtained during CSM in symptomatic and asymptomatic groups. This finding perhaps reinforces the hypotheses that CSH is not a diagnostic marker of a clinical syndrome. With a similar proposal to assess the prevalence of CSH and the diagnostic value of CSM, Tan et al.[24] have found altered responses in 25% of the patients referred for evaluation of syncope and unexplained falls. This prevalence of CSH was lower when compared to the prevalence in another report[25] in individuals older than 65 years, randomly sampled from an unselected community. In that study, the authors observed CSH in 39% of the patients, and, in a subgroup of patients with no history of syncope or falling, 35% had a hypersensitive response to CSM, and 36% had CSM-related symptoms. Thus, a positive test for CSH may not necessarily determine the cause of fainting, leaving the clinician with the difficult decision whether to accept the test as a confirmation of the cause of syncope, which sometimes might induce an incorrect diagnosis.

Solari et al.[26] have proposed a cut-off value of symptomatic SBP ≤ 85 mmHg as more appropriate to identify the VD form of CSH in a study with 164 patients with CSM who produced spontaneous symptoms in the presence of hypotension or bradycardia (Method of Symptoms), or diagnosis of carotid sinus syndrome. The method does not require any cut-off value of asystolic pause or of the SBP fall induced by CSM, as positivity of the test is based on the reproduction of symptoms. They concluded that one third of patients with isolated VD form could not be identified

by the classical blood pressure criteria for the diagnosis of CSH (a fall in SBP ≥ 50 mmHg), as compared with the ≤ 85 mmHg SBP cut-off value. Therefore, they offered this standardized objective methodology of classification of the VD reflex component to be used in clinical practice.[26] Few large-scale studies have evaluated the diagnostic value of CSM. When positive, it suggests a tendency or predisposition to carotid sinus syndrome; however, this does not establish it as the cause of the patient's syncope, with no "ideal" protocol, given that there is an inexorable trade-off between sensitivity and specificity without a "gold standard" test to prospectively validate it in populations with rigorously defined carotid sinus syndrome. Likewise, the reproduction of spontaneous symptoms to confirm the diagnosis as recommended by the European Society of Cardiology with the Method of Symptoms may be imprecise in this population, since prodromal symptoms are absent in up to 93% of patients with carotid sinus syndrome, and most of all with frequent memory and cognitive deficit, confounding the correlation. Additionally, any etiology that causes hypotension might result in symptoms similar to those determined by CSH, with the first symptoms of retinal and cerebral hypoperfusion expected in the upright position when SBP drops below 80 mmHg. An association between impaired cerebral autoregulation and the symptomatic presentation of CSH was demonstrated by Tan et al.[27] in a study using transcranial Doppler ultrasonography during lower body negative pressure-induced systemic hypotension.[27] They have demonstrated that individuals with symptomatic CSH have lower cerebral blood flow than do asymptomatic individuals with CSH in response to comparable reductions in systemic blood pressure, and have suggested that symptomatic individuals have an increased susceptibility to syncope or falls compared with individuals with asymptomatic CSH due to a lower ability to maintain cerebral blood flow in the face of a hypotensive challenge.

In our study, we observed that symptoms resulting from the CSM occurred mainly when the SBP dropped below 90 mmHg and/or the RR intervals extended longer than 2500 ms, regardless of the diagnosis associated with CSM. Associated with this factor, CSH is elicited by manual massage, which is a highly variable stimulus. This may be the reason for the low reproducibility of the positive response, as shown in this study.

While CSH has been observed in patients with syncope, and the symptoms were reproduced during CSM, there are no reports demonstrating that the hemodynamic alterations seen in the laboratory occur in a spontaneous event. Trying to establish the relationship between CSH and falls or syncopes, Schoon et al. have tested the hypothesis that head turning triggers hypotensive episodes in elderly with CSH. They have concluded that head turning may cause hypotensive episodes in the elderly. Head turning led to hypotension in 39% (total of 96 patients) of patients, with a mean SBP drop of 36 mm Hg (SD ± 13; range 20-76) with similar occurrence compared to healthy elderly, with 44% (total of 25 patients) and a mean SBP drop of 35 mmHg (SD ± 19; range 20-85). A drawback of the observational design is that it does not allow for conclusions about the causal relationships among head turning-triggered hypotension and syncope, and falls. They have also found a discrepancy between the occurrence of that head turning-triggered hypotension and related symptoms.[28] Thus, the positive correlation between CSH and syncope and/or falls still needs to be redefined due to the accumulating evidence that CSM causes a similar positive response in the asymptomatic population with the current criteria to diagnose CSH. The cut-off value of symptomatic SBP ≤ 85 mmHg to identify the VD form of CSH may cause overdiagnosis, sometimes leads to misdiagnosis, with no benefits in treatment plus potential side effects outweighing the benefits. Other options, such as long-lasting ECG monitoring with documentation of spontaneous events, are the only way to corroborate the diagnosis and its correlation with laboratorial findings.

Conclusion

In conclusion, no differences in the response to CSM were demonstrated between patients with and without syncope or presyncope. Carotid sinus hypersensitivity may be an unspecific condition in the evaluation of syncope. The best cut-off values of the asystolic pause and SBP based or not on the reproduction of symptoms are still a challenging task in medical practice. Consequently, clinical correlation and other methods of evaluation, such as long-lasting ECG monitoring, may be necessary to confirm CSH as a cause of syncope.

Study limitations

The control group was composed of not completely healthy individuals, but with no significant heart disease and in stable clinical condition. It is already known that elderly people have an average of three comorbidities per person. Asymptomatic patients in this study were recruited from an outpatient geriatric unit. The institution is a referral tertiary cardiology center, and the patients usually have substantial clinical complexity. Even with the exclusion criteria, which led to the inclusion of only patients without significant heart disease and in stable clinical conditions at the time of selection, we observed that more patients with diabetes and coronary artery disease were in the asymptomatic group. On the other hand, patients in the asymptomatic group were a little older than those in the symptomatic group, with a mean age of 73.0 and 69.6 years, respectively. Despite this difference, patients in both groups are representative of the elderly population, in whom a positive vagal maneuver is believed to define the etiologic diagnosis of syncope. The presence of systemic underlying comorbidities in the asymptomatic group may be an important concern. The advanced age and the presence of simultaneous underlying diseases in these patients reinforce the hypothesis that CSH could be not much more than a laboratory finding related to aging and vascular diseases. We recognize that the difference in age and in comorbidities between groups could constitute a bias, but we are sure that both groups are representative of the elderly population in which unexplained syncope is a great challenge.

In this study the CSM was performed with the patient in the 70° upright position after 5 minutes in the orthostatic position different from other studies performed in the supine position. Thus, our findings may be different and, therefore, could not be applied to the CSM in supine position. We chose the orthostatic position because it is the most sensitive to detect CSH according to the study performed by Parry et al.,[29] who have demonstrated that the specificity and sensitivity of

the initially supine positive test were thus 74% and 100%, respectively, while the upright positive test had 100% specificity and sensitivity. For this reason, we performed CSM only in the orthostatic position in this study.

Author contributions

Conception and design of the research e Analysis and interpretation of the data: Wu TC, Hachul DT; Acquisition of data, Statistical analysis, Obtaining financing and Writing of the manuscript: Wu TC; Critical revision of the manuscript for intellectual content: Wu TC, Hachul DT, Darrieux FCC, Scanavacca MI.

Potential Conflict of Interest

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

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Study Association

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Ethical approval and informed consent

This study was approved by the Ethics Committee of the Scientific and Ethics committees of clinical board of Hospital das Clínicas and Faculdade de Medicina da Universidade de São Paulo under the protocol number 424/01. 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.

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Carotid Sinus Massage in Syncope Evaluation: A Nonspecific and Dubious Diagnostic Method

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Short Editorial regarding the article: Carotid Sinus Massage in Syncope Evaluation: A Nonspecific and Dubious Diagnostic Method

The study by Wu et al.[1] questions the value of carotid sinus massage (CSM) for the investigation of syncope. It was well conducted, with two reasonably equivalent groups, with and without previous syncope, submitted to the same type of bilateral CSM, under rigorous evaluation of symptoms, cardiac rhythm and blood pressure. The authors found no difference in the response to CSM between the two groups. They concluded that CSM in the assessment of unexplained syncope would be a nonspecific and dubious diagnostic method. The results are clear and well structured. We agree with the authors' conclusion about the study findings. The limitations suggested are rightful. There is no doubt that CSM is an empiric method, of uncertain results, and this type of study serves to alert to its drawbacks. However, why is CSM still included in the guidelines? Certainly because it is a simple, well-tolerated, low-cost, low-risk procedure as long as the technique and the contraindications are respected, and can be performed rapidly during tilt-test, establishing the diagnosis in up to 30% of elderly patients with syncope of unknown origin.[2] However, as any other investigative method, it has important limitations that should be addressed cautiously. It is worth noting that the response to CSM depends on several investigator's and patient's factors, having value only when positive, when reproducing the spontaneous symptoms and when the patient's clinical findings are compatible with reflex syncope. In addition, it has no power of exclusion.

Thus, despite these drawbacks, CSM continues valid according to the European Society of Cardiology guidelines, which consider it is indicated as class I, level of evidence B, for patients older than 40 years of age with syncope of unknown origin compatible with reflex origin.[3] The diagnosis of carotid sinus syndrome (CSS) is confirmed if the CSM causes bradycardia (asystole) and/or hypotension that reproduce the spontaneous symptoms, and if the patients have clinical features compatible with the reflex mechanism of syncope, class I, level of evidence B. Although neurological complications are rare, the maneuver should be avoided in patients who already had an ischemic stroke, have a carotid murmur or important carotid vasculopathy. The history of syncope with positive CSM reproducing the symptoms confirms the diagnosis of CSS. However, a positive CSM without a history of syncope characterizes carotid sinus hypersensitivity, which, in elderly patients with unexplained syncope, can be a nonspecific finding and should be considered cautiously in the assessment of the syncope mechanism, because it is present in up to 40% of the cases.[4]

The American College of Cardiology/American Heart Association/Heart Rhythm Society guideline for the assessment and treatment of patients with syncope also considers CSM necessary for the diagnosis of CSS,[5] which is established by the reproduction of syncope during the maneuver in the presence of a cardioinhibitory response > 3 seconds, of atrioventricular block, of a significant vasodepressor response (a reduction ≥ 50 mmHg in systolic pressure) or of the association with mixed response.

