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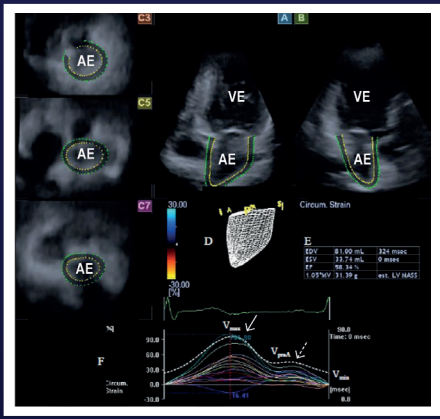

Figure 1 – *Images from three-dimensional (3D) full-volume dataset showing left atrium (LA) in a patient with corrected tetralogy of Fallot is presented: (A) apical four-chamber view, (B) apical two-chamber view, (C3) short-axis view at basal, (C5) mid- and (C7) superior left atrial level. A 3D cast (D), volumetric data (E), time – global volume and time – segmental strain curves (F) of the LA are also presented. Dashed curve (F) represents LA volume changes during cardiac cycle with maximum (V_{max}), minimum (V_{min}) LA volumes and LA volume at atrial contraction (V_{preA}). White arrow represents peak strain, while dashed arrow represents strain at atrial contraction (F). LA: left atrium; LV: left ventricle. Page 133*

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The Lack of Clinical Applications Would be the Cause of Low Interest in an Endothelial Dysfunction Classification

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Based on the assumption that a classification system is a very critical subject and may significantly improve the prediction of individual responses to treatment and related diseases, we proposed 16 years ago a classification for endothelial dysfunction including etiological, functional, and evolutionary aspects (Figure 1).[1]

Since our first publication, we wrote that a proposition for an endothelial dysfunction classification might deserve criticism because it could still be seen as unsuitable and pretentious. The first question is of a philosophical nature because the present concepts on endothelial function and dysfunction might eventually change dynamically over time. The classification could also be interpreted as a premature reductionism, sounding like an "end of the question" proposal. The lack of clinical applications could be the cause of the low interest in an endothelial dysfunction classification. This editorial aims to explore the differences among the three classification axes and the practical and clinical implications of each proposed category. Aspects relevant to the etiology of the dysfunctions, in addition to treatment directions, are also considered.

The dysfunction in the endothelial cell precedes the organic cellular dysfunction in most cardiovascular diseases and characterizes the primary endothelial dysfunction (etiological classification).[2] The endothelial dysfunction may be primary (or genetically inherited). This implies a need for the development of diagnostic methods applied to early detection and primary prevention of endothelial dysfunction as a useful measure to halt the development of cardiovascular diseases. Treatment in these cases is aimed at preventing cardiovascular risk factors through lifestyle modifications, such as diet and weight control, physical exercise, and smoking cessation.[3] From this point of view, endothelial dysfunction should be considered a public health problem. A secondary (or phenotypic) endothelial dysfunction may occur when endothelial cells lose their ability to produce nitric oxide (NO) and increase the expression of vasoconstrictor, proinflammatory, and prothrombotic factors, configuring a proatherosclerotic scenario. Such phenotypic alterations contribute to the formation, progression, and rupture of atherosclerotic lesions, and are commonly found in hypertension, coronary artery disease, and diabetes.[4] In this type of endothelial dysfunction, pharmacological treatment shows consistent results in terms of restoring the endothelial function. For example, antihypertensive medications to control blood pressure, statin treatment to reduce LDL cholesterol levels, and antidiabetics to reduce blood glucose levels.[5]

Studies in the 1990s definitively established the role of the endothelium in all cardiovascular diseases. Such diseases are associated with endothelial dysfunction due to impaired release of endothelium-derived relaxing factors and, consequently, a risk of spasm and thrombosis (atherosclerotic or nonatherosclerotic obstructive coronary disease, hypertension, diabetes, dyslipidemia, atherosclerosis, Raynaud's phenomenon, and heart failure, among others).[6,7] Therapeutic interventions have been developed for this type of endothelial dysfunction (vasotonic), which is characterized by functional impairment, aiming to improve the endothelial function and prevent its dysfunction in asymptomatic individuals and in patients with coronary artery disease. Beta-blockers, statins, angiotensin-receptor antagonists, angiotensin-converting enzyme inhibitors, antioxidants, and insulin sensitizers show benefits in these cases. Other substances, such as L-arginine, tetrahydrobiopterin, and folic acid, are also under investigation for their contribution to improving the endothelial function.[8-10]

The vasoplegic endothelial dysfunction classification includes the characteristic situations of severe vasoplegias, many of which are time resistant to the action of vasoconstrictive amines. This type of dysfunction is characterized by an excessive production of vasorelaxant substances produced by the endothelium, especially NO, and include, for instance, vasoplegias during and after cardiopulmonary bypass, sepsis, and anaphylactoid and anaphylactic reactions.[11] The vasoplegic syndrome has a multifactorial genesis and, in the case of patients undergoing cardiac surgery, occurs mainly due to exposure of the body to nonphysiological materials and the use of heparin/protamine,[12] triggering an inflammatory response syndrome. During this process, there is complement activation, cytokine release, leukocyte activation, and expression of adhesion molecules, as well as a production of oxygen free radicals, arachidonic acid metabolites, platelet activity factor, NO, and endothelin. The consequences of the inflammatory response syndrome may lead to dysfunction of multiple organs and systems, such as the one that occurs in septic shock. The decrease in systemic vascular resistance observed in vasoplegic syndromes is associated with excessive NO production and may be reversed by NO synthase (NOS) inhibitors and methylene blue.[13]

Keywords

Endothelium / dysfunction; Classification; Cardiovascular Diseases; Prevention; Risk Factors.

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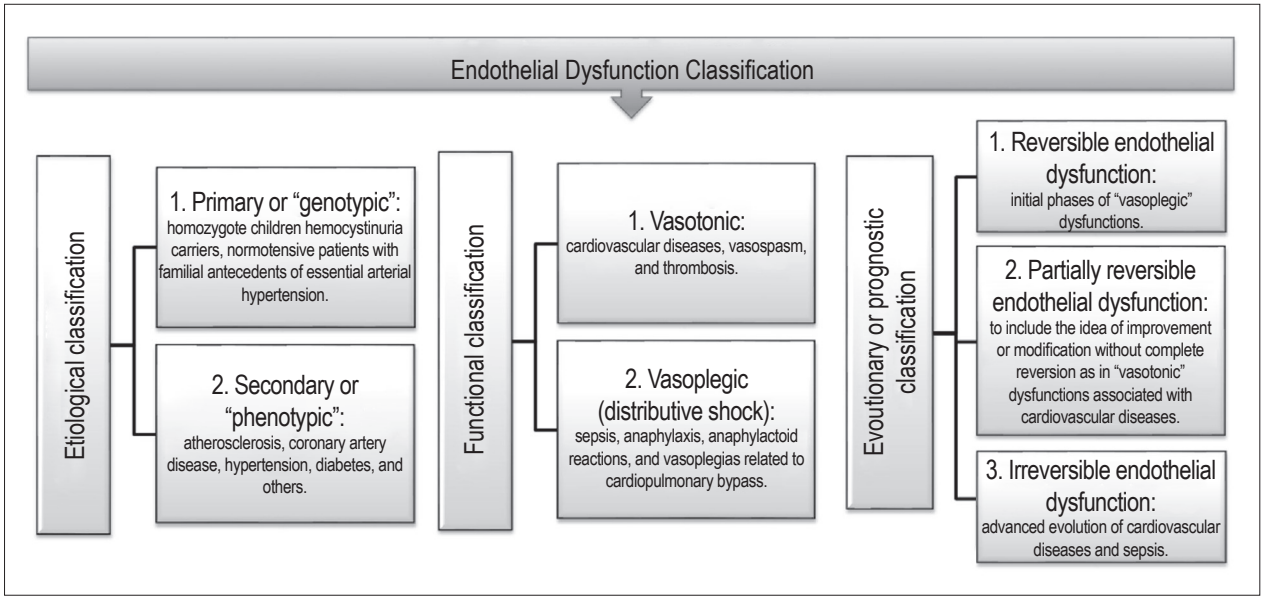

Figure 1 – *Proposal of an endothelial dysfunction classification. Modified from Evora et al.*[4]

The term "vasoplegic endothelial dysfunction" was created as part of the proposed classification and deserves some comments. Searching the MEDLINE database using quoted terms, we found: "endothelium dysfunction" (37,640 papers), "endothelial dysfunction" (69,115 papers), "vasoplegic endothelial dysfunction" (12 papers), "vasoplegia" (206 papers), and "vasoplegic syndrome" (243 papers). Assuming that the excessive release of NO is, in fact, an endothelial dysfunction, this terminology would be unified to the search of distributive shock (sepsis, anaphylaxis), anaphylactoid reactions, and vasoplegias related to cardiopulmonary bypass. In this manner, this issue demands special attention from the scientific community, at least in terms of unifying the terminology.[1]

Endothelial dysfunction may be reversible or partially reversible in such cases, according to the prognostic or evolutionary classification. Endothelial dysfunction should be considered in hypertensive postmenopausal women presenting with abnormal endothelium-dependent vascular function. However, a significant improvement in endothelial function may be reached after 6 months of antihypertensive therapy. These changes may identify patients with a more favorable prognosis.[14] Dysfunction of the coronary or peripheral vascular endothelium is an independent predictor of cardiovascular events and provides valuable prognostic information. In such cases, modification of risk factors and drug treatment (statins and angiotensin-converting enzyme inhibitors) may improve the endothelial function and prognosis.[15] Most risk factors related to atherosclerosis and cardiovascular morbidity and mortality have been found to be associated with the endothelium.[14] These risk factors include hyperlipidemia, hypertension, diabetes, and smoking, which may be reversed by pharmacological or nonpharmacological treatment. In other words, it is possible to improve endothelial dysfunction using medical treatment and exercise, even without completely reversing it.[16,17]

Irreversible endothelial dysfunction usually occurs during the progression of cardiovascular diseases and sepsis.

We have been using the proposed classification since 2000[1] as a didactic model, carefully emphasizing eventual biases concerning its misinterpretation. However, the current usefulness of an endothelial dysfunction classification still remains "an open discussion". Semiquantitative measurements of endothelial dysfunction may potentially amend the assessment of the proposed categories. We hoped that the classification system would be used to improve and uniformly diagnose patients, in addition to providing a route for collaborative studies on endothelial dysfunction across academic centers. However, as already mentioned, the lack of clinical applications could be the cause for the low interest in an endothelial dysfunction classification. Perhaps the development of biomarkers may strengthen the clinical reasoning of cardiovascular diseases from the point of view of endothelial dysfunction.[17-19]

Potential Conflict of Interest

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

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Editorial

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I Luso-Brazilian Positioning on Central Arterial Pressure

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Natural and accelerated vascular aging. Involved mechanisms and factors

The vascular aging process

In 2006, Dzau et al. presented the cardiovascular disease (CVD) continuum, represented by successive events/stages of disease progression from the incidence of known risk factors until death.[1] This whole concept had the genesis and progression of atherosclerosis as its nuclear mechanism of progression to underlying CVD. In 2010, Dzau et al. gave new emphasis to the importance of age-related structural changes in the middle layer of the arterial wall (arteriosclerosis) as a contributing mechanism for the risk of development of CVD.[2]

There is a natural process of wear and progressive modification of the arterial wall structure that arises from the mechanical stress of distension induced at each cardiac cycle in connection with the pulse wave amplitude and incident and reflex pressure.[3] In the absence of any other factor, this mechanism alone will produce wear on the arterial wall, promoting thickness reduction, fragmentation, and disorganization of the elastin layers. In parallel, this damaged elastic component is replaced by collagen and protein matrix, which is less capable of accommodating the incident pulse wave pressure. In addition, there is loss of integrative and functional connection between elastin layers and smooth muscle vascular cells,[4] resulting in reduced distensibility and increased stiffness of the large artery wall, which can be measured by an increase in the transmission of the pulse wave velocity (PWV) and the return of the reflex wave. Thus, there is an influence on the central systolic blood pressure (cSBP), central pulse pressure, "augmentation index", and other ventricular-vascular integration indices.[5]

The factors accelerating arterial aging are multiple: fetal programming, genetic factors, hypertension, dyslipidemias, diabetes mellitus, chronic renal disease, chronic diseases with an inflammatory component, and smoking, among others.

Keywords

Arterial Pressure; Cardiovascular Diseases/physiopathology; Coronary Diseases/physiopathology; Risk Factors; Endothelium, Vascular; Atherosclerosis

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Accelerated vascular aging

The identification of individuals with accelerated vascular aging may allow an earlier specific intervention, with control of the various risk factors. For each carotid-femoral PWV (cfPWV) increase of 1 m/s, the risk of cardiovascular death, cardiovascular event, or mortality from other causes increases between 14 and 15%.[6] The publication of cfPWV[7] reference values for different age groups has allowed an easier identification of individuals with early signs of arterial stiffness. However, ethnic and/or environmental exposure aspects that may also contribute to the arterial aging process should be taken into account in the definition of "normal".[8]

Arterial aging: relationship between microcirculation and macrocirculation, and between arteriosclerosis and atherosclerosis

We can identify four key milestones in the vascular aging process: 1) a progressive reduction in the distensibility of large muscular arteries; 2) a progressive increase in the reflected pressure wave, with a consequent increase in the various components of central arterial pressure; 3) a loss of the arterial stiffness gradient between the central and peripheral arteries; and 4) a progressive elimination of the impedance differential between the arterial macrocirculation and microcirculation.[9-11] This set of structural and functional changes in the arterial tree following the deterioration of the structure and function of the middle layer of the arterial wall (arteriosclerosis) is associated with the appearance and concomitant development of atherosclerosis lesions in the vessel wall, having endothelial dysfunction as a unifying mechanism.[12]

Measures of Central and Peripheral Pressures: Differences and Advantages

Brachial blood pressure (BP) measured with a sphygmomanometer cannot be considered equivalent to aortic pressure since the latter has invariably lower values. The BP varies continuously during the cardiac cycle, although in practice only the maximum value during systole and the minimum value during diastole are measured. Furthermore, the shape of the pulse wave varies along the arterial tree. With the advancement of the pulse wave from the more elastic central arteries to the more rigid peripheral arteries, the systolic peak becomes narrower and more elevated (Figure 1). Considering that the diastolic BP (DBP) and the mean BP are relatively constant, the brachial systolic BP (SBP) can be 30 mmHg higher than the central systolic aortic pressure in young individuals. This phenomenon, known as amplification

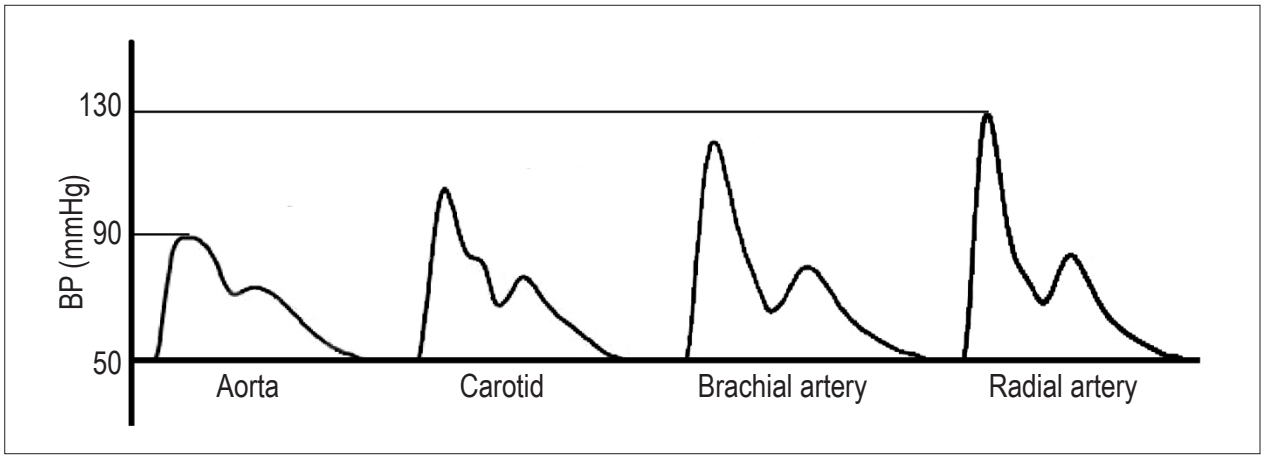

Figure 1 – *Amplification of systolic pressure from central to peripheral arteries.*

of systolic pressure (or pulse pressure), occurs due to several reasons, among them the smaller caliber and greater stiffness of the peripheral arteries. In addition, pulse wave reflections occur at several sites in the arterial network, such as areas with greater collagen/elastin gradient, with greater vasomotor tone and, especially, at bifurcation points. Multiple reflected pulse waves integrate into a single reflected wave that is added to the incident pulse wave, caused by the ventricular ejection. When the reflected wave reaches the incident wave earlier, there is an increase in the central systolic pressure and, consequently, a reduction in the amplification of the pulse pressure. In fact, this increase in pressure depends on several variables, especially age, gender, height, and heart rate.[13-15] Female gender, advanced age, short stature, and bradycardia are associated with a lower pulse pressure amplification. Even with the control of these variables, only about 70% of the variability in the pulse pressure amplification can be explained in multiple regression models.[13,16] This indicates that central pressure cannot be accurately estimated from the brachial pressure using statistical models, but it actually needs to be determined directly through appropriate methods.

Advantages

Measurement of central pressure could result in greater accuracy in the diagnosis of hypertension, greater safety in the therapeutic decision, and better definition of the prognosis.[17,18] Some authors have identified that central pressure, compared with brachial pressure, correlates better with intermediate cardiovascular risk markers such as carotid intima-media thickness and left ventricular hypertrophy.[19,20] Several studies have reported an independent relationship between central pressure and future cardiovascular events, including in elderly patients with coronary disease and chronic kidney disease.[14,21-23] However, other studies have not found a superior predictive value for central pressure over brachial pressure.[24] This controversy exists because the methodology is still heterogeneous and the peripheral pressure, necessary for the final result, explains more than 90% of the variation in central pressure. Furthermore, derivation of central pressure requires an additional measurement, usually radial tonometry, which is also subject to errors that may contribute to the remaining 10% of the variation.[18] Therefore, before recommending central pressure measurement for wide clinical use, standardization of the method and the calibration system, and technical limitations of the various devices available must be resolved.

Definition, evaluation and normal values of the main central parameters (central aortic pressure and carotid-femoral pulse wave velocity)

The SBP values vary considerably according to the place where they are obtained. The SBP is greater in the brachial artery when compared with the aorta. This difference in pressure values between the aorta and the brachial artery is a consequence of the phenomenon of peripheral amplification, which results from the difference in impedance between the large-, medium- and small-caliber arteries, especially in the bifurcations, and also the presence of several factors of interference, such as age, comorbidities (dyslipidemia, smoking, diabetes mellitus, etc.) and environmental factors (sodium).[25] Recent evidence indicates that central aortic pressure, the augmentation index, and cfPWV are robust markers for future cardiovascular events.[21,26]

An important aspect in relation to central systolic pressure concerns pressure values obtained with commercial equipment by noninvasive methods. Although these values correlate well with invasive studies, they do not fully represent the central systolic pressure values, but they correctly reflect the amplification phenomenon. This static measurement is considered insufficient for a definitive validation of these methods in the stratification of cardiovascular risk.[27]

Measurement of cfPWV is an appropriate method of assessing arterial aging with an excellent correlation with the risk of cardiovascular death, cardiovascular events, and mortality from other causes.[6] The stiffening of the distal aorta and large arteries, such as the carotid and iliac arteries, occurs due to the early return of the reflection wave, secondary to structural and functional alterations of the distal vascular wall.

Therefore, the great arteries differ from medium and small arteries in relation to histology, physiology, and elastic properties, which is why it is extremely important to define the anatomical target for the action of a drug and the therapeutic target to be achieved. Evidence regarding drug treatment points to a greater ease of reversal of alterations in small-caliber arteries (muscle) than in large arteries (elastic). Thus, results obtained in one arterial segment cannot be extrapolated to other segments in the same arterial tree. Tables 1 and 2 show the central aortic systolic pressure, augmentation index, and cfPWV values in the normal population.[28,29]

Evaluation methodology - available devices and their validations

The cfPWV, which directly reflects arterial stiffness, has a predictive value in cardiovascular morbidity and mortality and is currently considered the gold standard method to assess arterial stiffness.[5]

The devices used to measure cfPWV have evolved over the last two decades, and their new versions have received systematic validation. Numerous studies have been published comparing invasive and noninvasive methods in different populations and among several existing noninvasive cfPWV measurement devices such as oscillometric, piezoelectric, and tonometric. Most of them have a good correlation with the methods most used in epidemiological studies, such as Complior® or SphymoCor®, among others. Currently, these methods involve little operator training and the ease of use and time consumed in the exam have been optimized so that they are becoming more available for use in clinical practice with good intraobserver and interobserver correlations.[30]

Some differences have been found in studies comparing devices, with higher values of systematically hemodynamic parameters obtained with one device in particular. The mathematical models used in different devices can lead to different results. However, in most cases, this has no translation in clinical practice, since it does not imply a change in the risk class of the individual. Nevertheless, it is prudent that the same type of equipment is used in multicenter research studies.[31]

In addition to the validation of different equipment, different procedures for measuring cfPWV have also been proposed. These different procedures, such as measuring the carotid-femoral distance, can influence the results obtained if they are not also standardized. In this case, there are arguments that 80% of the direct carotid-femoral distance is the most accurate estimate for this same distance.[5]

Table 1 – Central systolic aortic pressure values and the augmentation index in normal individuals[28]

	Central aortic pressure (mmHg)				Augmentation index (%)			
	Female		Male		Female		Male	
Age (years)	Mean	Percentile (10–90)	Mean	Percentile (10–90)	Mean	Percentile (10–90)	Mean	Percentile (10–90)
<20	97	86 –109	105	96 – 113	14	9 – 20	19	11 – 24
20 – 29	95	80 – 110	103	92 – 115	12	5 – 19	15	6 – 24
30 – 39	98	84 – 119	103	88 – 120	8	0 – 17	13	4 – 23
40 – 49	102	87 – 123	106	90 – 123	6	0 – 15	11	2 – 21
50 – 59	110	93 – 127	110	96 – 126	5	0 – 13	9	2 – 18
60 – 69	114	97 – 129	114	97 – 128	6	1 – 12	8	2 – 17
> 70	118	100 – 131	116	99 – 130	6	1 – 13	8	1 – 17

% = percentage increase.

Table 2 – Carotid-femoral pulse wave velocity values (m/s) in normal individuals[29]

Age	Mean ± 2SD	Median (percentile 10 – 90)
<30 a	6.6 (4.9 – 8.2)	6.4 (5.7 – 7.5)
30 – 39 a	6.8 (4.2 – 9.4)	6.7 (5.3 – 8.2)
40 – 49 a	7.5 (5.1 – 10.0)	7.4 (6.2 – 9.0)
50 – 59 a	8.4 (5.1 – 11.7)	8.1 (6.7 – 10.4)
60 – 69 a	9.7 (5.7 –13.6)	9.3 (7.6 – 12.1)
> 70 a	11.7 (6.0 – 17.5)	11.1 (8.6 – 15.5)

SD: standard deviation.

Central parameters: differences according to age, sex, and ethnicity

The best way to define normal values for central aortic pressure would be a correlation between the central aortic pressure levels obtained and the cardiovascular risk, as known for the BP obtained by the conventional or brachial method. However, these data are not yet available as results of prospective studies designed for this specific purpose, although some publications have sought to obtain these correlations between cardiovascular outcomes and central aortic pressure.[21]

One strategy would be to obtain correlations between central aortic pressure values that correspond to conventional pressure values obtained in the casual brachial artery or in the clinic. Following this strategy, population studies suggest that an optimal systolic central aortic pressure would be represented by values < 110 mmHg, which would be equivalent to 120 mmHg when obtained by the conventional BP measurement. Likewise, a central aortic pressure < 120 mmHg would correspond to a brachial SBP of 140 mmHg, defining as stage 1 systemic arterial hypertension a systolic central aortic pressure ≤ 120 mmHg.[32]

Applicability and cost-benefit relationship of the measurement of central parameters

Although it is not part of the stratification routine in hypertensive patients, the central aortic pressure has attracted increasing interest due to its predictive value for the occurrence of cardiovascular events, as well as for the differential evaluation of the different anti-hypertensive drugs, when compared with the traditional determination of the brachial pressure.[33] The augmentation index and the pulse pressure measured by carotid tonometry have been considered independent predictors of cardiovascular mortality in end-stage renal disease. However, the predictive value of the central aortic pressure, when compared with that of the brachial BP showed no significant differences.[21] Nevertheless, the recommendation for its routine use requires further studies. As an exception and as an added value, isolated systolic hypertension is observed in youths, since the brachial artery SBP in these individuals may be increased due to an exaggerated amplification of the central pressure wave, which would be normal.[34]

There are no data verifying the cost-benefit relationship of central aortic pressure determination, extrapolating it from small studies with the use of angiotensin II receptor blocker (e.g., losartan), which reduces central aortic pressure and may bring some additional benefit when using it in addition to the reduction of brachial BP.[35]

Isolated systolic hypertension in young adults: true hypertension and spurious hypertension

The pathophysiological mechanism of isolated systolic hypertension in elderly and young individuals is not the same. In addition, information on the prognosis of both is scarce and the guidelines currently available offer different recommendations on how to address these situations depending on the age group.[34]

Isolated systolic hypertension in young adults (ISHY) was described in 1999 as a "spurious" elevation of the SBP or pseudo-elevation of the SBP (> 140 mmHg) with normal values of diastolic pressure (< 90 mmHg) resulting from a phenomenon of amplification of the peripheral arterial pulse waveform.[36] ISHY is more common in male athletes, in individuals who are taller, and in those with higher body mass index.[37] The prevalence of ISHY shows a significant variation (between 2% and 16%) in exclusively male cohorts and has obesity and tobacco as two of the main determinants.[38] The noninvasive evaluation of the central pressure and pulse wave amplification in the upper limbs has a precise indication in these cases, since it allows the identification of young adults with "spurious" isolated systolic hypertension, sparing them from being labeled as "hypertensive patients".[39] The identification of patients with ISHY should be complemented by outpatient monitoring to exclude white coat hypertension.[40]

ISHY has increased in prevalence and, given the lack of information about it, there are controversies about how to intervene in this situation. If on the one hand the values of central aortic pressure in individuals with ISHY are lower than those found in true hypertensive patients, they are higher than those obtained in normotensive patients.[39] The study by Yano et al.,[41] of 2015, showed a higher cardiovascular risk in this group when compared with individuals with optimal BP, but the study did not include an assessment of the central pressure for a possible differentiation between the groups.[41] With the information available, the management is to carefully monitor with nonpharmacological measures, with a more aggressive management reserved for situations of greater associated cardiovascular risk, at least until new data are available.[42]

Prognostic value of the ambulatory arterial stiffness index

The ambulatory arterial stiffness index (AASI) is used for the evaluation of arterial stiffness and is calculated based on the slope of the diastolic pressure *versus* the values from the systolic pressure in outpatient monitoring, evaluating the dynamic relationship between the DBP and the SBP in 24 hours.[43]

Thus, for any increase in the distension of the artery wall, the SBP and DBP values tend to increase in parallel, whereas in a rigid artery, there is an increase in the value of SBP accompanied by a lower elevation or even a decrease in DBP. Li et al.[44] confirmed in a healthy Chinese population that there was a significant correlation coefficient between AASI and cfPWV, which is the gold standard method.[44]

The AASI depends on the degree of functional and structural integrity of the arteries, and may also depend on the ejected systolic volume and the reflection waves.[45]

Because the AASI is dependent on the mechanical properties of small arteries and reflection waves, this index correlates well with pulse pressure and augmentation index,

and has a good correlation with some markers of lesion in target organs (ventricular hypertrophy, carotid lesion, and microalbuminuria).[46]

Some studies have shown a relationship between AASI and global and cardiovascular mortality, as well as a relationship with stroke in normotensive individuals.[47] Nevertheless, this prognostic value is still debatable and is related to the degree of decrease during sleep and other factors, such as heart rate and peripheral vascular resistance.[48] Moreover, its reproducibility is poor (around 50-68%).[49]

Central parameters as predictors of arterial hypertension

There is evidence that increased arterial stiffness is a precursor to the occurrence of hypertension and not a consequence of increased BP. The increase in cfPWV preceded the appearance of hypertension over 7 years in an analysis of the Framingham Heart Study.[50] The Baltimore Longitudinal Study of Aging also demonstrated an association between increased cfPWV and a higher incidence of hypertension.[51] Other central parameters emerged as predictors of hypertension, such as increased brachial-ankle pulse wave velocity, increased proximal aortic stiffness assessed by echocardiography, and increased carotid artery stiffness, as demonstrated in the Atherosclerosis Risk in Communities (ARIC) study.[52-54]

The increase in aortic stiffness correlated with a lower sensitivity of the baroreflex, a precursor mechanism for the development of hypertension, as well as an increase in the BP variability.[55,56]

Central parameters and cardiovascular risk

Role of the carotid-femoral pulse wave velocity as a predictor of cardiovascular outcomes

The cfPWV is the most studied central parameter; consequently, there is a greater amount of evidence related to this parameter. Thus, it has been demonstrated that the cfPWV has an independent predictive value for different cardiovascular outcomes in different subgroups, as in patients with hypertension, type 2 diabetes, elderly and in those with end-stage renal disease.[57] Even in apparently healthy individuals, cfPWV is an independent predictor of coronary disease and stroke.[58,59] When the predictive values for cfPWV and peripheral pressure have been compared, the cfPWV showed an infallible superiority.[60] A systematic review including 16 studies with 17,635 participants revealed that for each increase of one standard deviation in cfPWV, the risk ratio was 1.35 (95% confidence interval [95%CI] 1.22 – 1.50, $p < 0.001$) for coronary disease, 1.54 (95%CI, 1.34 – 1.78, $p < 0.001$) for stroke, and 1.45 (95%CI, 1.30 – 1.61, $p < 0.001$) for cardiovascular disease. These risk ratios were even higher in younger participants and remained significant even after adjustment for the presence of conventional cardiovascular risk factors.[59]

Small studies have shown that the persistent elevation of pulse wave velocity during the treatment of hypertension or cardiovascular disease is associated with a high risk for a cardiovascular event.[60]

Role of the carotid-femoral pulse wave velocity in the stratification of cardiovascular risk

Studies have shown that the addition of cfPWV to traditional risk factors involved in scores such as Framingham and SCORE, and even atherosclerosis measures, significantly increases the predictive value for cardiovascular outcomes.[61-64] They also indicated that cfPWV aggregates information for the stratification of cardiovascular risk, with the potential for clinical applicability. The use of cfPWV allowed to reclassify the cardiovascular risk range of the individuals and was able to improve the evaluation of the prognosis of cardiovascular risk in 10 years in individuals with intermediate risk by 13%, according to a recent systematic review.[59,65] Thus, the presence of an elevated cfPWV measurement added to classic risk factors indicates an excess of cardiovascular risk and suggests the need for a more rigorous multifactorial approach.

Role of central aortic pressure as a predictor of cardiovascular outcomes

One of the first publications to draw the attention of the scientific community to the role of central aortic pressure in cardiovascular outcomes, regardless of the peripheral BP values, was the Conduit Artery Function Evaluation (CAFE) study in 2006. In this analysis, the hypertensive patients who presented a greater reduction of the systolic component of the central aortic pressure to the same level of reduction of the BP values obtained by the conventional evaluation had a lower incidence of cardiovascular outcomes.[66] In that same year, the European Society of Cardiology published a position drawing attention to the fact that brachial measurements overestimate the central BP values and that the systolic component of central aortic pressure, as well as central pulse pressure, are better predictors of cardiovascular outcomes, especially in patients with hypertension and chronic kidney disease.[37] Other publications have also drawn attention to this superiority when comparing central measurements with brachial ones obtained from ambulatory BP monitoring (ABPM).[67] On the other hand, a meta-analysis of 11 longitudinal studies showed that both central aortic systolic pressure and central pulse pressure were independent markers of outcome and cardiovascular mortality, but were not superior to the values obtained by conventional measurement (peripheral pressure assessment, $p = 0.057$).[21]

Relationship of central parameters with target-organ lesions and associated clinical conditions

Numerous studies have demonstrated that central BP measurement is promising in terms of better correlation with cardiovascular events.[68] Differences in central and peripheral arterial pulsatility are difficult to be attributed to cardiovascular events.[69] No studies have so far demonstrated robust evidence that central BP adds a new model of cardiovascular risk stratification in relation to the conventional

SBP and DBP measurement. A recent analysis of data from the Framingham Offspring Cohort[70] demonstrated a strong correlation between central aortic pressure and the incidence of cardiovascular events. A follow-up of up to 6.8 years in a population of 2,492 individuals (mean age 66 ± 9 years) has shown that 6% had a cardiovascular event. In a multivariate analysis, the measurement of central aortic pressure in this population correlated significantly with cardiovascular events. The CAFE study[66] recruited 2,199 patients from the five centers of the ASCOT study and performed tonometry by radial artery applanation for analysis of central BP and pulse wave. Although the two arms of the study presented similar brachial pressure reduction (difference of 0.7 mmHg, 95%CI 0.4 – 1.7, p = 0.2), there was a reduction in central aortic pressure with statistical significance in the group that used amlodipine (central aortic systolic pressure 4.3 mmHg, 95%CI 3.3 – 5.4, p < 0.0001; and central aortic pulse pressure 3.0 mmHg, 95%CI 2.1 – 3.9, p < 0.0001). A *post hoc* analysis of this study demonstrated that central BP was significantly associated with combined cardiovascular outcomes and the development of renal failure (p < 0.05).

Implication of the central parameters in the strategy for the treatment of hypertension

Despite the adequate reduction of (peripheral) BP with anti-hypertensive treatment, the results on clinical outcomes have shown a significant difference attributed to the pleiotropic effects of anti-hypertensive drugs on the elastic properties of large arteries (aorta), on the central aortic pressure, and on the cfPWV.[71] Table 3 shows the effects of different classes of anti-hypertensive drugs on central hemodynamics.

Beta-blockers

The CAFE study compared the effect of beta-blockers on the central pressure for a similar peripheral BP, and the atenolol/thiazide group showed higher aortic central pressure values when compared with the amlodipine/perindopril group.[66]

Nebivolol (a beta-blocker with a vasodilatory effect) and carvedilol (an anti-hypertensive with alpha- and beta-blocking effects) compared with atenolol promoted a greater reduction in central aortic pressure and pulse amplification.[72,73] Nebivolol reduces central aortic pressure and the augmentation index in mildly hypertensive patients after 3 months of treatment.[74]

Calcium channel blockers

Calcium channel blockers reduce oxidative stress in experimental models and decrease central aortic pressure.[66] The AORTA study compared the addition of azelnidipine or amlodipine to hypertensive patients using olmesartan and demonstrated that the azelnidipine group achieved a greater reduction in central aortic pressure and in the augmentation index, and a greater regression in left ventricular hypertrophy and left ventricular diastolic dysfunction.[75,76]

Angiotensin converting enzyme inhibitors

The reduction in central aortic pressure demonstrated in comparative studies with angiotensin converting enzyme inhibitors (ACEi) can be attributed to possible mechanisms involving reduction in compliance and oxidative stress, structural remodeling of the vascular wall, collagen/elastin relationship, anti-inflammatory effect and consequent relaxation of the vascular smooth muscle.[77,78]

Angiotensin II AT1 receptor blockers

Valsartan and captopril reduce to a similar extent the central aortic pressure and the cfPWV.[79] The EXPLOR study compared valsartan/amlodipine *versus* amlodipine/atenolol for a similar BP reduction in the peripheral artery. Central aortic pressure and cfPWV showed a greater reduction in the valsartan/amlodipine group.[80] Studies with other AT1 receptor blockers have shown similar results.[81,82]

Diuretics

Diuretics appear to have no beneficial effect on central hemodynamics.[83,84]

Nitrates

The effects of nitrates on central aortic pressure are attributed to the relaxation of the vascular smooth muscle of medium-caliber arteries that result in a reduction in the reflection wave amplitude, a reduction in the pulse

Table 3 – Comparative effect of different classes of anti-hypertensive drugs on central hemodynamics

Classes of anti-hypertensive drugs	CSaP	CDaP	Amplification	Reflection	cfPWV	PAP
Beta-blockers	↑↑	↔	↓	↑	↔	↓
Calcium channel blockers	↓	↓/↔	↑	↓	↓	↓
Angiotensin-converting enzyme inhibitors	↓↓	↓	↑	↓	↓	↓
Angiotensin II AT1 receptor blockers	↓	↓/↔	↑/↔	↓	↓	↓
Diuretics	↔	↔	↔/↓	↔	↔	↓
Nitrates	↓	↓	↓	↓	↔	↔/↓

CSaP: central systolic aortic pressure; CDaP: central diastolic aortic pressure; cfPWV: carotid-femoral pulse wave velocity; PAP: peripheral arterial pressure.

wave velocity, and an increase in the effective reflection distance. Isosorbide mononitrate has also been evaluated in hypertensive patients and demonstrated a greater reduction in central aortic pressure than in peripheral BP and a greater reduction in the augmentation index without a significant change in the heart rate. On the other hand, nitrates do not influence cfPWV.