It is worth noting that, in our clinical practice, we have observed that the vasodepressor response measured by the absolute decline in systolic pressure to ≤ 85 mmHg seems more specific than the relative decline of 50 mmHg traditionally considered in several studies. This was reported by the authors in the present article.

Thus, we consider that the present study has great value to draw the attention of the specialist to the limitations of the CSM.

Keywords

Syncope/etiology; Syncope/physiopathology; Carotid sinus/physiology; Arrhythmias, Cardiac/complications

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Influence of Type 1 Diabetes on the Symbolic Analysis and Complexity of Heart Rate Variability in Young Adults

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Abstract

Background: **Type 1 diabetes mellitus can cause autonomic changes, which can be assessed by heart rate variability. Among the heart rate variability assessment methods, the symbolic analysis and Shannon entropy, based on the Chaotic dynamics, have gained prominence.**

Objective: **To compare heart rate variability indexes, obtained through symbolic analysis and Shannon entropy, in young adults with type 1 diabetes mellitus and healthy young individuals, associated with the analysis of linear indexes; and to verify if there are associations between the indexes obtained by the symbolic analysis and by Shannon entropy and linear indexes in diabetic individuals.**

Methods: **Heart rate variability data from 39 young adults with type 1 diabetes mellitus and 43 healthy young individuals were analyzed, using a cardio-frequency meter. Linear indexes (standard deviation of all normal RR intervals recorded in a time interval expressed in milliseconds; square root of the mean of the squared differences between adjacent normal RR intervals in a time interval expressed in milliseconds; low and high frequency components in millisecond squared; and normalized units and ratio between low and high frequency components) and nonlinear ones (Shannon entropy and symbolic analysis – standard without variation; with one or two variations; and with two different variations) of the heart rate variability were calculated. The statistical significance was set at 5%, and the confidence interval was 95%.**

Results: **Significantly lower values were observed in the DM1 group compared to healthy young adults for the standard deviation indexes of all normal RR intervals recorded in a time interval [37.30 (29.90) vs. 64.50 (36.20); p = 0.0001], square root of the mean of the squared differences between adjacent normal RR intervals in a time interval [32.73 (17.43) vs. 55.59 (21.60); p = 0.0001], low frequency component [402.00 (531.00) vs. 1,203.00 (1,148.00); p = 0.0001], high frequency component [386.00 (583.00) vs. 963.00 (866.00); p = 0.0001] and the pattern with two different variations [15,33 (9,22) vs. 20.24 (12.73); p = 0.0114], with the effect of this difference being considered large (standard deviation of all normal RR intervals recorded in a time interval, square root of the mean of the squared differences between adjacent normal RR intervals in a time interval and low frequency component), medium (high frequency component) and small (standard with two different variations). The agreement of the associations between the linear and non-linear indexes was considered elevated for the high frequency component index - normalized units (r = –0.776), with the standard index without variation, and moderate for the indexes square root of the mean of the squared differences between adjacent normal RR intervals in a time interval (r = 0.550), standard deviation of all normal RR intervals recorded in a time interval (r = 0.522), high frequency component - normalized units (r = 0.638) with the index standard with two similar variations, as well as for the indexes square root of the mean of the squared differences between adjacent normal RR intervals in a time interval (r = 0.627) and high frequency component - normalized units (r = 0.601) with the index standard with two different variations.**

Conclusion: **Type 1 diabetes mellitus influenced linear indexes and symbolic analysis, but not yet in the complexity of heart rate variability. Additionally, heart rate variability indexes correlated with the symbolic dynamics. (Arq Bras Cardiol. 2018; 111(1):94-101)**

Keywords: **Diabetes Mellitus / complications; Diabetes / diagnosis; Diabetes / therapy; Young Adult; Heart Rate; Autonomic Nervous System.**

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Introduction

Type 1 diabetes mellitus (DM1) is characterized by the autoimmune destruction of insulin-producing cells, resulting from both environmental and genetic processes. This condition affects approximately 382 million people worldwide, affecting more frequently children, adolescents and young adults.[1]

Individuals with DM1 may have complications such as Cardiovascular Autonomic Neuropathy (CAN), caused by damage to autonomic nerve fibers associated with the cardiovascular system, resulting in neurohumoral regulation disorders.[2] CAN may interfere with the individual's quality of life and prognosis, showing some clinical manifestations such as resting tachycardia, exercise intolerance, stroke and sudden death of cardiac origin, among others.[3]

Heart Rate Variability (HRV), a simple, reproducible and non-invasive tool that shows the oscillations between consecutive heart beats (R-R intervals) associated with the Autonomic Nervous System (ANS) influence on the sinus node,[4] is indicated for the early assessment of autonomic status in diabetic individuals.[5] Its analyses can be performed by linear methods, in the time and frequency domains, and non-linear methods, in the chaotic domain,[6] among which the symbolic analysis and entropy are highlighted.[7]

The symbolic analysis has been recently studied and stands out for being able to differentiate both components of ANS[6] and quantify their impairment as a function of pathology, showing its effectiveness in assessing autonomic behavior and seeming appropriate to elucidate the neural pathophysiological mechanisms.[6,8] Shannon Entropy (SE) demonstrates the degree of complexity of signal sample distribution,[9] which allows identifying conditions that may interfere with cardiovascular regulation.[9]

Few studies have used these methods to assess individuals with diabetes.[10,11] Using symbolic analysis to investigate individuals with type 2 diabetes mellitus (DM2) without CAN, Moura-Tonello et al.[10] have indicated that this population has greater sympathetic modulation and reduced parasympathetic modulation and global variability. In subjects with DM2 and CAN, entropy analyses have shown the lower complexity of these individuals when compared to individuals with DM2 without CAN.[11]

HRV is a technique that allows the assessment of autonomic behavior and can be analyzed through linear and non-linear methods.[4] It is also well established that HRV indexes may be altered in several conditions – among them diabetes mellitus. Furthermore, the literature indicates that SE and symbolic analysis, a new methodology for the analysis of HRV for autonomic behavior assessment, is altered in DM2, but the use of these HRV analysis methods in patients with DM1 is unknown.

Considering that DM1 more frequently affects children and young adults, and that this population is subject to several complications, including autonomic alterations, which may lead to CAN, studies such as this are necessary to identify whether the use of new methods of autonomic activity analysis are capable of observing changes in the ANS behavior of young adults with DM1 without CAN, as well as which alterations may occur in the autonomic modulation of these individuals.

Data such as these are important, because, in addition to adding elements to the literature related to the abovementioned topic, it can determine whether this type of analysis can be a relevant tool to identify and help in the understanding of DM1 influence in the autonomic modulation.

The aim of the study was to compare HRV indexes obtained through symbolic analysis and SE, in young adults with DM1 and healthy subjects, associated with the analysis of the indexes obtained in the time and frequency domain, as well as to verify whether there are correlations between them for the young adults with DM1. The initial hypothesis was that the symbolic analysis and SE could identify autonomic alterations in individuals with DM1, when compared to healthy subjects, as well as the traditional HRV indexes, and that there are good correlations between such indexes.

Methods

To develop this cross-sectional observational study, 43 young adults diagnosed with DM1 were enrolled by convenience and allocated to the DM1 group and 45 healthy young individuals without DM1 were enrolled in the Control Group. To participate in the study, the DM1 Group volunteers should have a clinical diagnosis of DM1, confirmed by medical diagnosis and/or blood test, and no diagnosis or clinical signs of autonomic cardiac neuropathy. Neither group should have individuals with cardiorespiratory diseases and none of them were smokers and/or alcoholics. Only series of R-R intervals with more than 95% of sinus beats were included in the study, that is, series with variations in the measurement greater than 5% were disregarded.[12]

To recruit the DM1 Group participants, endocrinologists and Basic Health Units were contacted and, for the Control group, students from a public university were invited to participate. To perform the sample calculation, considering the absence of studies with SE or symbolic analysis with DM1, the index corresponding to the square root of the mean of the squared differences between adjacent normal RR intervals (RMSSD) was used, which is a classic index in HRV analysis. For the RMSSD index, considering a difference of 19.85 milliseconds, for a standard deviation of 25.30 milliseconds,[13] with an alpha risk of 5% and beta of 80%, the sample size resulted in at least 25 individuals for each group; however, for eventual device reading errors, this number was increased in both groups.

All procedures used in this study followed the Helsinki Declaration and were approved by the Research Ethics Committee of *Faculdade de Ciências e Tecnologia* (FCT/UNESP), Presidente Prudente *Campus* (CAAE: 22530813.9.0000.5402, opinion 417.031). The individuals signed the Free and Informed Consent Form.

Initially, the volunteers underwent an interview to collect the following information: age, gender, time of diagnosis (for diabetics) and use of medications. Body mass (Welmy R/I 200 digital scale, Brazil) and height (Sanny stadiometer, Brazil) were also measured to obtain the Body Mass Index (BMI).[14] After these assessments, volunteers were submitted to the experimental protocol, which consisted in the assessment of autonomic modulation through heart rate (HR) monitoring, using a Polar S810i cardio-frequency meter (Polar Electro, Finland), and the use of the R-R interval series obtained for the analysis of HRV.[15]

In order to perform this stage, the volunteers were instructed to remain silent, awake, at rest, with spontaneous breathing for 30 minutes, in dorsal decubitus for HR measurement. All volunteers were instructed not to consume ANS stimulants, such as coffee, tea, soda, and chocolate, and not to perform physical activities 24 hours prior to the evaluation, in order not to interfere with cardiac autonomic modulation.

The evaluations were performed individually in a room with temperature between 21°C and 23°C, and humidity between 40% and 60%, in the afternoon, between 1 pm and 6 pm to minimize circadian rhythm influences.[16]

After HR measurement using a cardio-frequency meter, a thousand consecutive R-R intervals were selected from the period of greatest signal stability, and digital filtering was performed with a filter moderated by the software Polar Precision Performance™ SW (version 4.01.029), followed by the manual one, to eliminate premature ectopic beats and artifacts.

To evaluate the non-linear behavior of HRV, symbolic analysis and SE were used. The symbolic analysis evaluation is based on the quantification of the information carried in a temporal series, on the transformation of the previously selected R-R intervals into integers from zero to six, from which the symbolic patterns (three-symbol sequence) are constructed.

All possible patterns were grouped without loss into four families, according to the number and type of variations between subsequent symbols,[9] namely: (1) patterns, without variation (0V), that is, three equal symbols, for instance, "4,4,4"; (2) patterns with one variation (1V), that is, two subsequent equal symbols and a different one, for instance, "4,2,2"; (3) patterns with two similar variations (2LV), that is, the three symbols form an upward or downward slope, for instance, "1,3,4" or "5,4,2"; (4) patterns with two different variations (2ULV), that is, the three symbols form a peak or a valley, for instance, "3,5,3" or "4,1,2".

The pattern related to the sympathetic branch performance is represented by the 0V family, and the performance of the parasympathetic branch is represented by the 2LV and 2ULV patterns. The joint performance of the ANS branches is represented by the 1V family.[9] The frequencies of occurrence of these families (0V%, 1V%, 2LV% and 2ULV%) were evaluated in this study. To calculate these indexes, we counted the number of times a pattern, which belonged to a specific family, was found, using a specific non-linear analysis software.[9]

Another variable calculated in the same software was SE, which represents the complexity of pattern distribution. SE was used to quantify the complexity/regularity of heart rate fluctuations. Based on Shannon's framework, entropy is the measure of information of a given message – a message with low entropy/information is characterized by repetition.[9]

For the analysis of the linear HRV indexes, the RMSSD indexes and the standard deviation of the mean R-R intervals (SDNN) were used in the time domain.[4]

As for the frequency domain, the low (LF: 0.04 to 015 Hz) and high frequency (HF: 0.15 to 0.40 Hz) spectral components, in milliseconds squared and normalized units (n.u.), and the ratio of these components (LF/HF), were used. The spectral analysis was calculated using the Fast Fourier Transform algorithm.[4] The HRV analysis software (Kubios, Biosignal Analysis and Medical Image Group, Department of Physics, University of Kuopio, Finland) was used to calculate these indexes.[17]

Data analysis

In order to characterize the assessed volunteers, the descriptive statistical method was used, and the results are shown in absolute numbers, means and standard deviation for data with normal distribution (height, RMSSD, LF n.u., HF n.u., 2LV and SE) and median and interquartile range for those with non-normal distribution (age, body mass, BMI, SDNN, LF ms^2, Hf ms^2, LF/HF, 0V, 1V and 2ULV).

For comparison between the groups (control and DM1), the normality of the data was initially determined using the Shapiro-Wilk test. When the normal distribution was accepted, the Student's *t* test for independent groups was applied and, in the cases where the normal distribution was not accepted, the Mann-Whitney test was applied. The effect size of the difference between the comparisons was analyzed by Cohen's d and values above 0.80 were adopted with high magnitude.[18]

In order to verify the association and agreement between the indexes, correlations were carried out between linear and non-linear HRV indexes and, for this purpose, Pearson's correlation was applied to the data with normal distribution, or Spearman's correlation, for the ones that did not accept this distribution. Correlation values of r from 0.7 to 1 were considered strong, 0.4 to 0.6 were considered moderate and values of 0.1 to 0.3 were considered weak. The Intraclass Correlation Coefficient (ICC) was calculated.

The statistical significance was set at 5% and the Confidence Interval at 95% (95% CI). Data analysis was performed using the software MiniTab version 13.20 (Minitab, Pa, United States) and Statistical Package for Social Sciences (SPSS), version 15.0 (SPSS Inc., Chicago, IL, United States).

Results

Of the 88 assessed volunteers, six showed errors in the R-R interval series greater than 5% and were excluded. Therefore, we analyzed the data of 39 young adults with DM1 (20 females) and 43 healthy young individuals (22 females), whose characteristics can be seen in table 1. The DM1 group had higher values of body mass and BMI ($p < 0.05$).

Of the young individuals with DM1, 38.46% used other drugs in addition to insulin. Medications for the control of blood pressure (12.82%) and cholesterol (7.69%) were also used by these individuals. Moreover, 20.51% used drugs for thyroid disorders, 12.82% used contraceptives and 20.51% used medications for several diseases, such as rhinitis, diabetic polyneuropathy, peripheral neuropathy and epilepsy.

Table 2 shows the linear index values in the HRV time domain for both groups. Significantly lower values were observed in the DM1 group when compared to the control group for both indexes (SDNN and RMSSD). The effect of the difference between the groups was considered high, as demonstrated by the obtained value of $d = 1.210$ and $d = 1.203$ for the SDNN and RMSSD indexes, respectively.

Table 1 – Characteristics of the control and type 1 diabetes mellitus (DM1) groups

Variables	Control (n = 43)	DM1 (n = 39)	p value
Age, years*	21.00 (5.00)	21.00 (7.00)	0.5397
Body mass, kg*	60.30 (22.80)	68.15 (22.90)	0.0129
Height, m†	1.69 (0.09)	1.73 (0.17)	0.4680
BMI, kg/m²*	22.19 (4.67)	24.19 (5.84)	0.0216

*Values in bold represent p < 0.05. * Median (interquartile range); † mean (standard deviation). BMI: body mass index.*

Table 2 – Values of the heart rate variability linear indexes in the time domain of the control and type 1 diabetes mellitus (DM1) groups

Index	Control (n = 43)	DM1 (n = 39)	p value	Cohen's d Effect size	
SDNN*	64.50 (36.20)	37.30 (29.90)	0.0001	1.21	Large
RMSSD†	55.59 (21.60)	32.73 (17.43)	0.0001	1.203	Large

*Values in bold represent p < 0.05. * Median (interquartile range); † mean (standard deviation). SDNN: standard deviation of all normal R-R intervals recorded in a time interval, expressed in milliseconds; RMSSD: the square root of the mean of the squared differences between adjacent normal R-R intervals, in a time interval, expressed in milliseconds.*

Table 3 represents the linear index values in the HRV frequency domain for both groups. Significantly lower values were observed in the DM1 group when compared to the control group for the LFms² and HFms² indexes. Regarding the effect of the difference between the groups, we obtained d = 0.9703 for the LFms² index, showing a large effect, and, for the HFms² index, d = 0.7759, considered a medium effect. For the other indexes, the effect was considered small, with d < 0.2.

Table 4 shows the values obtained with the HRV symbolic analysis and SE for both groups. Significantly lower values were observed in the DM1 group when compared to the Control group for the 2ULV index, but this difference was considered as having a small effect (d = 0.4803).

Table 5 shows the values of r, ICC and 95%CI obtained at the correlation of the linear indexes with SE and the indexes obtained in the symbolic analysis for the DM1 Group. The agreement shown by the ICC values was considered moderate for the associations of the RMSSD, SDNN, HF n.u. indexes with the 2LV index. The same was found regarding the association of RMSSD and HF n.u. indexes with the 2ULV index. High agreement was found for the LF n.u. index with the 0V index. Additionally, the 0V, 2LV, 2ULV and SE indexes showed a moderate correlation with SDNN, RMSSD, LF and HF indexes in ms² and n.u. and the LF/HF ratio, with the exception of the 2ULV index with the SDNN index, SE with the HFms² index, and 0V with the HFms² index, which showed a weak correlation. A strong correlation was found for the 0V indexes with LF n.u., HF n.u. and LF/HF, for the 2LV index with LFms² and for the SE index with LF/HF. The 1V index was the only one that did not show a significant correlation with the other HRV linear indexes and the 2ULV only for the HFms² index.

Discussion

The aim of this study was to compare HRV indexes obtained through symbolic analysis and SE in young adults with DM1 and healthy young individuals, associated with the analysis of indexes obtained in the time (RMSSD and SDNN) and frequency (LF, HF in ms² and in n.u., and LF/HF) domains, as well as verifying the existence of correlations between them in diabetic individuals.

Our results show that individuals with DM1 have a reduction in the parasympathetic (RMSSD, HFms² and 2ULV), sympathetic (LFms²) and global (SDNN) activities of the ANS. They also showed that the 0V (sympathetic), 2LV (parasympathetic), 2ULV (parasympathetic) and SE indexes have moderate correlation with the SDNN, RMSSD, LF and HF indexes in ms² and n.u. and LF/HF ratio, with the agreement of this association being considered moderate for the RMSSD, HF n.u., 2LV and 2ULV indexes, and high for LF n.u. and 0V indexes.

The individuals with DM1 also had higher values of body mass and BMI in relation to the healthy subjects, which was also shown in the study of Javorka et al.,[19] for the BMI variable, when evaluating 17 young adults (22.4 ± 1.0 years) with DM1.

Based on the analysis of the HRV, it was possible to observe significantly lower values in the DM1 Group when compared to the Control, both for the SDNN and RMSSD indexes in the time domain and for the LFms² and HFms² indexes in the frequency domain, indicating a reduction in the global, sympathetic and parasympathetic activity of the ANS, with the effect of this difference being considered medium (HFms²) and large (SDNN, RMSSD and LFms²).

Similar results were indicated by other studies[19-21]. Jaiswal et al.,[20] when evaluating 354 young individuals with DM1 (18.8 ± 3.3 years), observed a reduction in the SDNN, RMSSD, HF n.u. LF n.u. indexes and LF/HF ratio. Javorka et al.,[19] evaluated a smaller sample of 17 individuals with DM1 (22.4 ± 1.0 years), indicating that it was possible to observe a significant reduction in the SDNN, RMSSD, LFms² and HFms² indexes. Also, Dungan et al.,[21] when evaluating 33 individuals with DM1 older than 18 years, also found a reduction in the HFms² index. These results show there is an autonomic alteration in DM1.