Author contributions

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Long-Term Follow-Up of Patients after Percutaneous Coronary Intervention with Everolimus-Eluting Bioresorbable Vascular Scaffold

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Abstract

Background: **Bioresorbable vascular scaffolds (BVS) were developed to improve the long-term results of percutaneous coronary intervention, restoring vasomotion.**

Objectives: **To report very late follow-up of everolimus-eluting Absorb BVS (Abbott Vascular, Santa Clara, USA) in our center.**

Methods: **Observational retrospective study, in a single Brazilian center, from August 2011 to October 2013, including 49 patients submitted to Absorb BVS implantation. Safety and efficacy outcomes were analyzed in the in-hospital and very late follow-up phases (> 2 years).**

Results: **All 49 patients underwent a minimum follow-up of 2.5 years and a maximum of 4.6 years. Mean age was 56.8 ± 7.6 years, 71.4% of the patients were men, and 26.5% were diabetic. Regarding clinical presentation, the majority (94%) had stable angina or silent ischemia. Device success was achieved in 100% of cases with 96% overall procedure success rate. Major adverse cardiovascular events rate was 4% at 30 days, 8.2% at 1 year, and 12.2% at 2 years, and there were no more events until 4.6 years. There were 2 cases of thrombosis (1 subacute and 1 late).**

Conclusions: **In this preliminary analysis, Absorb BVS showed to be a safe and effective device in the very late follow-up. Establishing the efficacy and safety profiles of these devices in more complex scenarios is necessary. (Arq Bras Cardiol. 2017; 108(2):109-115)**

Keywords: **Percutaneous Coronary Intervention; Absorbable Implants / utilization; Everolimus; Coronary Artery Disease; Clinical Evolution.**

Introduction

In the era of drug-eluting stents (DES), percutaneous coronary intervention (PCI) significantly improved clinical outcomes, with a reduction in excessive neointimal proliferation by adding antiproliferative agents. The permanent presence of intracoronary metal devices and long-lasting polymers, however, can delay natural vascular healing, resulting in constant inflammatory response and unfavorable clinical outcomes.[1-3]

Bioresorbable vascular scaffolds (BVS), thus, appeared as an alternative to those permanent prostheses: they can maintain the mechanical properties of metallic DES in the first months, and then be completely reabsorbed, eliminating possible adverse effects of their presence in the coronary arteries.

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Recently developed, the Absorb BVS (Abbot Vascular, Santa Clara, USA) is aimed at meeting the above-mentioned criteria, maintaining the efficacy profile of last-generation metallic DES. The Absorb BVS was assessed in humans for the first time in the ABSORB clinical trial (cohorts A and B), with promising results.[4-6]

Based on those results, the ABSORB EXTEND study, a multicenter single-arm study, has been conducted in 56 centers of several countries, aimed initially at including around 800 patients and at assessing the safety and performance of the Absorb BVS in a larger and more diversified population, as compared to that of initial studies, with more complex lesions.[7]

The present analysis reports the very late follow-up (>2 years) of the first patients submitted to Absorb BVS implantation in Brazil, as part of the ABSORB EXTEND multicenter registry.

Methods

Study design and target population

The present study included the patients treated with Absorb BVS between August/2011 and October/2013, in a tertiary cardiological center in Brazil, who were included in the

international multicenter single-arm study, ABSORB EXTEND study, as part of the first 512 patients recruited in 56 centers of Europe, Australia, New Zealand, Japan, Hong Kong, Malaysia, Singapore, Latin America and Canada.

It is worth noting that the participation in the EXTEND registry marks the beginning of the Brazilian experience with that new technology. This study was financed by Abbot Vascular, Santa Clara, USA. The Ethics Committee on Research of our institution approved the study protocol, and all patients provided written informed consent.

Inclusion/exclusion criteria

Patients with the following characteristics were included in the study: age ≥ 18 years; evidence of myocardial ischemia, such as stable or unstable angina; silent ischemia; and functional test or transient alterations on 12-lead electrocardiography compatible with ischemia.

The patients had up to two *de novo* lesions that could be percutaneously treated, each located in separate native epicardial vessels. The lesions should be in a native coronary vessel, whose target-vessel diameter was ≥ 2.0 mm and ≤ 3.3 mm, and whose target-lesion extension was ≤ 28 mm, both assessed by use of on-line quantitative coronary angiography (QCA) or intracoronary ultrasound (ICUS). The target lesions should be in an artery or branch of significant caliber and stenosis should be visually estimated ≥ 50% and < 100%, with TIMI (*Thrombolysis in Myocardial Infarction*) flow ≥ 1. Previous PCI in a non-target vessel was allowed, if performed at least 30 days after the index procedure or planned for 6 months after the index procedure; PCI in target-vessel lesions were allowed if performed at least 6 months before the index procedure or planned to 6 months after the index procedure.

Patients with the following characteristics were excluded from the study: previous acute myocardial infarction (AMI) up to 3 days before the index procedure; arrhythmias with hemodynamic instability; left ventricular ejection fraction < 30%; chronic renal failure; left main coronary artery lesions; lesions in arterial or venous grafts; in-stent restenosis; bifurcation lesions; total occlusion (TIMI flow 0); and significant calcification or excessive tortuosity.

Device

We used the Absorb BVS, the same device used in cohort B of the ABSORB study.[8,9] The Absorb platform is composed by the polymer poly-L-lactic acid (PLLA), the antiproliferative drug everolimus (Novartis Pharmaceuticals Corporation, Basel, Switzerland), and a matrix of poly-D, L-lactic acid (PDLLA), at a 1:1 ratio, forming an amorphous matrix covered with 100μ everolimus/cm^2. Both PLLA and PDLLA are metabolized and resorbed in the body. PDLLA is expected to be completely resorbed by the arteries in 9 months, while PLLA, in approximately 36 months. During resorption, the chains with PLLA and PDLLA are hydrolyzed, the last product of that reaction being lactic acid, biologically metabolized via Krebs cycle.[5]

At the time the patients were included in this study, Absorb devices were available only in two diameters (2.5 and 3.0 mm) and two lengths (18 and 28 mm).

Procedure

All procedures were performed electively, in accordance with current guidelines. The lesions were treated with the usual intervention techniques, which required pre-dilatation with a shorter balloon, with a diameter 0.5 mm smaller than that of the device used. The Absorb's deployment pressure should never exceed the manufacturer's maximum nominal reference value.

Post-dilatation was subjected to need and operator's assessment. It was performed with non-compliant balloons, within the expansion limits of the BVS (post-dilatation balloons should not exceed 0.5 mm the nominal diameter of the implanted BVS).

Preprocedural dual antiplatelet therapy comprised an attack dose of acetylsalicylic acid (300 mg) and clopidogrel (300 mg), at least 24 hours before the procedure, or 600 mg if < 24 hours. After the intervention, acetylsalicylic acid was prescribed indefinitely and clopidogrel (75 mg/day) was maintained for at least 6 months.

Quantitative coronary angiography and intracoronary ultrasound

The recommended limits of the target-vessel's diameter were established by use of on-line QCA on distal and proximal maximal luminal diameter (Dmax), the Dmax being assessed in the distal and proximal portions of the target segment to be coated with the BVS, or by use of ICUS. Overlapping of the BVS was allowed for lesions > 22 mm and ≤ 28 mm, with a recommended limit of 1-4 mm.

Follow-up

Clinical follow-up, via outpatient clinic consultation or telephone, was mandatory at day 30 (± 7 days), 6 months (± 14 days) and 1, 2 and 3 years (± 28 days), following the ABSORB EXTEND study protocol. After that, routine return visits were recommended. Minimum follow-up was 2.5 years. All adverse events and symptoms, such as angina, details of subsequent PCIs, as well as medication use and changes, were collected in the period. The patients did not undergo a new protocol coronary angiography, being only reassessed in case of clinical indication due to symptoms or evidence of ischemia.

Study outcomes

All outcomes were adjudicated by an independent clinical events committee abiding by the protocol definitions based on the Academic Research Consortium (ARC).[10]

Clinical success comprised device's success (based on the target lesion) and procedural success (assessed in each patient). In addition, it included scaffold thrombosis (ST), cardiovascular death, AMI (either related or not to the target vessel) and revascularization rate (target-lesion or target-vessel revascularization, or total revascularization). In addition, combined outcome rates, considering ischemia-driven (ID) major adverse cardiovascular events (MACE) (ID-MACE), ID target-vessel failure (ID-TVF), ID target-vessel revascularization and ID target-lesion revascularization (ID-TLR), were assessed.

The device's success was defined as successful device's deployment in the target lesion and successful withdrawal of the BVS delivery system, with residual stenosis < 50% assessed via QCA (or visual estimate, when QCA was unavailable).

The procedure's success was defined as device's success with no ID-MACE during hospitalization for up to 7 days after the procedure. If there were two lesions, both should meet the success criteria.

Cardiac death was defined as any death of cardiac cause, such as AMI, low output syndrome, and lethal arrhythmia. Unattended death and death of unknown cause were classified as cardiac death. This included the deaths related to the procedure.

The classification of AMI and the diagnostic criteria were defined based on the pre-established protocol:[11] Q-wave AMI, characterized by the development of a new pathological Q wave; Non-Q-wave AMI, defined as elevation of creatine phosphokinase (CK) levels ≥ 2 times the upper limit of normality with concomitant increase in CK-MB in the absence of new pathological Q waves.

The revascularization events were defined as follows:

- ID-MACE: composed of cardiac death, Q-wave/non-Q-wave AMI, target-lesion revascularization via PCI or coronary artery bypass graft (CABG);

- ID-TVF: composed of cardiac death, AMI with and without Q wave, target-vessel revascularization via PCI or CABG;

- ID-TLR: defined as any new PCI in the target lesion, either percutaneous or CABG in the target vessel with positive functional ischemia, ischemic symptoms or angiography evidencing lumen diameter at stenosis ≥ 50% by use of QCA, or revascularization of a target lesion with diameter ≥ 70% by use of QCA without ischemic symptoms or functional test.

Scaffold thrombosis was categorized as acute (< 1 day), subacute (1-30 days), late (> 30 days and < 1 year) and very late (>1 year), and defined based on the ARC guidelines as follows:[10] definite (acute coronary syndrome and pathological or angiographic confirmation of the BVS thrombosis) or likely (death of unknown cause ≤ 30 days or AMI related to the target vessel without angiographic confirmation).

Statistical analysis

Continuous variables with normal distribution were expressed as mean and standard deviation. Categorical variables were expressed as absolute numbers and percentages. The SPSS program (Statistical Package for the Social Science, Chicago, USA), version 19, was used for data tabulation.

Results

The present study represents the analysis of 49 patients (53 lesions/57 BVS) included in the ABSORB EXTEND study and submitted to PCI with Absorb BVS implantation, at a Brazilian tertiary cardiology center. Clinical 1-year follow-up was obtained in 100% of the cases, while 2-year follow-up, in 97.9% of the cases. Mean follow-up was 3.59 ± 0.72 years (2.5-4.6 years).

Table 1 shows the demographic and clinical characteristics of the population studied. The patients' mean age was 56.8 ± 7.6 years, most of them were men (71.4%), and 26.5% of the population studied had diabetes. In addition, only 6.1% of the patients had more than one target lesion, and 6.1% of the patients presented with clinical findings of acute coronary syndrome (55.1%, stable angina; 38.8%, silent ischemia). Neither ST-segment elevation AMI nor recent AMI occurred.

Table 2 illustrates the angiographic characteristics of the lesions treated and the procedure. Most lesions treated were in the anterior descending coronary artery (46.9%), followed by the right coronary (32.6%) and circumflex (26.5%) arteries. The mean grade of stenosis was 76.0 ± 8.5%. By use of on-line QCA or ICUS, the lesions had a mean diameter of 2.92 ± 0.28 mm (range, 2.2-3.5 mm) and a mean extension of 15.98 ± 5.55 mm (range, 7-28 mm).

The device's clinical success was 100%, while the procedure's clinical success was 96% (47/49) in the 49 patients submitted to PCI with Absorb implantation. Two patients (4%) had periprocedural AMI while hospitalized.

Table 3 shows the clinical outcome data at 30 days and 1 year, and the very late follow-up of the patients. At 30 days, the MACE rate was 4% because of the periprocedural AMI rate. Cardiac mortality, target-vessel revascularization and non-target-vessel revascularization was 0%.

At 1 year, the MACE rate was 8.2%, because of cardiac death and need for revascularization of the target vessel (but not of the target lesion) via PCI in one patient, the global AMI rate being

Table 1 – Demographic and clinical characteristics

	ABSORB BVS (n = 49)
Age (years), mean	56.8 ± 7.6
Male sex, n (%)	35 (71.4)
Diabetes, n (%)	13 (26.5)
Insulin-dependent diabetes mellitus, n (%)	5 (10.2%)
Hypertension, n (%).	39 (79.6)
Dyslipidemia, n (%)	38 (77.6)
Smoking, n (%)	30 (6.1)
Renal failure (CrCl < 60 mL.min), n (%)	0
Peripheral vascular disease, n (%)	4 (8.1)
Previous AMI, n (%)	30 (61.2)
Previous PCI, n (%)	30 (6.1)
Previous CABG, n (%)	2 (4.1)
Clinical presentation, n (%)	
Stable angina	27 (55.1)
NSTEACS	3 (6.1)
Silent ischemia	19 (38.8)

CrCl: creatinine clearance; AMI: acute myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; NSTEACS: Non-ST segment elevation acute coronary syndrome.

Table 2 – Angiographic and procedural characteristics

	ABSORB BVS (n = 49)
Target vessel, n (%)	
Anterior descending coronary artery	23 (46.9)
Right coronary artery	16 (32.6)
Circumflex artery	13 (26.5)
Multiple vessels	6 (12.2)
Diameter of the lesion, mm	2.92 ± 0.28
Length of the lesion, mm	15.98 ± 5.55
Mean grade of stenosis, (%)	76.0 ± 8.5
Number of target lesions, n (%)	
One	39 (93.9)
Two	3 (6.1)
Pre-dilatation, n (%)	49 (100)
Post-dilatation, n (%)	46 (93.8)
Angiographic success, n (%)	49 (100)
Device success, n (%)	49 (100)
Procedural success, n (%)	47 (95.9)

maintained as 0%. At 2 years, the MACE rate was 12.2% because of a non-Q AMI event related to the target vessel and one in-stent restenosis event requiring target-lesion revascularization. From 2 years of follow-up till now, there were neither cardiovascular nor cerebrovascular events, and the accumulated MACE rate remained as 12.2% among the patients followed up till almost 5 years.

Regarding device's thrombosis and based on the ARC criteria, the findings were as follows: one case of definite subacute thrombosis 13 days after implantation, need for urgent surgical vascular procedure and a new angiographic study with an unsuccessful recanalization attempt; and one case of likely late thrombosis 34 days after PCI (sudden death episode). After one year, there was no additional case of thrombosis.

Discussion

In this initial experience, at a single center, the Absorb BVS performed well in the long run, with a very low target-vessel failure rate.

In the past 3 years, more than 60,000 patients were treated with Absorb BVS worldwide, despite the lack of a robust randomized study comparing it with contemporary drug-eluting stents.[12]

The assessment of Absorb BVS has begun with the ABSORB cohort studies A and B and clinical trial.[13,14] After changes in the device's design and structure, the device's current version began to be used in cohort B, involving 101 patients, and showed a 1-year late lumen loss of 0.27 mm, the 2-year follow-up evidencing a MACE rate of 6.8% and no device's thrombosis.[5,15] At 5 years, the Absorb's structures were no longer discernible on optical tomography or ICUS, the MACE rate being 11%, with no evidence of thrombosis.[16]

The initial analysis of the first 512 patients recruited in the ABSORB EXTEND registry, in a 1-year follow-up, confirms the efficacy of Absorb BVS, with very low incidence of ID-MACE (4.8%), ID-TVF (4.4%) and device's thrombosis (0.8%).[7] At 3 years, with 250 patients, the MACE rate was 9.3%, the ID-TVF, 10.1%, and thrombosis, 1.2%.[17]

In our study, the MACE rate in a very late follow-up was equivalent, with no event after 2 years, corroborating the theory that the major benefit of the BVS occurs in the long run, with both low rate of events and the likelihood of new revascularization and BVS assessment by use of non-invasive imaging techniques.

Regarding the comparison with the results of drug-eluting metal stents, no long-term follow-up study has been published. In a recent meta-analysis encompassing the last four randomized studies comparing Absorb BVS with the everolimus-eluting metal stent Xience® (Abbot Vascular, Santa Clara, USA), ABSORB II,[18] ABSORB III,[19] ABSORB Japan[20] and ABSORB China,[21] the relative combined outcomes rates at the end of the first year did not differ between the Absorb and Xience groups (11.9% vs. 10.6%, respectively, p=0.38). Target-vessel AMI was significantly higher in the Absorb group as compared to the Xience group (5.1% vs. 3.3%, respectively, p=0.04), due partially to the higher rate of periprocedural AMI and partially to the higher rate of ST (definite or likely) in the Absorb group (1.3% vs. 0.6%, respectively, p=0.08). The results were similar after multivariate analysis adjusted to baseline characteristics, and were consistent even in the analysis of most subgroups.[22]

The EVERBIO-II Trial (*Comparison of Everolimus- and Biolimus-Eluting Stents With Everolimus-Eluting Bioresorbable Vascular Scaffold Stents II*), a single-center study, involved 240 patients randomized at the 1:1:1 proportion for everolimus-eluting stent, biolimus-eluting stent or Absorb BVS. In a 2-year follow-up, the MACE rate related to the device was 13% in the everolimus- and biolimus-eluting stent groups vs. 21% in the Absorb group (p=0.12), and the related MACE rate was 32% vs. 35%, respectively (p=0.67), with only one ST event in the Absorb group and none in the DES groups (p=0.33). Thus, once again DES were considered non-inferior to BVS.[23,24]

Regarding other BVSs, the DESolve® NX (Elixir Medical Corporation, Sunnyvale, USA) was the only BVS with late follow-up and recently published results. At 2 years, that new device showed the following rates: MACE, 7.4%; isolate cardiac death, 2.5%; AMI, 0.8%; target-lesion revascularization, 4.1%; and target-lesion failure, 7.4%. In addition, the thrombosis rate was minimal (0.8%).[25]

Tamburino et al., using a complex statistical analysis, have assessed the database of the GHOST-EU Registry (*Gauging coronary Healing with biOresorbable Scaffolding plaTforms in EUrope*), with 1,189 patients treated with Absorb BVS in Europe and 5,034 patients treated with everolimus-eluting metal stent (Xience) of the XIENCE V Registry in the USA. After propensity score matching, 905 pairs of patients were identified with similar characteristics. Of the total of 1,810 patients, there was no difference between the Absorb and Xience groups concerning the risk of MACE within 1 year (5.8% vs. 7.6%, respectively, p=0.12). Cardiac death was less likely to occur in the Absorb

Table 3 – Clinical outcomes in early, middle-term and long-term follow-up

	30 days n = 49	12 months n = 49	24 months n = 48	36 months n = 30	48 months n = 16
MACE, n (%)	2 (4)	4 (8.2)	6 (12.2)	6 (12.2)	6 (12.2)
Global mortality, n (%)	0	1 (2)	1 (2)	1 (2)	1 (2)
Cardiac death, n (%)	0	1 (2)	1 (2)	1 (2)	1 (2)
AMI, n (%)					
Q-wave AMI	0	0	0	0	0
Non-Q-wave AMI	0	0	1 (2)	1 (2)	1 (2)
Periprocedural AMI, n (%)	2 (4)	-	-	-	-
ID-target-vessel revascularization, n (%)	0	1 (2)	1 (2)	1 (2)	1 (2)
ID-target-lesion revascularization, n (%)	0	0	1 (2)	1 (2)	1 (2)
MR not related to ID-target-vessel or lesion, n (%)	0	0	1 (2)	2 (4)	2 (4)
Scaffold thrombosis, n (%)					
Acute	0	-	-	-	-
Subacute	1	-	-	-	-
Late	-	1	-	-	-
Very late	-	-	0	0	0
Stroke, n (%)	0	0	0	0	0

MACE: major adverse cardiovascular events; AMI: acute myocardial infarction; MR: myocardial revascularization; ID: ischemia directed.

group (0.7% vs. 1.9%, p=0.03) and there was a tendency towards reduction in AMI in the Absorb group as compared to the Xience group (2.4% vs. 4.0%, p=0.07). In addition, there was no difference in target-vessel revascularization (4.6% vs. 3.5%, p=0.22) and definite or likely thrombosis (1.8% vs. 1.1%) between the Absorb and Xience groups, respectively.[26] In most studies, the ST cases occurred in the immediate post-procedural period (<30 days), and cases after the sixth month were rare, as observed in the cohort reported.

Limitations

This was a retrospective and observational study, having, thus, obvious limitations. The sample was small, with low clinical and anatomical complexity, following the ABSORB EXTEND study protocol.

Conclusions

In this case series, Absorb BVS implantation was associated with a low incidence of adverse events, mainly in the very long-term follow-up (> 2 years). However, larger studies with a higher number of patients and more complex scenarios are necessary to confirm these preliminary observations.

Author contributions

Conception and design of the research: Meneguz-Moreno RA, Costa Junior JR, Staico R, Tanajura LFL, Centemero MP;Acquisition of data: Meneguz-Moreno RA, Moscoso FAB; Analysis and interpretation of the data: Meneguz-Moreno RA, Costa Junior JR, Moscoso FAB, Staico R, Centemero MP, Chaves AJ, Abizaid ACLS; Statistical analysis: Moscoso FAB; Obtaining financing: Abizaid AAC; Writing of the manuscript: Meneguz-Moreno RA, Costa Junior JR, Chaves AJ; Critical revision of the manuscript for intellectual content: Staico R, Tanajura LFL, Abizaid ACLS, Rego e Sousa AGM, Abizaid AAC.

Potential Conflict of Interest

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

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Original Article

Resveratrol Treatment Normalizes the Endothelial Function and Blood Pressure in Ovariectomized Rats

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Abstract

Background: Despite knowing that resveratrol has effects on blood vessels, blood pressure and that phytostrogens can also improve the endothelium-dependent relaxation/vasodilation, there are no reports of reveratrol's direct effect on the endothelial function and blood pressure of animals with estrogen deficit (mimicking post-menopausal increased blood pressure).

Objective: To verify the effect of two different periods of preventive treatment with resveratrol on blood pressure and endothelial function in ovariectomized young adult rats.

Methods: 3-month old female Wistar rats were used and distributed in 6 groups: intact groups with 60 or 90 days, ovariectomized groups with 60 or 90 days, and ovariectomized treated with resveratrol (10 mg/kg of body weight per day) for 60 or 90 days. The number of days in each group corresponds to the duration of the experimental period. Vascular reactivity study was performed in abdominal aortic rings, systolic blood pressure was measured and serum nitric oxide (NO) concentration was quantified.

Results: Ovariectomy induced blood pressure increase 60 and 90 days after surgery, whereas the endothelial function decreased only 90 days after surgery, with no difference in NO concentration among the groups. Only longer treatment (90 days) with resveratrol was able to improve the endothelial function and normalize blood pressure.

Conclusion: Our results suggest that 90 days of treatment with resveratrol is able to improve the endothelial function and decrease blood pressure in ovariectomized rats. (Arq Bras Cardiol. 2017; 108(2):116-121)

Keywords: Blood Pressure; Rats, Wistar; Resveratrol; Phytoestrogens; Ovariectomy; Endothelium, Vascular.

Introduction

The endothelium is a monolayer of tissue located inside the blood vessels and can have endocrine and paracrine functions, regulating vascular function by releasing trophic and vasoactive factors that regulate the vascular tone and even control the vascular wall inflammation.[1] Endothelial dysfunction is characterized mainly by a direct or indirect decrease of nitric oxide (NO) bioavailability[2].

NO release by the endothelium is modulated by several factors, including estrogen. This hormone is able to increase NO bioavailability and production through genomic and non-genomic factors. Among them, we can mention its action on estrogen receptor α (ERα) and the reduction of oxidative stress.[3,4] Thus, the reduction of this hormone that is observed after menopause can lead to endothelial dysfunction with a consequent increase in blood pressure.

In order to reduce some negative effects of estrogen deficiency, hormone replacement therapy (HRT) is commonly indicated. However, studies indicate that this treatment may be associated with adverse cardiovascular events, increased risk of the development of breast cancer and deep vein thrombosis in women with a predisposition to these conditions.[3,5,6]

In an attempt to find alternatives to HRT with fewer side effects, resveratrol (3,4,5'-trihydroxystilbene) has shown promising effect because of its similarity to diethylstilbestrol (a synthetic estrogen) and can be regarded as a phytoestrogen. In addition, resveratrol can exert its action on estrogen receptors and may then be regarded as a SERM (selective estrogen receptor modulator).[7,9]

Despite knowing that both phytoestrogens and SERMs are reported in the literature as acute improvers of endothelium-dependent relaxation/vasodilation[4] and that studies indicate the effect of resveratrol on blood pressure and blood vessels,[10,11] there are not many reports of its direct effect on both the endothelial function and blood pressure in animals with estrogen deficit only. Thus, the objective of this study was to verify the effect of two different preventive

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treatment protocols with resveratrol on blood pressure and endothelial function in young ovariectomized female rats.

Methods

Animals and treatments

The experimental protocol was performed in accordance with the guidelines of the Brazilian College for Animal Experimentation (COBEA) and was approved by the Ethics Committee of the Federal University of Sao Carlos – UFSCar (2-043/2013).

Sixty Wistar (*Rattus norvegicus albinis)* female rats (90 days old at the beginning of the experiment) were housed under controlled dark-light cycles (14h/10h from 6:00 pm to 8:00 am) and temperature (22 ± 2 °C) receiving standard diet and water *ad libitum* for 60 or 90 days.

The animals were randomly assigned to six experimental groups: intact - 60 Days Days (INT 60), ovariectomized - 60 days (OVX 60), ovariectomized + resveratrol - 60 days (OVX + RES 60), intact - 90 days (INT 90), ovariectomized – 90 days (OVX 90) and ovariectomized + resveratrol – 90 days (OVX + RES 90). The number of days in each group represented the duration of the experimental period. The animals in the intact groups received no intervention; the ovariectomized groups were ovariectomized and treated with a 0.9% saline solution (0.1ml/100g of body weight per day) by gavage until the end of the experimental period. Those in the ovariectomized + resveratrol group were ovariectomized and treated daily with a solution of 10mg/kg of body weight of resveratrol per day (solubilized in ethanol and diluted with distilled water, with the final concentration of ethanol at 5%), also by gavage for 60 or 90 days. At the end of the experimental period, the rats were anaesthetized with isoflurane and euthanized by decapitation. Blood and aorta artery were collected for experimental analysis.

Blood pressure

Systolic blood pressure (SBP) was measured by tail-cuff plethysmography (model Power Lab 8/35, AD Instruments, Pty Ltda, Colorado Springs, CO) in non-anesthetized animals, as described elsewhere by Rodrigues et al.,[12] two days before the animals were killed by decapitation at the end of each experimental period. The average of four consecutive measurements was taken as the mean systolic blood pressure of each animal.

Vascular reactivity studies

The thoracic aortas were isolated, cleaned of adherent connective tissues, and placed in Krebs solution, as described elsewhere.[13] The aortas were carefully dissected and mounted as ring preparations (≅4 mm in length) and placed in bath chambers (5 mL) containing Krebs solution at 37 °C (NaCl 130mM, KCl 47 mM, KH_2PO_4 1.2 mM, CaCl 1.6; $MgSO_4$ 1.2mM; $NaHCO_3$ 14.9 mM; glucose 5.5 mM) continuously bubbled with 95% O_2 and 5% CO_2, pH 7.4, in a Mulvany-Halpern isometric myograph (model 610 DMT-USA, Marietta, GA) and recorded by a PowerLab8/SP data acquisition system (AD Instruments Pty Ltd., Colorado Springs, CO). The aortic rings were submitted to a tension of 1.5 g, which was readjusted every 15 min for a 60-min equilibration period before addition of the given drug. Experiments were conducted in aortic rings with intact endothelium and also in endothelium-denuded aortic rings. Endothelial integrity was assessed by the degree of relaxation induced by 1μmol/l acetylcholine (Ach) in the presence of contractile tonus induced by phenylephrine (0.1μM). The ring was considered as with intact endothelium if relaxation with acetylcholine was higher than 80%. In endothelium-denuded aortas, the relaxation to Ach was lower than 5%. After the endothelial integrity test, aortic rings were pre-contracted with phenylephrine (0.1μM). When the plateau was reached, concentration–effect curves to acetylcholine (0.1nM to 0.1mM) in intact endothelium aortic rings or to sodium nitroprusside (SNP) in endothelium-denuded aortic rings were constructed. The potency (pD_2) and the maximal relaxant effect (ME) were measured.

Serum Nitrite and Nitrate (NOx)

Serum nitric oxide levels were obtained by measuring the serum concentrations of its stable end-products nitrite (NO_2^-) and nitrate (NO_3^-), collectively known as NO_x. The NO/ozone chemiluminescence method was performed using the NO Analizer 280i (Sievers, Boulder, CO, USA). The NO_x concentration was corrected by the factor obtained by the quotient of the measured NO_x and expected concentrations of sodium nitrate (5, 10, 25, 50, and 100 μM), yielding a standard curve.[14]

Statistical analysis

Normality of distribution of the variables studied (all quantitative and continuous) was verified by the Kolmogorov-Smirnov test. Differences in means among the groups in each experimental period were compared by one-way analysis of variance (ANOVA). When significance was indicated, a Newman-Keuls post hoc analysis was used with statistical significance set at $p<0.05$ (Software Statistica 7.0, StatSoft. Inc, Tulsa, USA).

Drugs and chemicals

Acetylcholine, phenylephrine and sodium nitroprusside, were purchased from Sigma–Aldrich (St.Louis, MO, USA). Resveratrol was purchased from Cayman Chemical (Ann Arbor, MI, USA).

Results

In Table 1 we can observe that 60 days of ovariectomy did not change the endothelium-dependent and independent vascular relaxation of aortic rings, and resveratrol supplementation had no effect in the OVX group. The maximal relaxant effect (ME) did not change in aortic rings with or without endothelium for all groups. Also, a decrease in the potency of acetylcholine in inducing relaxation (pD2 OVX 90: 6.99 ± 0.10) was

observed after 90 days of ovariectomy when compared to intact animals (pD2 INT 90: 7.51 ± 0.07, p<0.05). Ninety days of resveratrol supplementation was able to increase the pD2 to acetylcholine (pD2: OVX+RES: 7.50 ± 0.15, p <0.05) and also bring it to values similar to those of the intact groups, normalizing the endothelial function. In denuded aortic rings, no change was observed in the endothelium-independent relaxant effect in pD2 values in all groups. ME did not change after 90 days of ovariectomy or resveratrol supplementation in endothelium-dependent and independent relaxation induced by acetylcholine or sodium nitroprusside, respectively.

In Table 2 we can observe that ovariectomy induced an increase in systolic blood pressure (SBP) 60 and 90 days after surgery. The treatment with resveratrol for 60 days did not prevent the increase in blood pressure. However, 90 days of treatment with resveratrol prevented it, and normalized blood pressure. Nevertheless, no difference could be observed in serum NO concentration (Figures 1 and 2) in both treatment periods (60 and 90 days).

Discussion

The main finding of this study was that the treatment with resveratrol for 90 days prevented the changes in blood pressure and endothelial function induced by estrogen deficiency. In this trial period, we have verified that ovariectomy was effective to induce endothelial dysfunction and elevation of blood pressure. The 60-day estrogen deficiency was not enough to induce changes in endothelial function in aortic ring of rats; however, this period was enough to increase the blood pressure value and resveratrol treatment did not modify endothelial function and blood pressure.