Table 3 – Linear index values of heart rate variability in the frequency domain of the control and type 1 diabetes mellitus (DM1) groups

Index	Control (n = 43)	DM1 (n = 39)	p value	Cohen's d Effect size	
LF ms²*	1,203.00 (1148,00)	402.00 (531.00)	0.0001	0.9703	Large
HF ms²*	963.00 (866.00)	386.00 (583.00)	0.0001	0.7759	Medium
LF n.u.†	49.76 (16.72)	54.54 (14.83)	0.1770	-0.332	Small
HF n.u.†	50.23 (16.72)	45.45 (14.84)	0.1770	0.3325	Small
LF/HF*	0.97 (1.05)	1.13 (0.82)	0.3071	-0.537	Small

*Values in bold represent p < 0.05. * Median (interquartile range); † mean (standard deviation). LF: low-frequency component; HF: high-frequency component.*

Table 4 – Values of the symbolic analysis and Shannon entropy of the control and type 1 diabetes mellitus (DM1) groups

Index	Control (n = 43)	DM1 (n = 39)	p value	Cohen's d Effect size	
0V%*	17.93 (13.33)	23.04 (18.24)	0.1290	-0.352	Small
1V%*	47.69 (7.62)	48.79 (4.81)	0.4920	-0.091	Small
2LV%†	11.99 (6.49)	11.73 (6.71)	0.8613	0.0393	Small
2ULV%*	20.24 (12.73)	15.33 (9.22)	0.0114	0.4803	Small
ES†	3.74 (0.40)	3.61 (0.45)	0.1663	0.3053	Small

*Values in bold represent p < 0.05. *mean (standard deviation); †median (interquartile range). 0V: pattern without variation; 1V: pattern with 1 variation; 2LV: pattern with two similar variations; 2ULV: pattern with two different variations; SE: Shannon entropy.*

Despite the similar results, our study did not show a statistically significant difference between the groups when analyzing the LF and HF indexes in normalized units and in the LF/HF ratio.

Other methods of HRV analysis addressed in this study were non-linear: SE and symbolic analysis. This was recently described by Porta et al.[9] and is based on the quantification of the information carried in a time series, allowing the development of patterns, denominated symbols (0V, 1V, 2LV and 2ULV), through specific calculations[9] that indicate the autonomic behavior.

The values obtained with the symbolic analysis in this study were significantly lower in the DM1 group when compared with the control for the 2ULV index, showing a parasympathetic decrease, although the magnitude of this difference was small. A parasympathetic reduction through symbolic analysis has also been observed by other authors.[10,19]

Javorka et al.,[19] when comparing the symbolic analysis in young adults with DM1 (21.9 ± 0.9 years) with healthy subjects of the same age group, observed a reduction of 2LV%, which reflects sympathetic and parasympathetic modulation, with parasympathetic predominance. A similar result was observed in the study by Moura-Tonello et al.[10] who, when comparing adults (50.53 ± 6.96 years) with DM2 with healthy individuals, showed that, in diabetic individuals, there was a 2LV% reduction and an increase of 0V%, which reflects the sympathetic activity.

Regarding SE, used to quantify the complexity/regularity of heart rate fluctuations,[8] no statistically significant difference was found when comparing the DM1 group with the healthy group. Corroborating our results, other authors also pointed out the lack of alteration in the complexity evaluated by SE, both in adults with DM2[10] and in young individuals with DM1.[19] These results suggest that, despite the autonomic imbalance, identified through other HRV indexes, the autonomic complexity seems to have no influence in these populations.

Another point addressed in this study was the existence of an agreement in the correlations between linear and non-linear indexes (symbolic analysis). Moderate agreement was observed in the correlations of the RMSSD and HF n.u. indexes with the 2ULV and 2LV indexes of the symbolic analysis, and SDNN with 2ULV, in addition of a high concordance in the correlation between the LF n.u. and 0V indexes. These results demonstrate that the indexes obtained through the symbolic analysis show moderate and high agreement with the indexes obtained in the time and frequency domains, indicating they can also be used in the ANS analysis, since they showed similar results to those of the linear analyses and were able to identify changes in autonomic modulation, as well as the traditional HRV indexes.

HRV alterations have been pointed out as a strong indicator of risk related to cardiovascular events, both in healthy individuals and in those with an already established disease.[22] This condition increases the risk of sudden death due to cardiac arrhythmias and is associated with elevated mortality rates from other causes,[23] indicating that cardiac autonomic dysfunction in patients already at risk, such as those with DM, may be a complicating agent.[24] HRV reduction is described as the first sign of CAN,[25] with a mortality rate that

Table 5 – Association of linear and nonlinear indexes of heart rate variability in the group with type 1 diabetes mellitus

Index	0V%	1V%	2LV%	2ULV%	SE
SDNN					
r	-0.494	0.043	0.522	0.357	0.478
ICC	-1.204	0.058	0.410	0.295	0.037
95%CI	-3.204- -0.156	-0.795-0.506)	-0.126-0.690	-0.345-0.630	-0.836-0.495
RMSSD					
r	-0.690	-0.081	0.550	0.627	0.650
ICC	-3.337	-0.072	0.539	0.617	0.065
95%CI	-7.271- -1.274	-1.045-0.438	0.122-0.759	0.270-0.799	-0.782-0.510
LF ms²					
r	-0.692	0.034	0.721	0.495	0.669
ICC	-0.054	0.000	0.000	0.021	0.002
95%CI	-1.009-0.447	-0.907-0.476	-0.849-0.491	-0.866-0.487	-0.903-0.477
HF ms²					
r	-0.365	0.036	0.469	0.202	0.381
ICC	-0.032	0.001	0.020	0.010	0.001
95%CI	-0.967-0.459	-0.905-0.476	-0.869-0.486	-0.888-0.481	-0.905-0.476
LF n.u.					
r	0.776	-0.080	-0.638	-0.601	-0.640
ICC	0.871	-0.295	-1.840	-1.575	-0.081
95%CI	0.754-0.932	-1.470-0.321	-4.416- -0.489	-3.911- -0.350	-1.062-0.433
HF n.u.					
r	-0.776	0.080	0.638	0.601	0.640
ICC	-6.750	0.228	0.648	0.612	0.075
95%CI	-13.779- -3.064	-0.473- 0.595	0.329-0.815	0.260-0.796	-0.764-0.515
LF/HF					
r	0.776	-0.080	-0.688	-0.601	-0.704
ICC	0.321	-0.712	-0.658	-0.294	-0.702
95%CI	-0.294-0.644	-2.264-0.102	-2.161-0.131	-1.468-0.321	-2.246-0.107

Values in bold represent p < 0.05. 0V: pattern without variation; 1V: pattern with a variation; 2LV: pattern with two similar variations; 2ULV: pattern with two different variations; SE: Shannon entropy; SDNN: standard deviation of all normal R-R intervals recorded in a time interval, expressed in milliseconds; ICC: intraclass correlation coefficient; 95% CI: 95% confidence interval; RMSSD: square root of the mean of the squared differences between adjacent normal R-R intervals, in a time interval, expressed in milliseconds; LF: low frequency component; HF: high frequency component; n.u.: normalized units.

is five-fold higher than in patients without this complication,[26] being suggested as a diagnostic test by the American Diabetes Association® (ADA).[26]

Some limitations should be pointed out, such as the cross-sectional study design, which made it impossible to follow the individuals for a longer time, not allowing to know whether the influence of DM1 on the ANS would remain or worsen in the long term. Also, the anthropometric characteristics, such as weight and BMI, were different between the groups and higher in the group with DM1; however, the mean values were within the normal range, that is, below the values considered for obesity and overweight (BMI < 25 kg/m²).[14]

Despite the abovementioned limitations, some positive points should be emphasized, such as the use of new methods of non-linear HRV analysis, such as the symbolic analysis, which was able to identify autonomic alterations in DM1 and can be used to evaluate and monitor this population. Moreover, we observed that the symbolic analysis showed a moderate and high agreement with some indexes evaluated in this study, indicating that this method should be included in the HRV analysis, associated with the traditional indexes of the time and frequency domains, being crucial in the clinical follow-up of the ANS status in this population. However, considering the small number of studies with this population that used methods such as

symbolic analysis, further research should be encouraged so that more information can be disseminated about this method in other age groups and populations.

Conclusion

The results show that type 1 diabetes mellitus influences linear indexes (time and frequency domains) and the symbolic analysis; however, it does not yet influence the heart rate variability complexity. Symbolic analysis correlates with linear indexes of heart rate variability.

Author contributions

Conception and design of the research and analysis and interpretation of the data: Oliveira EA, Silva AKF, Christofaro DGD, Vanderlei FM, Vanderlei LCM; Acquisition of data: Oliveira EA, Silva AKF, Vanzella LM, Gomes RL; Statistical analysis: Oliveira EA, Silva AKF, Christofaro DGD, Vanderlei LCM; Obtaining financing: Oliveira EA, Silva AKF, Vanderlei LCM; Writing of the manuscript: Oliveira EA, Silva AKF, Vanzella LM, Gomes RL, Vanderlei FM, Vanderlei LCM; Critical revision of the manuscript for intellectual content: Oliveira EA, Silva AKF, Christofaro DGD, Vanzella LM, Gomes RL, Vanderlei FM, Vanderlei LCM.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Faculdade de Ciências e Tecnologia (FCT/UNESP), *Campus* Presidente Prudente under the protocol number CAAE: 22530813.9.0000.5402; opinion 417.031. 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.

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How to Evaluate Cardiac Autonomic Modulation

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Cardiac autonomic nervous system dysfunction has been implicated in several different pathological scenarios with a wide range of clinical relevance and risk. Early detection of autonomic changes, either provoked for therapeutic purposes[1] or as a complication of a primary disorder, such as diabetes mellitus (DM) is of essence for the best management of patients.

Classic (linear) analysis of heart rate variability (HRV) has been routinely used to assess autonomic behavior in diabetic patients in order to promptly detect neuropathy,[2] one of the most common and overlooked complications and a significant cardiovascular risk factor.