The increase in blood pressure due to ovariectomy and its subsequent reduction in the group treated with resveratrol in the 90-day experimental protocol also was observed previously by Patki et al,[15] who treated Wistar ovariectomized rats with frozen grape powder (in which one of the components is resveratrol). Still, the authors suggest that the effect of ovariectomy on blood pressure is induced by elevation in oxidative stress triggered by estrogen deficit and the effect of frozen grape powder may be related to its strong antioxidant effect,[15] a feature also verified with resveratrol.[16]

Table 1 – Values of power (pD2) and maximal relaxant effect (ME) to relaxation induced by acetylcholine and sodium nitroprusside, in aortic rings with (E+) or without (E-) its endothelium from intact (INT), ovariectomized (OVX) and ovariectomized + resveratrol (OVX + RES) groups in both experimental periods. Values are expressed as Mean±SD. Comparisons were made using One-way ANOVA followed by the Newman-Keuls post- hoc test. *p<0.05 compared to INT 60 group; +p<0.05 compared to INT 90 group; # p< 0.05 compared to OVX 90 group

Relaxation induced by acetyilcholine (E+) and sodium nitroprusside (E-)			
60 DAYS	**INT 60**	**OVX 60**	**OVX+ RES 60**
pD2 E+	7.69 ± 0.15	7.43 ± 0.18	7.63 ± 0.16
ME E+	94.28 ± 4.80	84.66 ± 4.93	89.00 ± 4.43
pD2 E-	8.55 ± 0.09	8.51 ± 0.11	8.56 ± 0.09
ME E-	105.40 ± 2.12	103.30 ± 2.17	105.50 ± 2.71
90 DAYS	**INT 90**	**OVX 90**	**OVX+ RES 90**
pD2 E+	7.51 ± 0.07	7.00 ± 0.10^{+}	7.50 ± 0.15$^{\#}$
ME E+	86.18 ± 4.32	85.50 ± 2.45	81.67 ± 3.61
pD2 E-	8.45 ± 0.02	8.45 ± 0.02	8.43 ± 0.01
ME E-	105.70 ± 2.62	105.20 ± 1.76	102.20 ± 4.21

Table 2 – Systolic blood pressure (SBP) and serum Nitric Oxide concentration (NO) in intact (INT), ovariectomized (OVX) and ovariectomized + resveratrol (OVX + RES) groups of both experimental periods. Values expressed as Mean±SD. Comparisons were made using One-way ANOVA followed by the Newman-Keuls post- hoc test. *p<0.05 compared to INT 60 group; +p<0.05 compared to INT 90 group; # p< 0.05 compared to OVX 90 group

60 DAYS	**INT 60**	**OVX 60**	**OVX+ RES 60**
SBP (mmHg)	120.39 ± 4.58	138.16 ± 5.42*	135.18 ± 5.42*
NO (uM)	33.91 ± 8.55	28.51 ± 7.47	30.42 ± 9.68
90 DAYS	**INT 90**	**OVX 90**	**OVX+ RES 90**
SBP (mmHg)	123.92 ± 4.98	145.21 ± 9.79^{+}	123.33 ± 3.66$^{\#}$
NO (uM)	30.96 ± 5.17	31.26 ± 9.06	30.61 ± 10.38

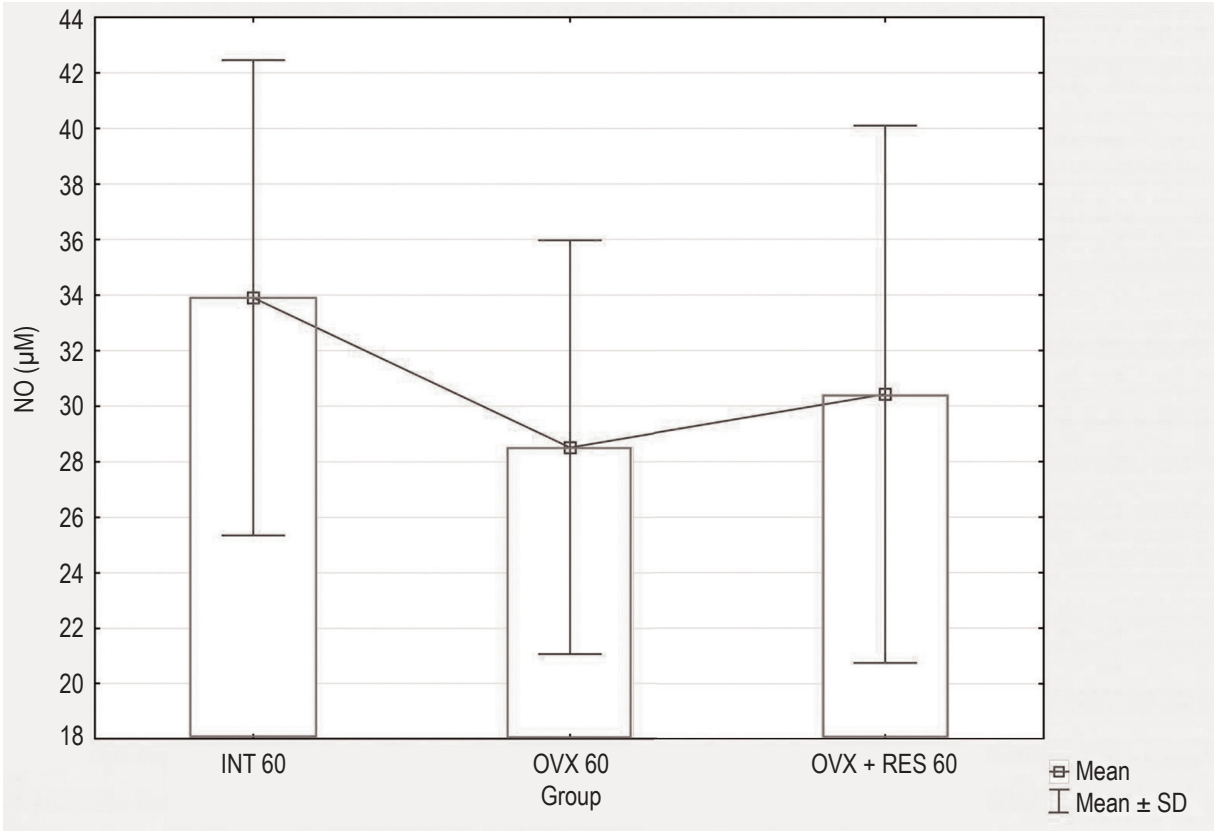

Figure 1 – *Serum nitric oxide concentration in µM in intact - 60 days (INT 60), ovariectomized – 60 days (OVX 60) and ovariectomized + resveratrol - 60 days (OVX + RES 60) groups. Values expressed as Mean±SD. Comparisons were made using One-way ANOVA followed by the Newman-Keuls post- hoc test. No differences were observed between the groups.*

The decrease in endothelium-dependent relaxation in aortic rings and consequent increase with the treatment with resveratrol in the 90-day experimental protocol agrees with the results presented by Mizutani and colleagues[10] in stroke-prone spontaneously hypertensive ovariectomized rats, supplemented dietetically with 5mg/kg of body weight of resveratrol. However, these authors indicate that the effect of the substance on the endothelium is through the increased bioavailability of NO, as reported by other studies[17,18], a fact not confirmed by our study.

An interesting result was that only prolonged resveratrol treatment (90 days) was able to improve the endothelial function and normalize blood pressure. Sixty days after surgery, no endothelium dysfunction was verified, and no improvement was induced by resveratrol. Thus, our result suggests that the improvement in the endothelial function induced by resveratrol normalizes the blood pressure in OVX rats by a NO independent mechanism.

Vanhoute et al[4] point out that in addition to NO there are other endothelium factors which can induce vasodilation, including the *endothelium*-derived hyperpolarizing factor (*EDHF*). Furthermore, Dolinsky et al[11] suggested that the effect of resveratrol on blood pressure can be different in accordance to the experimental model used, and these differences could result from the distinct mechanisms of hypertension developing. Considering that there are few studies that have evaluated the effect of estrogen deficiency on blood pressure and endothelial function in young/adult animal models, the results of this study represent an important contribution of resveratrol as a preventive treatment for postmenopausal cardiovascular effects.

Conclusion

Our results suggest that ninety days of treatment with resveratrol (10 mg/kg body weight per day) is able to normalize the endothelial function and blood pressure of ovariectomized rats via a NO-independent mechanism.

Limitations

There was not enough budget to perform other analyzes, such as the quantification of NO and of oxidative stress markers in blood vessels, that could better consolidate the causes of impairment and / or improvement in systolic blood pressure and vascular reactivity.

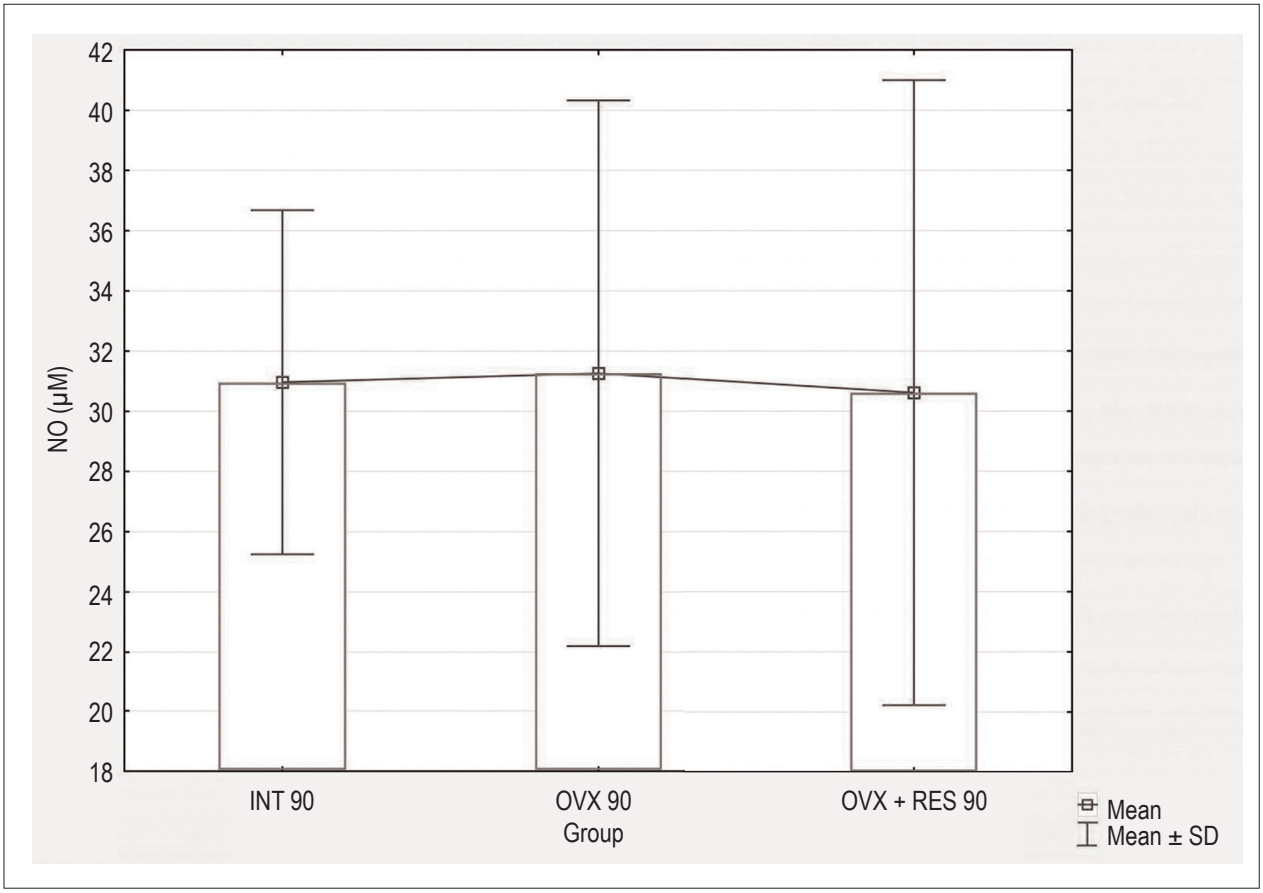

Figure 2 – *Serum nitric oxide concentration in µM in intact - 90 days (INT 90), ovariectomized – 90 days (OVX 90) and ovariectomized + resveratrol - 90 days (OVX + RES 90) groups. Values are expressed as Mean±SD. Comparisons were made using One-way ANOVA followed by the Newman-Keuls post- hoc test. No differences were observed between the groups.*

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Author contributions

Conception and design of the research: Fabricio V, Nonaka KO, Rodrigues GJ; Acquisition of data: Fabricio V, Oishi JC, Biffe BG, Ruffoni LDG, Silva KA; Analysis and interpretation of the data: Fabricio V, Oishi JC, Nonaka KO, Rodrigues GJ; Statistical analysis: Fabricio V, Oishi JC; Obtaining financing: Nonaka KO, Rodrigues GJ; Writing of the manuscript: Fabricio V, Oishi JC, Nonaka KO, Rodrigues GJ; Critical revision of the manuscript for intellectual content: Oishi JC, Biffe BG, Ruffoni LDG, Silva KA, Nonaka KO, Rodrigues GJ.

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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Dobutamine Stress Echocardiography Safety in Chagas Disease Patients

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Abstract

Background: A few decades ago, patients with Chagas disease were predominantly rural workers, with a low risk profile for obstructive coronary artery disease (CAD). As urbanization has increased, they became exposed to the same risk factors for CAD of uninfected individuals. Dobutamine stress echocardiography (DSE) has proven to be an important tool in CAD diagnosis. Despite being a potentially arrhythmogenic method, it is safe for coronary patients without Chagas disease. For Chagas disease patients, however, the indication of DSE in clinical practice is uncertain, because of the arrhythmogenic potential of that heart disease.

Objectives: To assess DSE safety in Chagas disease patients with clinical suspicion of CAD, as well as the incidence of arrhythmias and adverse events during the exam.

Methods: Retrospective analysis of a database of patients referred for DSE from May/2012 to February/2015. This study assessed 205 consecutive patients with Chagas disease suspected of having CAD. All of them had their serology for Chagas disease confirmed.

Results: Their mean age was 64±10 years and most patients were females (65.4%). No patient had significant adverse events, such as acute myocardial infarction, ventricular fibrillation, asystole, stroke, cardiac rupture and death. Regarding arrhythmias, ventricular extrasystoles occurred in 48% of patients, and non-sustained ventricular tachycardia in 7.3%.

Conclusion: DSE proved to be safe in this population of Chagas disease patients, in which no potentially life-threatening outcome was found. (Arq Bras Cardiol. 2017; 108(2):122-128)

Keywords: Chagas Disease; Echocardiography, Stress; Atropine; Trypanosoma cruzi / drug effects.

Introduction

Chagas disease continues to be a serious health problem, as well as an economic burden in most Latin-American countries. The World Health Organization has recently estimated that 18 million people are chronically infected with *Trypanosoma cruzi,* and approximately 200,000 new cases are diagnosed per year.[1]

A few decades ago, patients with Chagas disease were mainly rural workers, with low risk profile for coronary artery disease (CAD). As urbanization has increased since 1980, they became exposed to the same risk factors for CAD of uninfected individuals. Thus, the prevalence of CAD, as a cause of acute myocardial infarction, is expected to be similar in individuals with and without Chagas disease.[2]

The prevalence of CAD in patients with Chagas disease, however, is controversial.[3-7] It is worth noting the inherent diagnostic difficulty concerning chest pain, which can be atypical or intense.[8,9] Coronary angiography should only be indicated in special situations, such as typical angina and presence of classic CAD risk factors, or when large ischemic areas are seen on non-invasive tests.[9]

For 25 years, stress echocardiography has proven to be an important tool for the diagnosis of CAD. The dobutamine-atropine protocol [dobutamine stress echocardiography - DSE)] is safe and has accuracy similar to that of other non-invasive diagnostic methods, but higher specificity.[10]

Dobutamine is the most commonly used agent in most pharmacological stress tests.[11,12] Severe ventricular arrhythmias can occur during the exam, but are rare, confirming, thus, the safety of using dobutamine for stress echocardiography.[13,14]

In clinical practice, however, the indication of DSE in chronic Chagas heart disease (CCHD) is controversial, because of the arrhythmogenic potential of the drug in an also arrhythmogenic heart disease. In the literature, there is no study aimed at specifically assessing the safety of DSE in a group of Chagas disease patients. Thus, this research, aimed at assessing the DSE safety for CAD diagnosis in that group of patients, is relevant.

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Methods

Selection of patients and study site

This is a retrospective analysis of a database to raise a hypothesis. A population of consecutive patients with CCHD and suspected of having CAD was assessed. They were referred for DSE from May/2012 to February/2015 at two echocardiography centers, one of them outside a hospital.

Confirmation of serology for Chagas disease was required in all patients. Those who spontaneously presented with at least two positive serologies at the time of DSE were confirmed as having Chagas disease. Those who had no serology were invited, via telephone, to undergo the serological tests, and to provide written informed consent at the time of blood sample collection. They underwent at least two serological tests of different principles, which confirmed the existence of anti-*T. cruzi* antibodies. The following conventional serological tests were used: immunoenzymatic assay (ELISA); indirect immunofluorescence; and indirect hemagglutination assay. Patients refusing to undergo the tests were excluded from the analysis.

Echocardiographic assessment, analysis of safety and arrhythmias

Before DSE, the patients were asked about previous cardiovascular diseases, including Chagas disease, heart procedures they had already undergone, and regularly used medications.

Echocardiography was performed with a HD-11 echocardiographer (Philips Ultrasound Systems, Andover, MA, USA), by an echocardiography professional from a group of four, equally trained, and in a standardized and uniform way, according to the ASE recommendations.[15] That group of professionals has a large experience with stress echocardiography, each performing, on average, 200 exams/month. The exams were performed systematically in all participants, regardless of the serological confirmation for Chagas disease.

Initially, the patients underwent a baseline echocardiographic study, with linear measurement of the heart structures and valvar flows. Ejection fraction was assessed by using the Teichholz or Simpson method, depending on the extent of the segmental contractility alteration. When using the latter, sometimes the end-systolic diameter was not measured. After acquiring baseline standard images in the parasternal, longitudinal, transverse, 4- and 2-chamber apical views, intravenous dobutamine infusion began, at an initial dose of 5 μg/kg/min, with increasing increments of 10, 20, 30 and 40 μg/kg/min every 3 minutes. If the patient had no echocardiographic sign of myocardial ischemia and did not reach the minimum heart rate of 100 bpm in the stage of 20 μg/kg/min, 0.25 mg/min of atropine was administered every 1 minute, up to the maximum cumulative dose of 2 mg. There was no standardization concerning monitoring time after the end of infusion, and the time necessary for heart rate to reach less than 100 beats per minute was respected.

The patients were kept under clinical, electrocardiographic and continuous blood pressure monitoring. The measures of blood pressure, heart rate and 12-lead electrocardiography were recorded at baseline, at the end of each stage and during recovery. The patients' symptoms were recorded either through direct questioning or direct patient's complaint at any time.

The DSE was effective when one of the following objectives was met: at least 85% of maximum heart rate predicted for age, calculated with the Karvonen equation (maximum heart rate = 220 - age);[16] echocardiographic signs of ischemia (new changes in left ventricular contractility); or end of the infusion protocol.

The submaximal criteria for test interruption, considered non-diagnostic were: unbearable symptoms; limiting side effects, such as arterial hypertension (systolic blood pressure > 230 mm Hg or diastolic blood pressure > 120 mm Hg); relative or absolute hypotension (systolic blood pressure drop > 30 mm Hg at rest, or systolic blood pressure < 80 mm Hg); supraventricular arrhythmias (sustained supraventricular tachycardia and atrial fibrillation); and ventricular arrhythmias (non-sustained and sustained ventricular tachycardia).[17]

The safety criteria for exam interruption were established as life-threatening complications, defined in the meta-analysis by Geleijnse et al.[18] as cardiac rupture, acute myocardial infarction, stroke, asystole, ventricular fibrillation, and sustained ventricular tachycardia.

The cardiac arrhythmias observed during the exam were defined as follows: supraventricular tachycardia, presence of well-defined, regular and similar narrow QRS complexes (<120 ms), in the absence of conduction disorder; atrial fibrillation, absence of P wave associated with irregular rhythm, narrow QRS complexes (<120 ms), in the absence of conduction disorder; frequent ventricular extrasystoles, presence of premature ventricular complexes with more than 6 complexes per minute; ventricular bigeminism, presence of ventricular extrasystoles alternating with normal QRS complexes; non-sustained ventricular tachycardia, presence of more than 3 premature complex ventricular beats, lasting less than 30 seconds and with heart rate greater than 100 beats per minute; and sustained ventricular tachycardia, presence of more than 3 premature complex ventricular beats, lasting more than 30 seconds and with heart rate greater than 100 beats per minute.[19]

The left ventricle was divided into 17 myocardial segments, according to the ASE recommendations.[15] The qualitative analysis of segmental myocardial contractility was based on visual assessment of myocardial thickening and wall motility graded into a segmental contractility index, each segment being scored as follows: 1 - normal; 2 - hypokinesia; 3 - akinesia; and 4 - dyskinesia. The normal value of that index is 1 (17 points/17 segments). Any value greater than 1 was considered abnormal segmental contractility index. Segmental myocardial contractility was positive for ischemia in the presence of altered segmental myocardial contractility in at least one left ventricular segment during pharmacological stress.[13,15]

Statistical analysis

Non-probability convenience sampling was chosen and comprised patients with Chagas disease, suspected of having CAD, referred for DSE in the predetermined study period. The sample size was limited to the study's operational capacity.

Multivariate analysis was conducted using binary multiple logistic regression to identify covariables associated with the occurrence of binary outcome. When indicated, given the reduced number of binary outcome events, the use of penalized maximum likelihood ratio test was considered.

Multiple regression models were determined with the simultaneous introduction (*full model*) of the variables with $p<0.05$ in univariate regression analysis and that showed neither multicollinearity nor percentage loss greater than 10%.

Categorical variables were described as counts and percentages. Quantitative variables of normal and asymmetric distribution were described as mean ± standard deviation or median (interquartile range), respectively.

Normality was assessed via visual inspection of histograms. The R software (R Foundation, Vienna, Austria) was used for statistical analysis. All probabilities of significance presented are bilateral, and values smaller than 0.05 were considered statistically significant.

Results

The general population referred for DSE underwent 23,935 exams. Of that sample, 415 patients claiming to have Chagas disease were selected. Of those, 210 patients whose serology was not confirmed were excluded, resulting in a final group of 205 patients to be assessed.

The mean age of the 205 patients analyzed was 64±10 years, and most of them (65.4%) were of the female sex. Regarding pharmacological treatment, the most used drugs were angiotensin II receptor blockers (35,1%) and amiodarone (29.3%). Of the reported risk factors for CAD, dyslipidemia was the most frequent (33.2%). Regarding the presence of previous coronary event, 6.3% reported myocardial infarction, and 5.9% surgical or percutaneous myocardial revascularization. Table 1 shows the clinical characteristics of the group and pharmacological treatment, and Table 2, the risk factors for CAD.

Regarding the echocardiographic parameters and vital signs (Table 3), most patients had preserved ejection fraction, normal systolic and diastolic blood pressure, but heart rate tending to the lower limit of normality.

More than half of the group (105 patients – 51.2%) had some alteration in segmental contractility at rest: in the apical segments of the ventricle, 30 patients; in the basal segments of the inferior and/or inferolateral wall, 35; association of the two alterations described, 32; and diffuse hypokinesia, 8. Regarding electrocardiographic changes, 98 patients had the following tracing alterations at rest: isolated right bundle branch block, 60 patients; association of right bundle branch block with left anterior hemiblock, 27; left bundle branch block, 5; atrial fibrillation rhythm, 3; and pacemaker rhythm, 3. In addition, only segmental contractility alteration, electrocardiographic alteration, or association of both was present in 50, 43 and 55 patients, respectively.

Table 1 – Clinical characteristics of the total sample

Characteristic	
Age (years)	64±10 (Mean ± SD)
Sex	n= 205
Female	65.4%
Drug treatment	n = 205
CCB	9.8%
ACEI	9.8%
ARB	35.1%
Beta-blocker	12.2%
Nitrate	0.5%
Amiodarone	29.3%
Pacemaker	2.9%
Atrial fibrillation at rest	1.5%
CI to the use of atropine	2.4%

SD: standard deviation; CCB: calcium-channel blocker; ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker; CI: contraindication.

Table 2 – Risk factors for atherosclerotic disease

Risk factor	n= 205
SAH	64.3%
DM	12.7%
Smoking	7.8%
Dyslipidemia	33.2%
Previous AMI	6.3 %
MR	5.9%
FH	11.7%

SAH: systemic arterial hypertension; DM: diabetes mellitus; AMI: acute myocardial infarction; MR: previous myocardial revascularization; FH: family history of atherosclerotic disease.

Negative result for myocardial ischemia was the most frequent finding in 139 exams (67.9%). That result was positive in 29 exams (14.1%), and inconclusive (did not reach submaximal heart rate) in 37 (18%). Of the patients with inconclusive result, 22 (59.5%) used maximum dose of dobutamine and underwent all stages of the protocol, but some had their exams interrupted because of the following: severe chest pain, 1 (2.7%); important blood pressure elevation (> 230/120 mm Hg), 1 (2.7%); severe headache, 2 (5.4%); and cardiac arrhythmias, 11 (29.7%). Frequent and polymorphic ventricular extrasystoles and non-sustained ventricular tachycardia were the most common arrhythmias related to exam interruption. Most patients with frequent ventricular extrasystoles during the exam had

Table 3 – Echocardiographic characteristics, blood pressure and heart rate

Variable	n	Mean	SD	95%CI	Median	IQR	Min	Max
LA (mm)	205	36.02	5.402	(35.28; 36.77)	36	(32; 40)	25	52
VST (mm)	205	8.698	1.504	(8.49; 8.905)	8	(8; 9)	5	14
PW (mm)	205	8.517	1.363	(8.329; 8.705)	8	(8; 9)	4	14
LVEDD (mm)	205	49.81	7.388	(48.79; 50.83)	50	(45; 54)	29	75
LVESD (mm)	171	30.13	5.566	(29.29; 30.97)	29	(26; 34)	20	61
EF (%)	205	62.36	11.16	(60.82; 63.89)	63	(58; 70)	28	88
SCIr*	205	1.23	0.362	(1.18; 1.279)	1.06	(1; .29)	1	2.47
SCIp*	205	1.249	0.415	(1.192; 1.306)	1	(1; 1.29)	1	2.8
SBP (mm Hg)	205	123.8	18.74	(121.2; 126.3)	120	(110;140)	80	180
DBP* (mm Hg)	205	74.54	9.518	(73.23; 75.85)	80	(70; 80)	60	110
HR (beat/min)	205	67.88	12.43	(66.17; 69.59)	66	(59; 75)	45	103

**Significant: variables without normal distribution. SD: standard deviation; 95%CI: 95% confidence interval; IQR: interquartile range; LA: anteroposterior measure of left atrium; VST: ventricular septal thickness; PW: posterior wall thickness; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; EF: ejection fraction; SCIr: segmental contractility index at rest; SCIp: segmental contractility index at peak; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate at rest.*

isolated extrasystoles at rest. Likewise, most arrhythmias were dose-dependent, occurring at pharmacological stress peak. Of the patients receiving maximum dose of dobutamine, 16 (72.7%) were on negative chronotropic drugs, such as beta-blocker or amiodarone.

Table 4 shows the arrhythmias induced during DSE. Of the 205 patients, 18 (8.7%) had more than one type of arrhythmia during the exam.

The protocol was interrupted because of the appearance of significant arrhythmias (atrial fibrillation, sustained supraventricular tachycardia, non-sustained ventricular tachycardia and sustained ventricular tachycardia). Those patients required neither specific drug nor electrical cardioversion. No patient had hemodynamic instability. All patients underwent routine observation.

Headache was the most frequent unwanted symptom (2.4%) during the exam, followed by chest pain (2.0%). No patient had hypotension during the exam, and only one (0.5%) had a hypertensive response.

No patient had significant adverse events, such as acute myocardial infarction, ventricular fibrillation, asystole, stroke, cardiac rupture or death.

Discussion

The use of DSE to diagnose CAD in patients who cannot undergo exercise test has increased. In addition, more aggressive protocols with high doses of dobutamine and atropine have been more often used.[20]

To our knowledge, this is the first study designed to assess the safety of DSE, as well as the occurrence of arrhythmias, in an exclusive population of patients with Chagas disease.

Despite the potential risk of complications, mainly arrhythmogenic ones, the method was safe when applied to 205 patients. None had significant complications, such as death, acute myocardial infarction, cardiac rupture, stroke, ventricular fibrillation or asystole. Most safety studies have reported a very low incidence of those events: the meta-analysis by Geleijnse et al.,[18] with 55,071 patients, has found an incidence of death, cardiac rupture and stroke lower than 0.01%, of acute myocardial infarction of 0.02%, and a rate of major complications of 1:475 (adding sustained ventricular tachycardia, asystole and ventricular fibrillation). Those figures are in accordance with those reported in the International Stress Echo Complication Registry,[21] with a rate of 1:595 in the assessment of 35,103 patients.

The population studied belongs to the same age group of those of the studies on DSE safety assessed in the meta-analysis cited.[20] Recently, a study conducted by O'Driskll et al.[22] with 550 octogenarian patients has demonstrated that DSE was safe in that population and capable of identifying individuals at high risk for cardiovascular event.

The patients with Chagas disease had a lower prevalence of risk factors for CAD as compared to those without Chagas disease, in previous studies.[20,23,24] Of those risk factors, the most prevalent were hypertension and dyslipidemia, the only ones that got closer to those of the non-chagasic populations studied, such as the group assessed by San Roman et al.[25], with the following prevalence: hypertension, 61%; diabetes mellitus, 29%; dyslipidemia, 46%; smoking, 23%; history of previous infarction, 23%; and revascularization, 31%.

Regarding pharmacological treatment, Chagas disease patients used less frequently antianginal therapy, such as beta-blockers, nitrates and calcium-channel blockers, as compared to those of previous studies.[20,25] However, 30% of the patients used amiodarone, an antiarrhythmic and negatively chronotropic drug, which might have accounted for not reaching submaximal heart rate in most inconclusive results.

Table 4 – Arrhythmias induced during stress echocardiography

Arrhythmias	n (%)
AF	1 (0.5%)
SSVT	2 (1%)
VE	100 (48%)
Bigeminismo	9 (4.4%)
NSVT	15 (7.3%)
SVT	2 (1%)

AF: atrial fibrillation; SSVT: sustained supraventricular tachycardia; VE: ventricular extrasystole; NSVT: non-sustained ventricular tachycardia; SVT: sustained ventricular tachycardia.

In our study, the positive result for ischemia was less frequent than in other studies, maybe because of the smaller number of risk factors for CAD in the group of patients with Chagas disease.[20,23,24] A cohort of 4,033 patients conducted by Mathias et al.[26] has shown a positive result in 37% of them, and inconclusive result in 10%. Sicari et al.,[27] in a cohort of 7,333 patients, has reported a positive result for ischemia in 39% of the exams.

The only study published, assessing Chagas disease patients submitted to DSE, has been conducted by Aquatella et al.[28] That study aimed at assessing whether the stimulation with dobutamine could trigger an abnormal contractility response, as seen in ischemic myocardium. In that small cohort (24 Chagas disease patients vs 10 controls), dobutamine has shown a chronotropic incompetence and a reduced contractile response, even in those without apparent cardiac manifestation. That study might explain part of the inconclusive results found in ours, because of that probable chronotropic deficit.

Most patients with Chagas disease studied had some degree of segmental impairment, frequent in that pathology.[29] The segmental contractility index, which reflects the segmental myocardial impairment extent, was slightly altered (median value, 1.06), reflecting mild alterations and few impaired segments.

Regarding arrhythmias, ventricular extrasystoles were the most frequently found, similarly to that reported in the safety studies analyzed in the meta-analysis by Geleijnse et al.[18] However, the incidence was higher than that reported in most studies, that by Takeuchi et al. [30] being the one that got closer. That study, with 1,090 patients, has assessed different dobutamine-atropine protocols, with a 43.6% incidence of ventricular extrasystoles.[30] Non-sustained ventricular tachycardia had the second highest incidence, 15 patients (7.3%), which was also greater than those already published, with a mean of 2.19% (range, 0.2% to 7.3%).[18] The study conducted by Bremer et al.,[31] with 4,035 patients, assessing the safety of stress echocardiography performed by nurses, was the only to show an incidence similar to the one of that group. Sustained ventricular tachycardia occurred in 2 (1%) patients, and that incidence was also higher than the one reported in previous studies for patients without Chagas disease, whose mean was 0.15% (range, 0.0% to 0.78%). Regarding supraventricular arrhythmias, the incidence was similar to that of other studies, where atrial fibrillation had a mean incidence of 0.9%, and sustained supraventricular tachycardia, of 1.3%.[18] Our patients had 0.5% and 1.0%, respectively.

Unwanted adverse effects, such as chest pain, had a lower incidence than in previous studies, such as that by Mathias et al.,[32] San Roman et al.[25] and Mertes et al.,[20] where chest pain occurred in 12.6%, 8.5% and 12.7%, respectively. Headache had the same frequency of that in other studies, as demonstrated by Mathias et al.,[32] Mertes et al.[20] and San Roman et al.,[25] with incidence of 1.9%, 4% and 1.9%, respectively.

In addition, the incidence of hypertensive response and hypotension was lower than that of the safety studies assessed in the meta-analysis by Geleijnse et al.,[18] in which the mean incidence of hypertension as the cause of protocol interruption was 1.3%, and that of hypotension, 1.7%. A recent retrospective analysis by Abram et al.,[33] with 2,968 patients with no cardiovascular disease and normal findings on stress echocardiography, has shown that blood pressure variation during the exam depends on age, sex and use of atropine. A greater increase in systolic blood pressure was seen in men and young individuals, with a more pronounced effect of atropine among the young.

Study limitations

This study is a retrospective analysis of a database, with the limitations inherent in that type of analysis. However, the exams were systematically performed by the same trained medical and nurse team, with large experience in that type of exam.

The database is small as compared to those of safety studies of stress echocardiography, but the identification of that type of patient is limited.

We had no coronary angiography of the patients who reported previous history of acute myocardial infarction. Thus, one might argue whether the segmental contractility alteration of such patients, when present, could be attributed to acute myocardial infarction or to Chagas heart disease. However, the number of those patients in our sample was reduced.

The interobserver variation analysis of the echocardiographic data could not be performed, because the digital images were not stored.

Conclusions

Stress echocardiography with dobutamine and atropine showed to be safe in the population of patients with Chagas disease, in which no life-threatening outcome was observed.

The incidence of arrhythmias during the exam was higher than that found in studies with populations without Chagas disease.

The incidence of adverse effects, such as chest pain, arterial hypertension and hypotension, was lower than that found in studies with populations without Chagas disease.

Author contributions

Conception and design of the research, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Rassi DC, Vieira MLC, Furtado RG, Turco FP, Melato LH, Hotta VT, Nunes CGO, Rassi Jr. L, Rassi S; Acquisition of data: Rassi DC, Furtado RG, Turco FP, Melato LH, Nunes CGO, Rassi Jr. L; Statistical analysis: Rassi DC, Vieira MLC, Rassi S; Writing of the manuscript: Rassi DC, Vieira MLC, Hotta VT, Rassi S.

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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Left Atrial Deformation Analysis in Patients with Corrected Tetralogy of Fallot by 3D Speckle-Tracking Echocardiography (from the MAGYAR-Path Study)

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Abstract

Background: Three-dimensional (3D) echocardiography coupled with speckle-tracking echocardiographic (STE) capability is a novel methodology which has been demontrated to be useful for the assessment of left atrial (LA) volumes and functional properties. There is increased scientific interest on myocardial deformation analysis in adult patients with corrected tetralogy of Fallot (cTOF).

Objectives: To compare LA volumes, volume-based functional properties and strain parameters between cTOF patients and age- and gender-matched healthy controls.

Methods: The study population consisted of 19 consecutive adult patients with cTOF in sinus rhythm nursing at the University of Szeged, Hungary (mean age: 37.9 ± 11.3 years, 8 men, who had repair at the age of 4.1 ± 2.5 years). They all had undergone standard transthoracic two-dimensional Doppler echocardiographic study extended with 3DSTE. Their results were compared to 23 age- and gender-matched healthy controls (mean age: 39.2 ± 10.6 years, 14 men).

Results: Increased LA volumes and reduced LA emptying fractions respecting cardiac cycle could be demonstrated in cTOF patients compared to controls. LA stroke volumes featuring all LA functions showed no differences between the 2 groups examined. LA global and mean segmental uni- and multidirectional peak strains featuring LA reservoir function were found to be diminished in adult patients with cTOF as compared to controls. Similarly to peak strains reduced global and mean segmental LA strains at atrial contraction characterizing atrial booster pump function could be demonstrated in cTOF patients as compared to controls.

Conclusions: Significant deterioration of all LA functions could be demonstrated in adult patients with cTOF late after repair. Arq Bras Cardiol. 2017; 108(2):129-134

Keywords: Echocardiography, Three-Dimensional / methods; Heart Atria / abnormalities; Tetralogy of Fallot; Heart Defects, Congenital.

Introduction

Nowadays the angle-independent speckle-tracking echocardiography-derived (STE) myocardial deformation analysis is one of the main focus of cardiac ultrasound technology.[1] Three-dimensional (3D) echocardiography coupled with STE capability is a novel methodology which has been demonstrated to be useful for the assessment of volumes and functional properties of cardiac chambers.[2] 3DSTE allows complex assessment of atrial and ventricular morphology and function including volumetric and strain measurements from the same acquired 3D dataset.

There is increased scientific interest on myocardial deformation analysis in adult patients with corrected tetralogy of Fallot (cTOF).[3-5] Recently, alterations in right (RV)[3,4] and left ventricular (LV)[4] and right atrial (RA)[5] functional properties could be demonstrated by 3DSTE. However, quantitative left atrial (LA) deformation assessment has never been performed in cTOF patients. Therefore, the present study aimed to detect changes in LA volumes, volume-based functional properties and strain parameters in cTOF patients as compared to age- and gender-matched healthy controls.