As the linear analysis provides important data, non-linear indexes of HRV have been proposed as well, emerging as potential ancillary tools to investigate dysautonomia in type 1 and 2 DM. In the paper "Nonlinear Dynamics in young people with diabetes",[3] the authors compared linear and nonlinear indexes and studied their correlation. While symbolic analysis presented partial correlation with linear methods, Shannon entropy index was similar in DM individuals and controls, and these findings raise two important issues:

1. What could be the clinical value of determining the complexity and randomness of HRV by nonlinear methods?
2. Are they sensitive and efficient?

Keywords

Autonomic Nervous System Diseases; Heart Rate; Diabetes Mellitus; Nonlinear Dynamics; Primary Dysautonomias; Diabetic Neuropathies/prevention

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Several authors agreed that linear indexes (time and frequency domains) are simple and reproducible methods to evaluate the cardiac autonomic system and are consistently reduced in diabetic patients.[2-7] The observed lack of correlation of nonlinear methods with standard measures may imply low sensitivity, and it stands in disagreement with Javorka et al.,[4] which claim that "The complexity of HRV appears to be even more affected (in DM patients) than the magnitude of HRV that is commonly assessed by cardiac autonomic tests."

On the other hand, a perfect correlation between nonlinear techniques and standard HRV measures would provide only limited additional diagnostic information. In fact, previous authors verified that linear HRV indexes performed even better than most complexity measures in discriminating DM patients from controls.[4]

So, where do we stand on the noninvasive diagnosis of dysautonomia?

To the best of our knowledge, time and frequency domain indexes remain the most accepted and used methods to assess HRV. Nonlinear measures are potential tools, but to reach optimal HRV assessment, the methods must be standardized: it is possible to find studies with 24-hour,[8] medium-term (~1h),[4,7] ultra short-term (<5 min)[9] and short-term (from 5-10 min)[2,5,6,10] data recording indexes, all of them dealing with noninterchangeable information.

Nonlinear methods' contribution to evaluate diabetic autonomic system dysfunction is yet to be demonstrated by large-scale comparison studies. Once complexity evaluation proves its value, however, one last question will remain: to what extent would it help patients prevent diabetic neuropathy progression?

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Indications of PCSK9 Inhibitors for Patients at High and Very High Cardiovascular Risk

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Atherosclerotic cardiovascular disease (CVD) is the major cause of ischemic acute coronary events and a significant proportion of ischemic strokes and peripheral artery ischemia. Such events result in significant mortality, physical and/or mental incapacity and costs for the individual and society.[1]

LDL-C as a risk factor

The causality of plasma LDL-C levels and reduced LDL-C uptake mediated by the LDL-C receptor in the pathophysiology of CVD has been very consistently established.[2] For patients at very high risk for premature events, such as those with familial hypercholesterolemia (FH), an elevated LDL-C level is an extremely prevalent risk factor.[3]

Difficulty of achieving the goals with statins

A relevant clinical question is the difficulty of achieving the LDL-C levels recommended by the guidelines for patients at very high cardiovascular (CV) risk. Even using high-potency statins, a substantial proportion of those patients will not achieve the LDL-C target, partially because of the pharmacogenetic effects that determine wide inter-individual variability in the response to statins. This emphasizes the need for an additional reduction in LDL-C levels with new therapeutic options aimed at those atherogenic particles.[4]

PCSK9 inhibitors

The proprotein convertase subtilisin/kexin type 9 (PCSK9), a member of the serine protease family, plays a central role in the regulation of the liver LDL-C receptor activity. Individuals with mutations in the PCSK9 gene and function loss, and consequent lower LDL-C levels, have a substantially reduced risk of developing coronary artery disease. Inversely, heterozygous individuals for the PCSK9 mutation, with function gain, have a phenotype consistent with FH.

Those findings have stimulated the investigation of the use of PCSK9 inhibitors (PCSK9-I) as an innovative therapeutic alternative to improve the control of elevated LDL-C levels.[5,6]

Several clinical studies with different monoclonal antibodies against circulating PCSK9, both in isolation and combined with statins, have confirmed significant reductions in LDL-C levels, reaching up to 60%.[7,8]

FOURIER, SPIRE and ODYSSEY

The FOURIER trial, published in 2017, showed a significant reduction in relevant clinical events, such as acute myocardial infarction (AMI) and atherothrombotic ischemic stroke, in patients with established CVD and plainly treated with moderate- and high-potency statins, associated or not with ezetimibe. The median LDL-C level was 92 mg/dL, and patients receiving evolocumab reached a median LDL-C level of 30 mg/dL. Safety data showed no significant adverse effect, except for injection-site reactions, in the median follow-up of 2.2 years.[9]

The recently published EBBINGHAUS trial, assessing patients who received either PCSK9-I or placebo in addition to statin therapy, has shown no significant difference in cognitive function, even in individuals with very-low LDL-C levels.[10]

Another study using the monoclonal antibody bococizumab has shown a significant reduction in CV events, which is aligned with the result obtained with evolocumab in the FOURIER trial. However, the SPIRE trial was interrupted because of the development of high rates of antidrug antibodies and consequent reduction in the therapeutic response.[11]

The ODYSSEY trial, recently presented as a late-breaking clinical trial at the American College of Cardiology Scientific Session, has assessed patients who had acute coronary syndrome within 1 to 12 months before randomization. All individuals were on moderate- and high-potency statins, associated or not with ezetimibe. The mean follow-up was 2.8 years.[12] The trial has shown a significant reduction in non-fatal AMI, unstable angina and ischemic stroke in patients randomized to receive the PCSK9-I alirocumab. The subgroup of individuals with LDL-C levels greater than

Keywords

Cardiovascular Diseases/complications; Cardiovascular Diseases/mortality; Coronary Artery Disease; Proprotein Convertase 9; Hyperlipoproteinemia Type II; Ezetimibe, Simvastatin Drug Combination.

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or equal to 100 mg/dL (already treated with statins) and receiving alirocumab had the highest benefit, with a 29% reduction in total mortality as compared to placebo.

Cost *versus* benefit of new therapies

Although the advent of precision medicine and the innovative treatments have guided to an individualized approach in prevention and patient's management, the financial restrictions to the progressive increase in health system costs worldwide often requires balancing the therapeutic benefit and the cost of a certain intervention.

Brazilian guideline

The recently updated Brazilian Guideline on Dyslipidemias and Atherosclerosis Prevention recommends the use of PCSK9-I (evolocumab and alirocumab) only to patients at high CV risk, receiving optimized treatment with statins at the highest tolerated dose, either associated or not with ezetimibe, and who have not met the recommended LDL-C or non-HDL-C targets.[13]

The Brazilian guideline, however, does not indicate which individuals will benefit most from the use of that new class of drugs.

Some studies have demonstrated that the quantification of the absolute benefit of an additional therapy is an important factor to support the clinical decision of using or not the new treatment. In addition, financial aspects should be taken into account, but so far cost-effectiveness analyses of the PCSK9-I in Brazil have not been made.[14]

Considering that the costs of PCSK9-I are greater than those of the other drugs for the treatment of CVD, it is important to identify among high-risk individuals those whose treatment is associated with greater clinical relevance, which can be estimated by the number needed to treat (NNT) to prevent the first outcome within a certain time.[15]

In addition, calculating the NNT can help identify groups of patients who will benefit most from the addition of a non-statin therapy, by combining absolute risk and LDL-C thresholds.

In this position statement of the Atherosclerosis Department of the Rio Grande do Sul Society of Cardiology, the selection of patients to use PCSK9-I is more conservative than that of most current guidelines on the use of those drugs. Thus, it is worth emphasizing that the use of antibodies against PCSK9 for individuals who do not meet the criteria presented in this document is not contraindicated, because the therapeutic decision involves clinical judgement and consensus between physicians and patients.

Therefore, this position statement was aimed at identifying the individuals who will benefit most from the use of that new class of drugs to treat hypercholesterolemia.

This first position statement will not address indications of that new class of drugs for statin-intolerant individuals or those on high-risk primary prevention, such as FH.

Considering that evolocumab and alirocumab consistently reduce LDL-C levels by 50% at least, two factors should be observed to quantify the benefit of the treatment: the individuals' clinical characteristics and the LDL-C levels obtained after maximum treatment with statin/ezetimibe.

1) Clinical characteristics of the patients

The clinical characteristics of the patients at CV risk should be identified based on the absolute risk of CV events in 10 years.[16] The greatest benefit derived from the use of PCSK9-I is obtained in individuals at CV risk higher than 20% in 10 years. Thus, patients with previous coronary events or procedures, stroke or aortic aneurysm are classified as "high risk" (20-29% in 10 years).

Patients at "very high risk" for CV events (over 30% in 10 years) are those with recurrent acute coronary syndrome, repeated arterial revascularization or repeated strokes within the first year from the initial event. Advanced age, and the association of diabetes or peripheral occlusive arterial disease are aggravating factors.

2) LDL-C cutoff points after maximum treatment with statin/ezetimibe

In addition to the patients' clinical characteristics, the LDL-C cutoff points from which the treatment with PCSK9-I provides the greatest benefits should be indicated.

The FOURIER trial has shown that even individuals in the lowest quartile of LDL-C levels had a significant reduction in CV events when receiving evolocumab.

However, when assessing that variable, it is worth noting that the reduction in the absolute risk for the same relative reduction in LDL-C level will be smaller when the baseline LDL-C level is lower (Figure 1). In other words, the higher the LDL-C level after treatment with statins/ezetimibe, the greater the benefit deriving from the treatment with PCSK9-I and the smaller the NNT.[17]

The relative reduction in CV events resulting from the use of statins, ezetimibe and monoclonal antibodies against PCSK9 has shown consistency with the relationship reported in the Cholesterol Treatment Trialists meta-analysis, in which every 39-mg/dL reduction in LDL-C was associated with a 21% reduction in major CV events.[18]

Criteria to support decision-making

By associating the two variables presented in an excellent analysis and according to the CV risk and LDL-C levels of patients receiving treatment with statins, Robinson et al.[16] have estimated the NNTs in 5 years to prevent a CV event.[16] (Table 1)

Although there is consensus that NNTs up to 50 are acceptable[19] for new interventions, it is worth noting that PCSK9-I are high-cost drugs. On the other hand, NNTs under 20 are rarely obtained for interventions to treat or prevent CVD resulting from the current studies.[20]

Assuming that PCSK9-I consistently reduce LDL-C levels by at least 50%, we consider that NNTs under 30 are totally acceptable and identify a subgroup of individuals who will greatly benefit from receiving that new class of drugs.

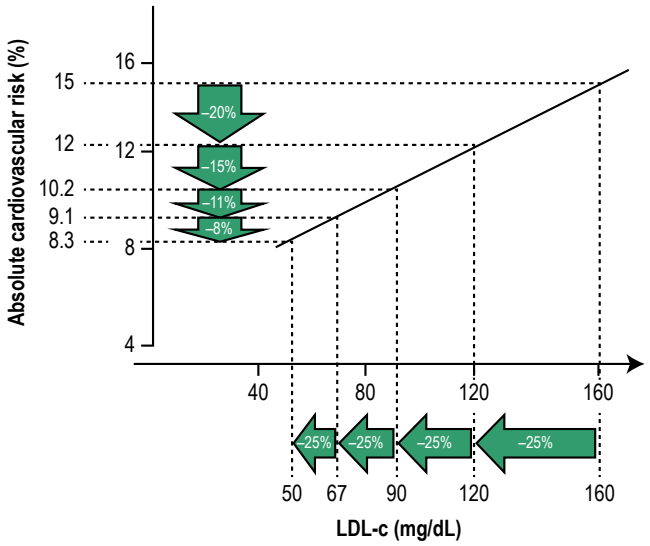

Figure 1 – *Absolute risk reduction for the same relative LDL-C level reduction from different initial LDL-C levels. (Reprint with permission from Oxford University Press).*[17]

Table 1 – NNT in 5 years to prevent a cardiovascular (CV) event in "high" and "very high CV risk" individuals receiving treatment with high-potency statins by adding the PCSK9 inhibitor (PCSK9-I)

Initial LDL-C	50% reduction in LDL-C (with PCSK9-I)	65% reduction in LDL-C (with PCSK9-I)
High risk (20-29% risk of ACVD in 10 years)		
190	19	15
160	23	18
130	28	22
100	37	28
70	53	40
Very high risk (risk of ACVD in 10 years ≥ 30%)		
190	13	10
160	15	12
130	19	15
100	25	19
70	35	27

LDL-C: low-density-lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin/kexin type 9; ACVD: atherosclerotic cardiovascular disease. (Table adapted with permission from Elsevier).[16]

Therefore, patients at high CV risk, plainly treated with high-potency statin associated with ezetimibe, and whose LDL-C levels are higher than 130 mg/dL, will significantly reduce their risk of CV events by adding PCSK9-I to their treatment.

Similarly, individuals at very high CV risk, treated with statin and ezetimibe, and whose LDL-C levels are higher than 100 mg/dl, have a very good chance of significantly reducing outcomes and the residual CV risk by adding that new class of drugs to their treatment.

Conclusion

This position statement of the Atherosclerosis Department of the Rio Grande do Sul Society of Cardiology identifies patients who can derive the greatest secondary clinical benefit from PCSK9 inhibition. Those patients have higher CV risk associated with the highest probability of achieving a significant LDL-C reduction. In addition, this document takes into account the financial limitations of the healthcare system and the current economic scenario.

It is worth emphasizing that the use of antibodies against PCSK9 for individuals who do not meet the criteria presented in this document is not contraindicated, because the therapeutic decision involves clinical judgement and consensus between physicians and patients.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Behr PEB, Moriguchi EH, Castro I, Bodanese LC, Dutra OP, Leães PE, Pimentel Filho P.

Potential Conflict of Interest

Paulo Eduardo Ballvé Behr, MD, received lecture fees in continuing medical education programs from Amgen.

Emilio Hideyuki Moriguchi received lecture fees in continuing medical education programs from Amgen and Sanofi.

Luiz Carlos Bodanese, MD, participated as an investigator for the Odyssey and Rourier studies.

Oscar Pereira Dutra, MD, participated as an investigator for the Rourier study.

Paulo Ernesto Leães, MD, participated as an investigator for the Odyssey and Rourier studies.

Pedro Pimentel Filho, MD, participated as an investigator for the Odyssey and Rourier studies.

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Study Association

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

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Case 4/2018 – Important Mitral Valve Regurgitation Caused by Hammock Mitral Valve in 8 Year-Old Girl

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Clinical data

Heart murmur was auscultated during routine examination at 6 years of age, with complaints of tachycardia and chest pain at that time. A diagnosis of mitral regurgitation caused by hammock mitral valve was performed and enalapril 2.5 mg/day (0.1 mg/kg) was started. She reported being asymptomatic, capable of performing physical activity.

Physical examination: good overall health status, eupneic, acyanotic, normal pulses in the four limbs. Weight: 25 kg; height: 130 cm; right upper limb blood pressure: 90 x 60 mmHg; Heart Rate (HR): 96 bpm; Oxygen Saturation (O_2Sat): 97%.

Precordium: diffuse apex beat, palpated in the sixth left intercostal space, deviated from the midclavicular line and with systolic impulses in the left sternal border. Muffled heart sounds, holosystolic murmur in the mitral and axillary regions with a diastolic rumble after the third heart sound, both of moderate intensity. Liver palpable at the right costal margin, painless.

Complementary examinations

Electrocardiogram: sinus rhythm, with signs of overload of the left cavities. High R waves, preceded by positive Q waves and with normal T waves, in the left leads, indicating left ventricular (LV) diastolic overload. The P wave was negative at V1 and V2 and enlarged at the other leads. Ventricular repolarization was normal. AQRS + 30º; AP + 50º and AP +60º.

Chest X-ray: Increase in the cardiac area at the expense of the left heart cavities and with prominent pulmonary vascular network in the upper pulmonary area, indicating of pulmonary venocapillary congestion (Figure 1).

Echocardiogram: showed markedly dilated left cavities. The mitral valve was thickened, with short chordae tendineae and with leaflets almost attached to the two papillary muscles (hammock mitral valve). The mitral annulus was thickened, with important valve regurgitation, which allowed the appearance of a maximum diastolic gradient of 28 mmHg and a mean of 10 mmHg. The pulmonary arteries were confluent and slightly dilated (13 mm). MPAP: 36 mmHg; Right Ventricle (RV): 12; LV: 56; Left Atrium (LA): 59; Ao: 17; septum and posterior wall: 7; LV Ejection Fraction (LVEF): 63%; mitral annulus: 30; tricuspid annulus: 21 mm (Figure 2).

Keywords

Heart Defects, Congenital / surgery; Mitral Valve Insufficiency; Heart Murmurs; Echocardiography; Electrocardiography, X-Rays.

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Clinical diagnosis: important mitral regurgitation caused by hammock mitral valve with enlargement of the left heart cavities in an 8-year-old girl without apparent symptoms.

Clinical rationale: There were clinical elements pointing to a diagnosis of important mitral valve regurgitation, related to the presence of a regurgitation systolic murmur and diastolic rumble in the mitral area and in the axillary region. The clinical effect was accentuated due to the large increase of the left heart cavities, disclosed by the usual complementary examinations. The diagnosis was well established by the echocardiography regarding the congenital etiology of the defect in the anatomical characterization of the hammock mitral valve. It was observed that, despite the marked consequence of the defect, the patient remained symptom-free and under natural evolution until 8 years of age.

Differential diagnosis: with the diagnostic characterization of marked mitral valve regurgitation, the differential diagnosis refers to the search for its etiology. At this age, one should remember the rheumatic cause, even without suggestive prodromes. Other causes may be related to mitral valve prolapse, valve lesion due to endocarditis or an ischemic lesion of anomalous origin in the left coronary artery directly from the pulmonary trunk.

Conduct: Considering the marked consequence of the mitral valve defect, there was a surgical indication aimed to correct the defect and prevent more severe disease evolution alterations, such as ventricular dysfunction, pulmonary artery hypertension and cavity thrombosis with systemic embolism, among the main ones. It was presumed that the most appropriate technique would be the mitral valve replacement, which was markedly affected, but with a chance of success through a plasty procedure, to be evaluated at the time of the surgery.

Comments

The hammock mitral valve was first described as a direct connection of the papillary muscles with the mitral leaflets, either directly or by the interposition of unusually short chordae tendineae. This congenital malformation of the tensile system is sometimes called a "hammock mitral valve", as it mimics a hammock when it is observed from the atrium. The chordae tendineae are thick and extremely short, reducing inter-cordial spaces and leading to an abnormal excursion of the leaflets, which can cause stenosis and regurgitation.

When the space between the abnormal chordae is completely obliterated, a fibrous and muscular bridge joins the two papillary muscles. In its most severe form, with no chordae tendineae, the papillary muscles are directly fused with the free margin of the leaflets. Mitral regurgitation progressively worsens, with or without concomitant stenosis.