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Methods

Patient population

Since 1961, more than 2,700 congenital heart disease patients have been treated and/or operated on at the Department of Pediatrics, Department of Heart Surgery, and 2nd Department of Medicine and Cardiology Center at the University of Szeged. From this patient population a registry was created (CSONGRAD Registry),[6] from which 19 consecutive adult patients with cTOF in sinus rhythm were willing to participate in the present study (mean age: 37.9 ± 11.3 years, 8 men) who had repair at the age of 4.1 ± 2.5 years. In our department several hundreds of

healthy control subjects without risk factors or known disorders in different age groups were examined by 3DSTE to assess the normal values of 3DSTE-derived parameters. From this pool 20 age- and gender-matched healthy subjects (mean age: 39.2 ± 10.6 years, 14 men) were selected who served as a control group in this particular study. All cTOF patients and controls were examined by two-dimensional (2D) Doppler, tissue Doppler echocardiography (TDI) and 3DSTE. The present study is a part of **MAGYAR-Path Study** (**M**otion **A**nalysis of the heart and **G**reat vessels b**Y** three-dimension**A**l speckle-t**R**acking echocardiography in **Path**ological cases) which has been organized at our department to examine diagnostic and prognostic significance of 3DSTE-derived variables. The institutional human research committee approved the study which complied with the 1975 Declaration of Helsinki. Informed consent was obtained from all cTOF patients and control subjects.

Two-dimensional Doppler and tissue Doppler echocardiography

All M-mode (MME), 2D Doppler and TDI studies were performed in the left lateral decubitus position with a commercially available Toshiba Artida™ echocardiography equipment (Toshiba Medical Systems, Tokyo, Japan) using a PST-30SBP phased-array transducer in all patients. LV dimensions were assessed by MME using the Teichholz method.[7] Valvular regurgitations were confirmed by colour Doppler echocardiography-derived visual grading. Following Doppler assessment of E/A, the ratio of transmitral E velocity to early diastolic mitral annular velocity (E/E') was measured by TDI.

Three-dimensional speckle-tracking echocardiography

All 3D echocardiographic data acquisitions were performed using a 1-4 MHz PST-25SX matrix phased-array transducer (Toshiba Medical Systems, Tokyo, Japan).[2] During a single breathhold full volume 3D datasets were created from the apical view from 6 wedge-shaped subvolumes using 6-beat electrocardiographically gated acquisitions. LA was quantified by the 3D Wall Motion Tracking software version 2.7 (Toshiba Medical Systems, Tokyo, Japan).[8] Each 3D dataset was displayed in a five plane-view, namely apical two- (AP2CH) and four-chamber (AP4CH) views and three short-axis views at different levels of the LA. After positioning the main axis line through the center of the LA cavity the reader traced LA endocardial border in both orthogonal long-axis views. Firstly, the edge of the septal side of the mitral valve ring was traced, then markers were set in a counterclockwise rotation around the LA to the edge of the lateral side of the mitral valve ring. Subsequently, 3D wall motion tracking was then automatically performed through the entire cardiac cycle.

3DSTE for left atrial volumetric measurements

To characterize systolic reservoir and diastolic conduit and active contraction phases of the LA function, calculation of volume-based functional properties respecting cardiac cycle is an available option (Figure 1).[8-12] End-systolic LA volume [largest LA volume before mitral valve opening (V_{max})], end-diastolic LA volume [smallest LA volume before mitral valve closure (V_{min})] and diastolic LA volume before atrial contraction [at time of P wave on ECG (V_{preA})] could be measured using the LA 3D cast, from which the following functional properties were calculated:

Reservoir function:

- Total Atrial Stroke Volume (TASV): $V_{max} - V_{min}$.
- Total Atrial Emptying Fraction (TAEF): $TASV/V_{max} \times 100$.

Conduit function:

- Passive Atrial Stroke Volume (PASV): $V_{max} - V_{preA}$
- Passive Atrial Emptying Fraction (PAEF): $PASV/V_{max} \times 100$

Active contraction:

- Active Atrial Stroke Volume (AASV): $V_{preA} - V_{min}$.
- Active Atrial Emptying Fraction (AAEF): $AASV/V_{preA} \times 100$.

3DSTE for left atrial strain measurements

Several unidirectional [radial (RS), longitudinal (LS) and circumferential (CS) strains] and complex [area (AS) and 3D (3DS) strains] LA strain parameters could be calculated from the same 3D model, as demonstrated before.[10-14] Not only global and mean segmental peak strains featuring LA reservoir function were measured for each patient, but strains at atrial contraction, characteristics of LA active contraction, were also evaluated (Figure 1).

Stastical analysis

Continuous data are presented as mean values ± standard deviation, while categorical data are summarized as a count and percentage. For comparing variables, the Student's *t*-test, chi-square analysis, and Fisher's exact test were used. All statistical tests were two-tailed and statistical significance was defined with a probability value less than 0.05. Recently, intra- and interobserver agreements for LA volumes and functional properties were performed in papers originating from MAGYAR-Healthy and MAGYAR-Path Studies.[8,11] Data were analysed using Medcalc software (MedCalc, Mariakerke, Belgium).

Results

Clinical data

Risk factors, medications applied and 2D echocardiographic data are presented in Table 1. Significant (>grade 2) mitral and tricuspid regurgitations could be detected in 2 (11%) and 8 (42%) cTOF patients. None of the healthy controls had significant regurgitations. The TAPSE and RV-FAC values of cTOF patients proved to be 18.2 ± 4.6 mm and 34.2 ± 3.9%, respectively.

3DSTE-derived LA volumes and volume-based functional properties

Increased LA volumes and reduced LA emptying fractions respecting cardiac cycle could be demonstrated in cTOF patients compared to controls. LA stroke volumes featuring all LA functions showed no differences between the groups examined (Table 2).

3DSTE-derived LA peak strain parameters

LA global and mean segmental uni- and multidirectional peak strains featuring LA reservoir function were found to

Table 1 – Demographic and clinical data of patients with tetralogy of Fallot and that of controls

	cTOF patients (n=19)	Controls (n=23)	p value
Risk factors			
Age (years)	37.9 ± 11.3	39.2 ± 10.6	0.70
Male gender (%)	8 (42)	14 (61)	0.35
Hypertension (%)	3 (16)	0 (0)	0.08
Hypercholesterolemia (%)	1 (5)	0 (0)	0.45
Diabetes mellitus (%)	0 (0)	0 (0)	1.00
Medications			
β-blockers (%)	5 (26)	0 (0)	0.01
ACE-inhibitors (%)	3 (16)	0 (0)	0.08
Diuretics (%)	3 (16)	0 (0)	0.08
Two-dimensional echocardiography			
LA diameter (mm)	42.4 ± 6.8	33.2 ± 3.8	<0.0001
LV end-diastolic diameter (mm)	54.6 ± 19.6	48.3 ± 6.9	0.16
LV end-diastolic volume (ml)	113.7 ± 31.7	102.2 ± 21.1	0.17
LV end-systolic diameter (mm)	32.7 ± 7.1	30.4 ± 4.1	0.20
LV end-systolic volume (ml)	43.8 ± 23.2	35.6 ± 10.6	0.14
Interventricular septum (mm)	9.9 ± 1.5	9.5 ± 2.0	0.46
LV posterior wall (mm)	9.8 ± 1.5	9.4 ± 2.3	0.55
LV ejection fraction (%)	62.7 ± 11.5	65.4 ± 6.5	0.34

ACE: angiotensin-converting enzyme; LA: left atrial; LV: left ventricular; cTOF: corrected tetralogy of Fallot.

be diminished in adult patients with cTOF as compared to controls (Table 3).

3DSTE-derived LA strain parameters at atrial contraction

Similarly to peak strains reduced global and mean segmental LA strains at atrial contraction characterizing atrial booster pump function could be demonstrated in cTOF patients as compared to controls (Table 3).

Discussion

Three-dimensional speckle-tracking echocardiography, which is an echocardiographic technique based on block-matching algorithm of the myocardial speckles,[2] has been increasingly used as a tool for volumetric and functional assessment of atria[5,8-14] and ventricles.[3,15-21] In recent studies 3DSTE-derived complex evaluation of LA function including assessment of volume-based functional properties and strains has been demonstrated.[8-14] The study reported here is the first to analyse 3DSTE-derived LA deformation in adult patients with cTOF. Increased LA volumes and diminished LA emptying fractions and strains could be demonstrated in this detailed analysis. Results suggest significant deterioration of all LA functions (reservoir, conduit and booster pump) in adult patients with cTOF late after repair.

STE was found to be a valuable tool for volumetric and functional assessment of cardiac chambers in adult patients with cTOF.[3-5] In a recent study RV free wall strain and strain rate were found to be decreased in adults late after TOF repair, especially at the apical segment suggesting that apical function is most affected in these RVs.[4] Regarding the LV, septal strain was decreased indicating that RV dysfunction adversely affects LV function, probably by mechanical coupling of the ventricles. In another study, the majority of adults with cTOF showed a reduced LV twist.[22] Strikingly, one-quarter of these patients had an abnormal apical rotation which has been found to be associated with decreased systolic LV and RV function. These findings suggested that abnormal apical rotation could be a new objective diagnostic criterion for detection of ventricular dysfunction in cTOF.

The complexity of RA dysfunction could also be demonstrated by 3DSTE in cTOF patients.[5] Comparing this with the present study, both RA and LA volumes seemed to be increased in adult patients with cTOF. Moreover, large similarity of RA and LA deformation could also be demonstrated: while RA/LA emptying fractions were found to be decreased, RA/LA stroke volumes remained unchanged. All the peak LA strains and LA strains at atrial contraction were found to be reduced and this reduction was more pronounced in cTOF as compared to the values related to RA. Therefore it seems that the LA is very important. From other studies also the LA proved to be important.[23]

Several factors may play a role in the altered atrial function in cTOF, such as the interaction between both atria, the presence

Table 2 – Comparison of 3DSTE-derived volumes and volume-based functional properties between patients with corrected tetralogy of Fallot and controls

	Calculated volumes (ml)			Stroke volumes (ml)			Emptying fractions (%)		
	V_{max}	V_{min}	V_{preA}	TASV	PASV	AASV	TAEF	PAEF	AAEF
cTOF patients	53.3 ± 28.1	35.1 ± 24.4	42.7 ± 26.0	18.2 ± 7.4	10.6 ± 6.4	7.6 ± 4.4	37.1 ± 11.7	21.4 ± 11.6	20.1 ± 10.8
Controls	36.8 ± 6.6	18.2 ± 6.3	26.3 ± 8.1	18.6 ± 4.1	10.5 ± 4.6	8.1 ± 3.2	51.4 ± 11.4	29.5 ± 13.3	31.1 ± 9.1
p value	0.009	0.003	0.006	0.84	0.96	0.71	0.0003	0.04	0.0009

V_{max}: maximum left atrial volume; V_{min}: minimum left atrial volume; V_{preA}: left atrial volume before atrial contraction; TASV: total atrial stroke volume; TAEF: total atrial emptying fraction; AASV: active atrial stroke volume; AAEF: active atrial emptying fraction; PASV: passive atrial stroke volume; PAEF: passive atrial emptying fraction. cTOF: corrected tetralogy of Fallot.

Table 3 – Comparison of 3DSTE-derived peak strains and strains at atrial contraction between patients with tetralogy of Fallot and controls (global and mean segmental parameters)

	Radial strain (%)		Circumferential strain (%)		Longitudinal strain (%)		Three-dimensional strain (%)		Area strain (%)	
	Global	Mean segmental	Global	Mean segmental	Global	Mean segmental	Global	Mean segmental	Global	Mean segmental
					Peak strains					
cTOF patients	-12.8 ± 9.5	-17.0 ± 8.5	13.2 ± 9.2	18.3 ± 8.8	17.4 ± 8.3	19.7 ± 8.1	-7.0 ± 6.3	-11.5 ± 6.2	33.1 ± 14.2	38.9 ± 13.7
Controls	-18.0 ± 9.9	-21.7 ± 8.9	29.0 ± 13.4	34.2 ± 13.1	26.3 ± 7.7	29.6 ± 7.4	-11.0 ± 8.2	-15.1 ± 6.9	59.7 ± 22.0	67.9 ± 21.7
p value	0.10	0.09	0.0001	0.0001	0.0008	0.0002	0.09	0.09	0.0001	<0.0001
					Strains at atrial contraction					
cTOF patients	-2.8 ± 4.6	-6.5 ± 5.6	4.5 ± 5.0	7.3 ± 5.0	2.9 ± 4.6	4.7 ± 3.9	-1.7 ± 6.4	-4.7 ± 4.8	8.1 ± 9.7	12.4 ± 8.9
Controls	-7.2 ± 7.9	-8.2 ± 5.5	11.2 ± 10.4	13.9 ± 9.2	8.1 ± 8.8	9.0 ± 5.8	-5.5 ± 5.1	-6.4 ± 4.8	16.7 ± 16.1	20.3 ± 14.2
p value	0.03	0.33	0.01	0.008	0.03	0.10	0.04	0.24	0.04	0.04

cTOF: corrected tetralogy of Fallot.

of mitral/tricuspid regurgitation, arrhythmias and changes in both ventricular features as demonstrated before. Further studies are warranted to understand the real pathophysiologic background of these findings.

Limitation

The present study covered only a relatively small number of patients from a single center by a single observer (DP). Therefore, future multicenter studies with larger patient populations are necessary. Another limitation of image acquisition for 3DSTE is the relatively slow volume rate. During creating 3D model of the LA, septum was considered as a part of the LA similarly to other studies evaluating RA.[5] Finally, LA appendage and pulmonary veins were excluded which could theoretically affect results. During the present study, LV, RV and RA functional characterization was not aimed to be performed.

Conclusions

Significant deterioration of all LA functions could be demonstrated in adult patients with cTOF late after repair.

Author contributions

Conception and design of the research: H Kálmán, Nemes A; Acquisition of data: H Kálmán, Domsik P, Kalapos A; Analysis and interpretation of the data and Statistical analysis: Domsik P, Kalapos A; Writing of the manuscript and Critical revision of the manuscript for intellectual content: H Kálmán, McGhie JS, Roos-Hesselink JW, Forster T, Nemes 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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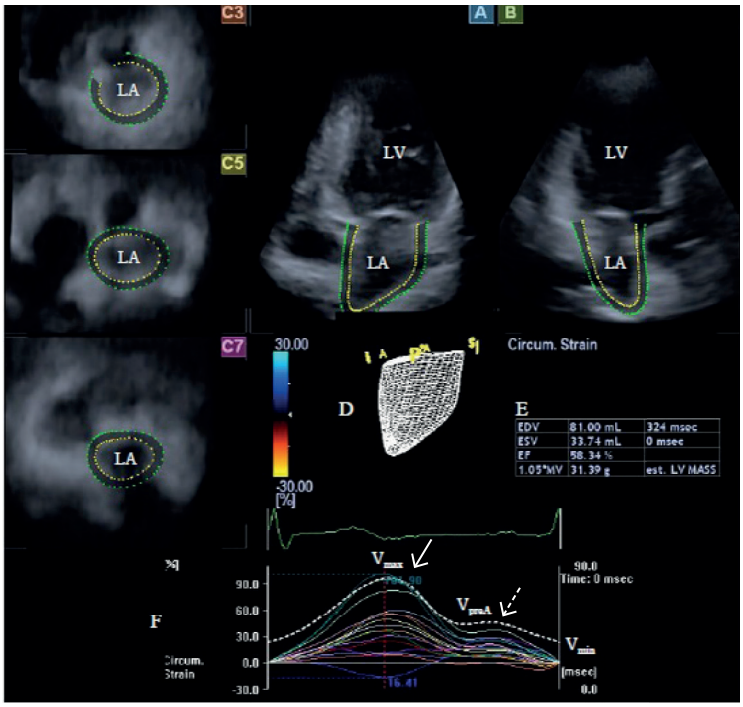

Figure 1 – *Images from three-dimensional (3D) full-volume dataset showing left atrium (LA) in a patient with corrected tetralogy of Fallot is presented: (A) apical four-chamber view, (B) apical two-chamber view, (C3) short-axis view at basal, (C5) mid- and (C7) superior left atrial level. A 3D cast (D), volumetric data (E), time – global volume and time – segmental strain curves (F) of the LA are also presented. Dashed curve (F) represents LA volume changes during cardiac cycle with maximum (V_{max}), minimum (V_{min}) LA volumes and LA volume at atrial contraction (V_{preA}). White arrow represents peak strain, while dashed arrow represents strain at atrial contraction (F). LA: left atrium; LV: left ventricle.*

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Compliance with the Prescription of Antihypertensive Medications and Blood Pressure Control in Primary Care

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Abstract

Background: Hypertension is the most prevalent risk factor for cardiovascular disease, and its proper control can prevent the high morbidity and mortality associated with this disease.

Objective: To assess the degree of compliance of antihypertensive prescriptions with the VI Brazilian Guidelines on Hypertension and the blood pressure control rate in primary care.

Methods: Cross-sectional study conducted between August 2011 and November 2012, including 332 adults ≥ 45 years registered in the Family Doctor Program in Niteroi and selected randomly. The analysis included the prescribed antihypertensive classes, doses, and frequencies, as well as the blood pressure (BP) of the individuals.

Results: The rate of prescription compliance was 80%. Diuretics were the most prescribed medications, and dual therapy was the most used treatment. The most common non-compliances were underdosing and underfrequencies. The BP goal in all cases was < 140/90 mmHg, except for diabetic patients, in whom the goal was set at < 130/80 mmHg. Control rates according to these goals were 44.9% and 38.6%, respectively. There was no correlation between prescription compliance and BP control.

Conclusions: The degree of compliance was considered satisfactory. The achievement of the targets was consistent with national and international studies, suggesting that the family health model is effective in BP management, although it still needs improvement. (Arq Bras Cardiol. 2017; 108(2):135-142)

Keywords: Hypertension; Arterial Pressure; Control; Drug Prescription; Antihypertensive Agents.