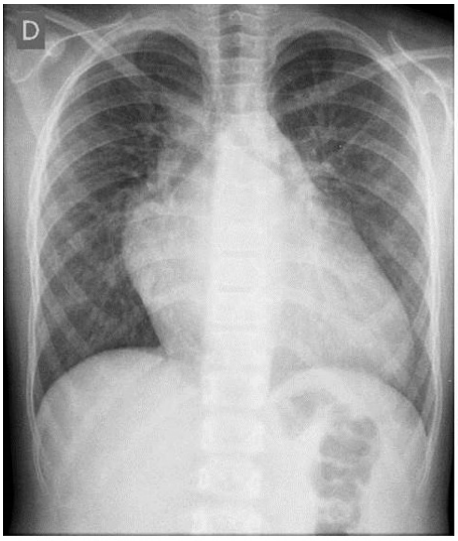

Figure 1 – *Chest X-ray showing a clear increase in the cardiac area at the expense of the left heart cavities and the prominent pulmonary vascular network in the upper pulmonary area, indicating pulmonary congestion.*

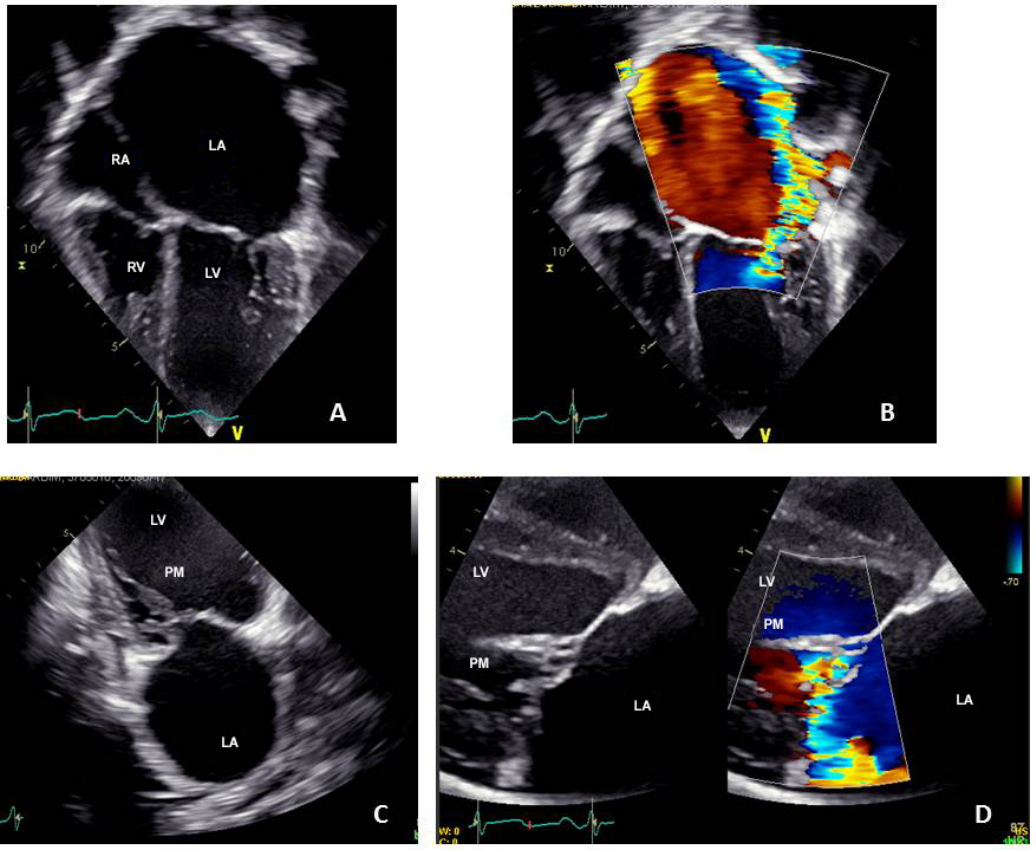

Figure 2 – *Echocardiogram showing the marked enlargement of the left heart cavities, especially the left atrium in A and B, due to the evident mitral regurgitation in B. The close connection of the leaflets with the papillary muscle occurs without chordae tendineae in C and D. RA: right atrium; LA: left atrium; RV: right ventricle; LV: left ventricle; PM: papillary muscle.*

However, even with these anatomical alterations, the valve may show a relatively normal function for many years, as shown by some recent findings.[1]

Most reported cases are in the pediatric age group, and there are only a few reports of hammock mitral valve anomaly in adults. In cases of hammock mitral valve, the repair can be performed through annuloplasty, commissurotomy, modified techniques of posterior annulus shortening and papillary muscle division, according to the presentation of the valve apparatus morphology.[2-4]

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Left Ventricular Assist Device as a Bridge to Candidacy in End-stage Chagas Cardiomyopathy

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Introduction

Chronic Chagas cardiomyopathy manifests late after *Trypanosoma cruzi* infection, and it is still one of the major causes of end-stage heart failure in Latin America.[1] Published experiences[2,3] with heart transplantation for chronic Chagas disease have shown the feasibility and efficacy of this therapy, being the disease reactivation not a major concern when appropriately diagnosed and timely treated.[4]

Nevertheless, the need for some sort of mechanical circulatory support on the waiting list has progressively increased, according to the International Society for Heart and Lung Transplantation Registry annual report.[5] Since the experience with mechanical circulatory support in Latin America is very limited, and biventricular systolic failure is common in Chagas cardiomyopathy, many unanswered questions regarding modalities of support need to be elucidated.

This case report describes the successful implant of an axial flow left ventricular assist device in a patient with end-stage heart failure with severe biventricular failure secondary to Chagas cardiomyopathy.

Case Report

A 26-year-old male, with a history of long-standing heart failure had multiple hospital admissions in the past year despite optimal medical management. The diagnosis of end-stage heart failure due to Chagas cardiomyopathy was confirmed by serology a while ago, and an implantable cardioverter defibrillator was used for sudden death secondary prevention. Echocardiography revealed a severely dilated left ventricle (end-diastolic diameter of 72 millimeters), with severely depressed function (ejection fraction of 18%) and 4+ mitral regurgitation. The right ventricle also exhibit severe dysfunction with 3+ tricuspid regurgitation, tricuspid annular plane systolic excursion of 15, and right ventricular systolic pressure of 65 mmHg. The patient has been followed up in a different city of ours by another cardiology team. At this point, he has never been considered for heart transplantation.

Keywords

Chagas Cardiomyopathy; Heart Failure; Shock, Cardiogenic; Hypertension, Pulmonary; Extracorporeal Circulation.

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Nonetheless, the patient was admitted in the emergency room with cardiogenic shock, in Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) level 2. He was initially managed with the use of two inotropes, intra-aortic balloon pump and hemodialysis. No temporary or durable mechanical assist devices were available at this hospital.

A right heart catheterization revealed low cardiac output (cardiac index of 0.9 L/min/m^2, with systolic pulmonary pressure of 70 mmHg, transpulmonary gradient of 16 mmHg and pulmonary vascular resistance of 6 Wood units. Filling pressures were elevated (central venous pressure and pulmonary wedge pressure of 30 mmHg).

The patient was transferred to our hospital for heart transplantation assessment. At admission, he had sudden hemodynamic instability that deteriorated into cardiac arrest. Cardiopulmonary resuscitation measures were effective, but circulation was maintained with escalating doses of vasopressors. A percutaneous venous arterial extracorporeal life support (ECLS) (Maquet Getinge™, Germany) through the femoral vessels was inserted as a bridge to decision strategy. Hemodynamics stabilized, vasopressors were discontinued, tissue perfusion indices normalized, and the patient neurologic status was intact. He was extubated on the next day, renal function normalized, an aggressive diuresis allowed a twelve-liter negative fluid balance in the following five days (Figure 1).

Eighteen days after ECLS initiation, the patient was submitted to an axial flow left ventricular assist device (HeartMate II, Abbott Laboratories™, Chicago, IL) implantation with ECMO explant under median sternotomy with cardiopulmonary bypass.

Postoperatively (Figure 2), the patient had mediastinal bleeding requiring surgical revision; coagulopathy and pericarditis. A transient right ventricular dysfunction required a five-day administration of intravenous inotropic support, aggressive diuresis and oral pulmonary vasodilators. He was eventually discharged home on postoperative day 35 in fair condition, requiring rehabilitation due to malnutrition and muscular weakness.

Sixteen months later, he is in functional class I with unremarkable recovery except for a single episode of hemolysis that was treated with intravenous heparin. Pump has functioned well with no evidence of failure or thrombosis. Late right heart failure was not an issue, and his exercise performance is excellent. Echocardiography revealed mild tricuspid regurgitation and right ventricular systolic pressure of 30 mmHg. At this point, the patient does not manifest interest in being transplanted.

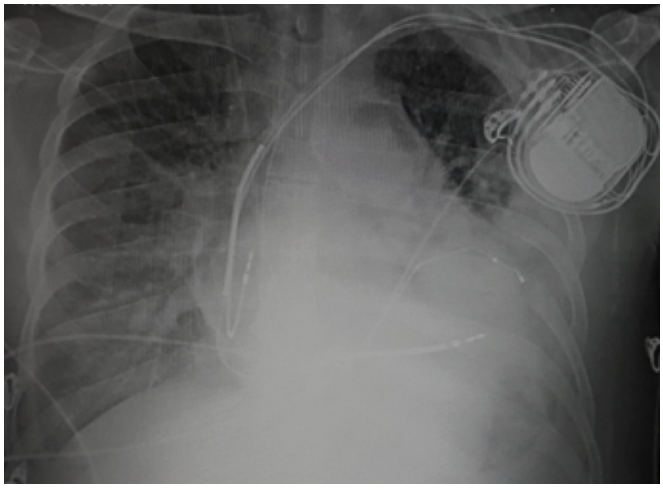

Figure 1 – *Chest radiography after ECLS implantation.*

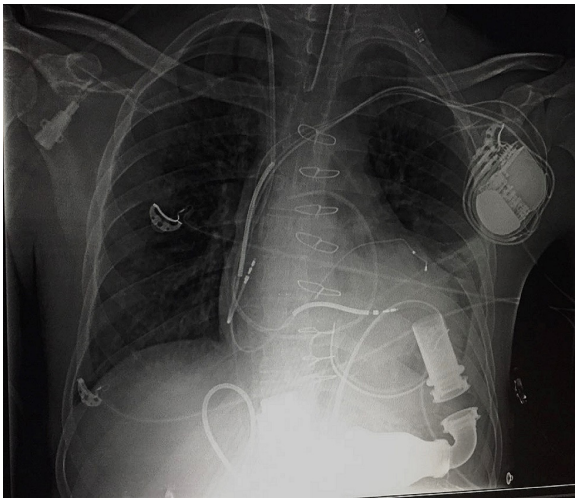

Figure 2 – *Chest radiography after left ventricular assist device implantation.*

Discussion

The present report illustrates that, in patients with Chagas cardiomyopathy with severe biventricular failure, a left ventricular assist device (and not necessarily a biventricular support) may be considered as a modality of mechanical circulatory support as a bridge to candidacy or transplantation. Frequent pathologic findings that need to be observed are apical aneurysms, mural thrombi, very thin ventricular walls and complex ventricular arrhythmias refractory to ablation. Destination therapy, in theory, is a possible alternative for those patients that do not present with late right heart failure, which is a possible natural manifestation of the disease.

Since published data is very limited and the experience with mechanical circulatory support in Latin America is scarce, there are no consensus regarding the best strategy. Moreira et al were the first to report the use of paracorporeal devices in Chagas cardiomyopathy, with inconsistent results.[6] More recently, Kransdorf et al[7] reported the United States experience on 11 heart transplants for Chagas cardiomyopathy. Three out of 11 patients (27%) had mechanical circulatory support in place at the time of transplant (two patients had paracorporeal devices in biventricular configuration and one patient had a HeartMate II device). Ruzza et al[8] described the successful support with a total artificial heart prior to heart transplantation. They argue that this approach is justifiable because it allows treatment of extracardiac Chagas disease, and it potentially reduces the infectious burden of the causative organism that may make progress the disease on a heart supported with a device.

This particular case presented cardiogenic shock, fluid overloaded, with a recent cardiac arrest that required the use of venous arterial ECLS. It was very difficult to determine whether the pulmonary hypertension was severe enough to contraindicate the heart transplantation. Therefore, a bridge to candidacy strategy seemed reasonable in this regard. After six months of support, it proved to be effective in reducing the pulmonary vascular resistance making the patient eligible for heart transplantation.

Author contributions

Conception and design of the research: Atik FA. Acquisition of data: Atik FA, Cunha CR, Chaves RB, Barzilai VS. Analysis and interpretation of the data: Atik FA, Ulhoa MB. Writing of the manuscript: Atik FA, Ulhoa MB. Critical revision of the manuscript for intellectual content: Atik FA, Ulhoa MB, Chaves RB, Barzilai VS. Supervision / as the major investigador: Atik FA.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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

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Challenging Evaluation of Aortic Regurgitation: More Than a Quadricuspid Valve

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A 61-year-old female patient with chronic obstructive pulmonary disease, and no other comorbidities, was referred for cardiological assessment due to aggravated exertional dyspnea (New York Heart Association - NYHA class III) and atypical chest pain. Physical examination disclosed only a diastolic murmur in the second intercostal space in the right sternal border.

The transthoracic echocardiogram (TTE) showed aortic regurgitation (Figure 1A), with non-dilated cardiac chambers and preserved biventricular function. The acoustic window limited the evaluation of the valvular lesion severity and its importance in the context of the complaints, although the continuous Doppler spectrum suggested significant regurgitation (Figure 1B). The evaluation was further impaired by a systolic flow acceleration in the Left Ventricular Outflow Tract (LVOT), with no significant gradient and an undetermined cause. The aortic root had normal size, but it was not possible to carry out an adequate morphological and functional characterization of the valve.

The Transesophageal Echocardiogram (TEE) disclosed a quadricuspid aortic valve with central coaptation defect of 0.35 cm^2 through three-dimensional planimetry causing severe aortic regurgitation (Figures 1C and 1D). The three-dimensional evaluation also showed a practically circumferential thickening in the LVOT, corresponding to a non-obstructive subaortic membrane, resulting in the observed flow acceleration (Figures 1E and 1F).

Medical therapy was optimized, and the patient was referred to valve replacement surgery.

This case highlights the incremental role of TEE, complemented by three-dimensional imaging, in the thorough assessment of valvular disease, crucial for the correct therapeutic management. This association between aortic quadricuspid valve and the subaortic membrane is a rare finding, described in only one previous report in the literature.[1]

Keywords

Aortic Valve Insufficiency; Echocardiography, Transesophageal; Echocardiography, Three-Dimensional; Pulmonary Disease, Chronic Obstructive.

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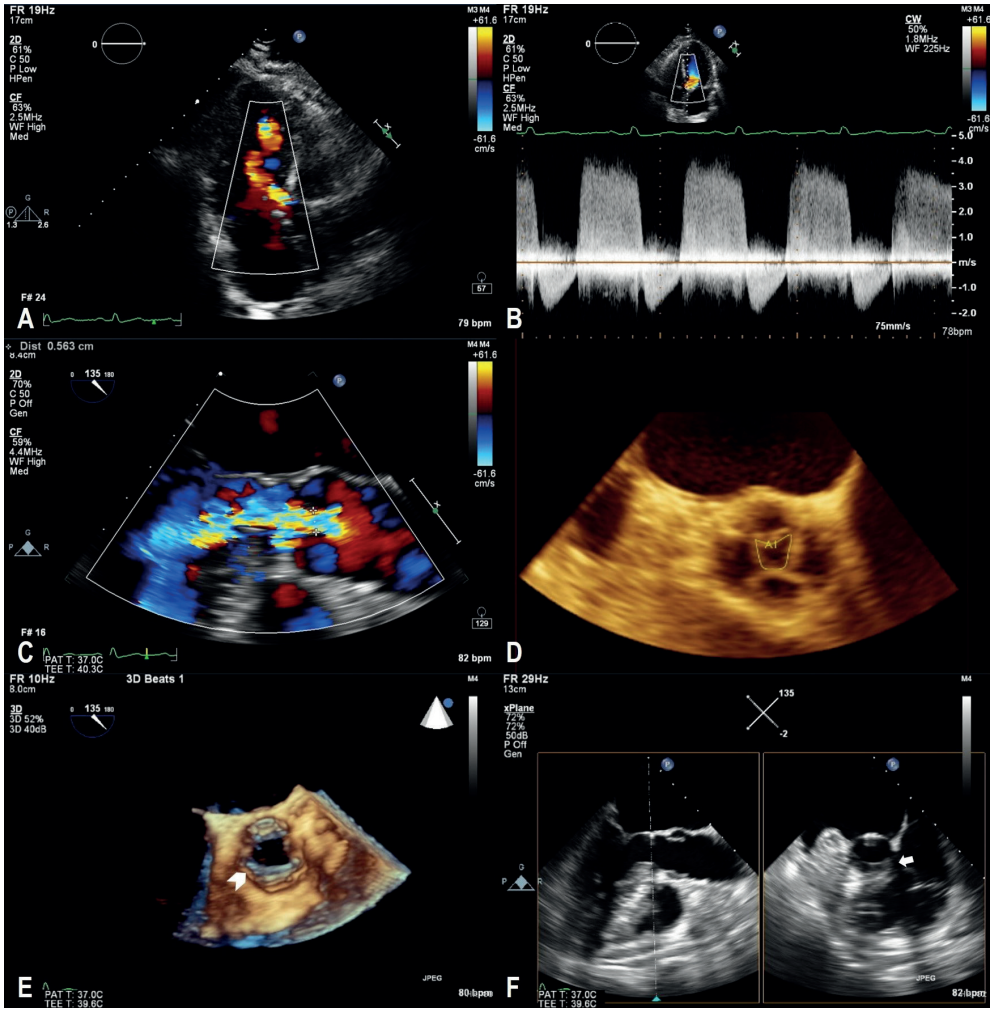

Figure 1 – *Aortic regurgitation jet visualized by transthoracic echocardiogram with color Doppler (A) and its respective spectrum on continuous Doppler wave (B); large jet visualized by transesophageal echocardiogram, with a 6 mm vena contracta (C), originating from the central coaptation defect of the quadricuspid aortic valve, with a regurgitant orifice of 0.35 cm² in three-dimensional planimetry (D); Almost circumferential thickening of the left ventricular outflow tract readily identified in the three-dimensional image in systole (E), confirming the presence of a subaortic membrane with evaluation of orthogonal planes (F).*

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Challenges For Percutaneous Left Atrial Appendage Closure: Imaging And Residual Flow

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We have read with great interest the paper entitled 'First results of the Brazilian Registry of Percutaneous Left Atrial Appendage Closure' by Guérios et al[1]. is a very important study. We have some suggestions about this trial.

Firstly, two-dimensional transeosophageal echocardiography (2D-TEE) can evaluate the morphology of left atrial appendage in multiple views. But real-time three-dimensional transeosophageal echocardiography (3D-TEE) provides more detailed images of the left atrial appendage (LAA) anatomy than 2D-TEE.[2] A competent physician can accurately evaluate the LAA depth and landing zone. Moreover LAA closure depends on an accurate determination of anatomical structure. Therefore the 3D-TEE may show advantantages in relation to 2D-TEE in transcathater LAA closure.

Secondly, we wonder which indicators were used the device selection. For example, Lefort occluder devices are appropriate for single-lobe appendage, but LAmbre occluder can be used in LAA depth < 21 mm.[2]

Lastly we would like to know about the two patients whose devices showed thrombus formation, as incomplete LAA closure may be associated with an increased risk of thrombus formation and then the second device may be inserted.[3] Did the authors do further investigation and intervention in these patients?

Keywords

Atrial Appendage; Septal Occluder Devices; Echocardiography, Three-Dimensional; Medical Records.

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Reply

Thank you for your interest in our paper and the pertinent comments. We agree that in comparison to 2D, 3D-TEE provides far more information, security and predictability to percutaneous left atrial appendage closure. In our Service, real-time 3D-TEE is the default tool used for guidance in these procedures. However, the Brazilian Registry of Percutaneous Left Atrial Appendage Closure is a multicenter Registry, which data has been collected since 2010. At that time, and even today, not all centers involved in the Registry had 3D-TEE available in the cath lab, and in those cases, guidance to the procedure was based solely on 2D-TEE information.

Device selection was restricted due to the limited device availability in the Brazilian market. Only the Amplatzer Cardiac Plug (ACP, St Jude Medical, St Paul, MN) was available for use in Brazil until mid-2015, when the Watchman device (Boston Scientific, Marlborough, MA) came into national market. We still do not have the Amulet device (St Jude Medical, St Paul, MN) in Brazil, and LAmbre (Lifetech Scientific, Shenzhen, China) became available in our market only in January 2018.

Regarding the 2 patients in whom thrombus formation was detected at follow-up, in both cases the LAA was completely closed. Thrombus formation was not related to residual LAA flow - hence there was no indication for further procedure – but developed over the surface of the device. Both patients were treated with reinstitution of oral anticoagulation for 3 months with thrombus resolution, and there were no other adverse clinical consequences.

Ênio E. Guérios, on behalf of the authors of the Brazilian Registry of Percutaneous Left Atrial Appendage Closure