Introduction

Hypertension is highly prevalent in Western populations, easily identifiable, and susceptible of treatment, comprising one of the most important risk factors for cardiovascular disease.[1] The prevalence of hypertension has been increasing along with the increase in life expectancy and changes in lifestyle, with emphasis on the increase of overweight and obesity.[1] According to estimates, one-third of the world population will be hypertensive in 2025, a fact that will inexorably bring serious consequences to global public health, particularly through damage in target organs.[1,2]

In spite of solid scientific evidence showing benefits of antihypertensive treatment in the reduction of cardiovascular risk,[3,4] control of blood pressure (BP) to values < 140/90 mmHg is achieved in less than one-quarter of the individuals diagnosed with hypertension and in one-third of those receiving treatment for hypertension, even in countries with a well-structured health system.[5-7] In Brazil, the rates of effective BP control are between 10% and 57%.[8] Health system deficiencies, low adherence to treatment by the patients, and inertia to start and intensify the therapy and achieve therapeutic goals contribute to the ineffectiveness in controlling this disease.[6,9]

In hypertensive patients, BP control within the recommendations of the guidelines is one of the ways to evaluate the quality of care in hypertension.[10-12] Although most physicians consider the hypertension guidelines as valid, the degree of compliance with the recommendations varies widely, with low implementation of the recommendations in clinical practice resulting in impaired quality of care.[13-17] The compliance of the prescriptions of antihypertensive drugs to current recommendations has also been used as a way of assessing the quality of care.[18]

The aim of this study was to assess the quality of care of hypertensive patients aged 45 to 99 years enrolled in the Family Doctor Program (*Programa Médico de Família*, PMF) in Niterói, Rio de Janeiro, through the assessment of compliance of the prescription of antihypertensive drugs to the VI Brazilian Guidelines for Hypertension (*VI Diretrizes Brasileiras de Hipertensão*, VI DBH) and the rate of BP control.

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Methods

The present study is part of the Digitalis Study, a cross-sectional study conducted between August 2011 and November 2012, including a random sample of the population registered in the PMF in Niterói (state of Rio de Janeiro, Brazil), of both sexes, aged between 45 and 99 years. Details of the methodology of the Digitalis Study have been previously published.[19]

The individuals were invited to attend the PMF unity close to their homes. The researchers were trained and tested in a pilot study carried out in one of the units not included in the analysis.

All patients were evaluated with medical history, complete physical examination (including anthropometry), and complementary tests. The BP was determined with the patient in the sitting position, using a digital sphygmomanometer (Omron 711 HC, Omron, Kyoto, Japan),[20] with three measurements with an interval of 1 minute between each measurement. In the event of a difference greater than 5 mmHg, a fourth measurement was obtained. The mean BP was calculated considering all the measurements obtained. The precautions taken before and during the BP assessment followed the recommended by the Brazilian Society of Cardiology.[21]

The evaluations performed in this study included the level of physical activity of the individuals, classifying them according to the International Physical Activity Questionnaire (IPAQ) into four items: sedentary, irregularly active, active, and very active.[22] The individuals who did not perform any physical activity for at least 10 continuous minutes during the week in which the questionnaire was applied were considered to be sedentary. To evaluate the consumption of alcohol, we considered a consumption of risk when the daily average exceeded two doses for males and one dose for females.[23]

The inclusion criteria comprised declared hypertension and/or use of antihypertensive pharmacological treatment, and ability to provide information about medications in use (prescription and/or medication package and/or complete verbal information about the prescription).

The goals recommended by the VI DBH[21] were adopted and BP < 140/90 mmHg was defined as the cut-off point for therapeutic efficacy. An exception was made for diabetic patients, whose goal was defined as BP < 130/80 mmHg. The indicators of prescription compliance were defined after revision of the VI DBH,[21] establishing the classes of medications that should ideally be prescribed (alone or in combination), as well as the recommended doses and frequencies. In the case of monotherapy, we considered as compliant those prescriptions including the following classes: angiotensin-converting enzyme inhibitors (ACEi); angiotensin receptor blockers (ARB); adrenergic beta-blockers; thiazide, loop, and potassium-sparing diuretics; or calcium channel blockers. In cases of associations, we evaluated whether the associations were known to be effective and if there were associations of drugs of the same class, with the exception of loop or thiazide diuretics with spironolactone. In the case of triple therapy, we observed whether the prescription included one diuretic, as recommended by the VI DBH.[21]

We considered as "underdoses" those doses prescribed below the minimum recommended dose by the VI DBH[21] and as "underfrequencies" those prescriptions containing medications prescribed in a frequency of administration below the recommended minimum. Opposite criteria were used to define the "overdoses" and "overfrequencies". A table with all doses and frequencies recommended by the VI DBH was used to classify the prescriptions.

The analysis of the prescriptions was initially performed considering only the drugs prescribed, without considering the effectiveness of the treatment (BP control). According to this analysis, the prescriptions were categorized as “compliant” or “non-compliant”.

A consolidated analysis considering both the prescription compliance and the adequacy of the BP control categorized patients as being “treatment compliant” when having a compliant prescription associated with controlled BP.

Statistical analysis

The characteristics of the individuals and the prescriptions are presented in absolute and relative frequencies. We used Pearson's chi-square test for comparison between groups. The level of statistical significance was set at 5%. All analyses were performed using the statistical package SPSS, version 21 (IBM Corp., Armonk, NY, USA).

Ethical considerations

This study was conducted according to the principles set in the Resolution 466/2012 of the National Commission for Research Ethics (CONEP). The study protocol was submitted to the Committee for Ethics in Research of the Hospital Antônio Pedro and approved at the plenary meeting of June 11, 2010, under the CAAE number: 0077.0.258.000-10. All subjects signed an informed consent form.

Results

The Digitalis Study evaluated 633 individuals, of whom 332 (53%) were included in the present analysis after meeting the inclusion criteria. Table 1 presents the demographic and clinical characteristics of the study patients. The prescribed medications were analyzed in most cases through direct verification of the prescriptions (56.4%), followed by precise information given by the patient or family member (34.3%), and from the medication packaging presented by the patient or family member (9.3%). Table 2 shows the main prescribed medications according to their classes. Table 3 presents the prescription types (monotherapy or association).

In 80.72% of the cases (268 prescriptions), the prescriptions were compliant with the VI DBH[21] with respect to the medication chosen and their dosages and frequencies prescribed by the family doctor.

Table 4 shows the main non-compliances encountered. Of note, only 1.8% (six prescriptions) presented more than one simultaneous non-compliance. We observed that the non-compliances relative to underdosing and underfrequencies of medications were the ones most

Table 1 – Characteristics of the patients

Characteristics	Individuals analyzed n (%)
Sex	
Male	103 (31.0)
Female	229 (69.0)
Age (years)	
45 – 59	167 (50.3)
60 – 69	90 (27.1)
≥ 70	75 (22.6)
Self-declared color[$]	
White	108 (32.7)
Hybrid (Black/White)	126 (38.2)
Black	96 (29.1)
Smoking	
Never smoked	168 (50.6)
Ex-smoker	108 (32.5)
Smoker	56 (16.9)
Excessive intake of alcohol	
Yes	24 (7.2)
No	308 (92.8)
Physical activity[&]	
Sedentary	77 (27.9)
Irregular	40 (14.5)
Active	140 (50.7)
Very active	19 (6.9)
Obesity[#]	
BMI < 26 (ideal weight)	106 (32.1)
BMI 26 - 29.99 (overweight)	104 (31.5)
BMI ≥ 30	120 (36.4)
Diabetes	
Yes	107 (32.2)
No	225 (67.8)

BMI: body mass index. ($) The color was not informed by two individuals. (&) The level of physical activity was not verified in 56 individuals. (#) The BMI (kg/m²) was not evaluated in two individuals.

Table 2 – Main prescribed medications (n=332)

Name	N (%)
Diuretics	209 (63.0)
Hydrochlorothiazide	178 (53.7)
Furosemide	16 (4.8)
Chlorthalidone	10 (3.0)
Spironolactone	3 (0.9)
Indapamide	2 (0.6)
ACEi	192 (57.8)
Enalapril	108 (32.5)
Captopril	81 (24.4)
Lisinopril	1 (0.3)
Ramipril	1 (0.3)
Cilazapril	1 (0.3)
BB	89 (26.8)
Atenolol	53 (16.0)
Propranolol	27 (8.1)
Carvedilol	7 (2.1)
Metoprolol	1 (0.3)
Bisoprolol	1 (0.3)
CCB	84 (25.3)
Amlodipine	41 (12.3)
Nifedipine	37 (11.2)
Diltiazem	4 (1.2)
Verapamil	1 (0.3)
Lercanidipine	1 (0.3)
ARB	61 (18.4)
Losartan	52 (15.7)
Valsartan	9 (2.7)
Others	14 (4.2)
Clonidine	8 (2.4)
Hydralazine	4 (1.2)
Aliskiren	1 (0.3)
Methyldopa	1 (0.3)

ACEi: angiotensin-converting enzyme inhibitors; BB: beta-blockers; CCB: calcium channel blockers; ARB: angiotensin receptor blockers.

commonly found. The use of losartan potassium twice daily, prescribed in approximately 30% of the cases, was not considered a non-compliance despite a recommendation by the VI DBH of a single daily dose, since the prescription of two daily doses has pharmacological support[24] and is recommended by other guidelines.

The rate of achievement of the BP goals according to the VI DBH was 44.9%.[21] When we considered a lower cut-off point in the case of diabetic patients (target of 130/80 mmHg), the control rate dropped to 38.6%. The BP control showed no significant association with the compliance of the prescription (Table 5). The achievement of the BP target among patients with a compliant prescription was 32.5% when the goal was BP < 140/90 mmHg and 28.6% in the case of diabetic patients with a BP goal < 130/80 mmHg.

We conducted subgroup analyses to identify differences related to the characteristics of the population. We found no significant correlation between the compliance rate

Table 3 – Main associations of medications (n=332)

Type of therapy	Prescriptions N (%)	Diuretics N (%)	ACEi N (%)	BB N (%)	CCB N (%)	ARB N (%)
Monotherapy	115 (34.6)	25 (21.7)	61 (53.0)	8 (7.0)	7 (6.1)	14 (12.2)
Dual therapy	136 (41.0)	112 (41.6)	85 (31.6)	30 (11.2)	24 (8.9)	18 (6.7)
Triple therapy	60 (18.1)	50 (28.8)	34 (19.5)	34 (19.5)	35 (20.1)	21 (12.1)
> 3 medications	21 (6.3)	21 (27.6)	12 (15.8)	17 (22.4)	18 (23.7)	8 (10.5)

ACEi: angiotensin-converting enzyme inhibitors; BB: beta-blockers; CCB: calcium channel blockers; ARB: angiotensin receptor blockers.

Table 4 – Main non-compliances encountered

Prescribed Medication	Total	Underdosing	Overdosing	Underfrequency	Overfrequency	Triple therapy without diuretic	Wrong association
	N (%)	N (%) medication	N (%) medication	N (%) medication	N (%) medication	N (%)	N (%) medication
Diuretics	11 (16)	0	0	0	2 (18) HCTZ	8 (73)	1 (9) HCTZ + Chlorthalidone
ACEi	20 (29)	1 (5) Enalapril	0	10 (50) Captopril	3 (15) Enalapril	-	6 (30) ACEi + ARB
BB	15 (21.7)	3 (20) PPL	0	3 (20) Carvedilol 7 (47) PPL	2 (13) Atenolol	-	-
CCB	18 (26.1)	3 (16.7) Nifedipine 3 (16.7) Diltiazem	4 (22.2) Amlodipine	8 (44.4) Nifedipine	0	-	-
ARB	0	0	0	0	0	-	ARB + ACEi #
Other (Clonidine / Hydralazine / Methyldopa)	5 (7.2)	2 (40) Hydralazine	0	2 (40) Hydralazine	0	-	1 (20) Clonidine + HCTZ
TOTAL	69 (100)	12 (17.4%)	4 (5.8%)	30 (43.5%)	7 (10.1%)	8 (11.6%)	8 (11.6%)

ACEi: angiotensin-converting enzyme inhibitors; BB: beta-blockers; CCB: calcium channel blockers; ARB: angiotensin receptor blockers; PPL: propranolol; HCTZ: hydrochlorothiazide.
#: The association ACEi + ARB (six prescriptions) was counted only once, although it was described as non-compliant in regards to ACEi and ARB.

Table 5 – Relationship between BP control and prescription compliance according to cut-off points

	BP < 140 / 90 mmHg All patients			BP < 140 / 90 mmHg BP < 130 / 80 mmHg – diabetic patients		
	C	NC	p	C	NC	p
Prescription	N(%)	N(%)	0.75	N(%)	N(%)	0.6
Non-compliant	24 (16.1)	40 (21.9)		22 (17.2)	42 (20.6)	
Compliant	125 (83.9)	143 (78.1)		106 (82.8)	162 (79.4)	
Total	149 (44.9)	183 (55.1)		128 (38.6)	204 (61.4)	

C: controlled; NC: not controlled; p: p-value (Pearson's chi-square test).

and BP control in different subgroups (elderly or sedentary individuals, women, alcoholics, smokers, blacks, and obese). A lower BP control rate was only observed in the group of elderly individuals (> 60 years), corroborating data from the literature.[25]

Discussion

In the present study, we observed that the rate of compliance of medical prescriptions of antihypertensive drugs with the VI DBH[21] recommendations was 80%. We found no publications in the consulted bases directly assessing the

degree of compliance of prescription of antihypertensive drugs. A study in the evaluation of patterns of prescription of ACEi to users of the Brazilian Unified Health Care System (*Sistema Único de Saúde,* SUS) has shown that the average prescribed doses of captopril and enalapril maleate followed the doses recommended by the VI DBH,[21] with only 0.3% of the patients using captopril overdoses and 0.65% using enalapril overdoses.[26] A study on the compliance with the guidelines of the Brazilian Society of Cardiology in regards to heart failure[27] revealed a significant gap between the practice in the primary network and the Brazilian guidelines, contrasting with what we observed in the present study in regards to hypertension.

Several studies have evaluated the most often used antihypertensive drugs in Brazil[28,29] and demonstrated the preference for thiazide diuretics, particularly hydrochlorothiazide. Other studies have also demonstrated a preference for the prescription of ACEi in public health units.[26,30] The findings of our study followed the same direction: the main prescribed medications by family doctors were diuretics and ACEi.

As for the number of medications used, we observed that monotherapy and dual therapy were the most frequent, which is compatible with Brazilian and international hypertension studies.[28,31] The most frequent association of drug classes was that of diuretics with ACEi, a fact that is also in agreement with the literature.[32] Among the non-compliances found, underdosing and underfrequencies predominated, suggesting that physicians are often slow or too cautious to intensify the antihypertensive treatment, possibly due to fear of adverse effects. We highlight the underfrequency with which captopril and nifedipine extended release were prescribed. Although the VI DBH recommend a minimum administration of twice daily, in practice many doctors are observed to prescribe these drugs only once a day.[33]

Among patients who used underdoses of negative inotropes (propranolol and diltiazem), none had a heart rate below 60 bpm, suggesting that dose escalation was an option. A possible non-compliance related to beta-blockers was the administration (especially of atenolol) to elderly individuals and patients without coronary artery disease. However, these drugs were included in the list of options for treatment of hypertension, according to the guideline in effect at the time of the data collection, and are even included in the group of drugs distributed free of charge by the government. Although these are currently known not to be antihypertensive drugs of choice, these options were considered as compliant.

We identified a lower rate of prescription of less usual medications, such as hydralazine, diltiazem, or clonidine; additionally, more than 50% of the cases of prescription errors of any kind involved these drugs. All patients using underdoses of hydralazine had systolic BP ≥ 160 mmHg and could have the doses of this medication adjusted.

We observed the non-recommended association of ACEi with ARB in 3.7% of the total ACEi prescriptions. This value corresponds to 11.5% of the total ARB prescriptions. This association is currently no longer accepted,[34] but it was tolerated when recommended with caution in patients with proteinuria, according to the VI DBH.[21] It should be noted that we did not evaluate the occurrence of proteinuria in the individuals evaluated in this study. However, among the patients who used ACEi associated with ARB, only one was diagnosed with chronic renal disease, corroborating the fact that the association of these medications was indeed not compliant.

Among the patients treated with three or more medications, about 90% used diuretics, showing that family doctors usually associate one diuretic in cases of multiple therapies, as recommended by the guidelines.[7,21] With regard to the diuretics chosen, we observed that 4.8% of the patients used furosemide. Unless these individuals had some justifiable associated edematous condition (such as heart failure, chronic kidney disease, liver failure, glomerulopathy, etc.), this could have been a wrong indication. However, this was not considered a non-compliance, since this drug was part of the list of options for the treatment of hypertension, according to the VI DBH.

With respect to BP control, we found that 44.9% of the patients had BP levels within the target value < 140/90 mmHg. Obviously, there were lower rates of BP control when the target was reduced to < 130/80 mmHg in hypertensive patients with diabetes. A North-American survey[35] has shown an estimated rate of 50.1% of BP control in 2008. On the other hand, a study in 5,023 adults in 2003 in Portugal showed that only 11.2% of the patients had BP control,[36] while a study with more than 120,000 patients between 2005 and 2011 in Italy showed a control rate of 33.6%.[37] In Canada, in 2009, the percentage of hypertensive patients with BP < 140/90 mmHg was 64.6%.[38] The levels of BP control found in the present study are consistent with other Brazilian studies.[8] A recent review has shown highly variable rates of BP knowledge (22% to 77%), treatment (11.4% to 77.5%), and control (10.1% to 35.5%), depending on the population studied.[39] It should be pointed out that among all the cited studies of BP control, only two Brazilian studies[8] included participants aged above 45 years, as in the present study. Knowing that the maintenance of BP < 140/90 mmHg is more difficult at more advanced ages, it can be said that in this study the frequency of BP control achieved values close to the largest values ever reported in Brazil, despite having been below 50%.

There was no statistically significant correlation between the compliance of the prescription and BP control, suggesting that the prescription, even in doses and frequencies different from those recommended by the VI DBH,[21] was not a determinant factor in the achievement of BP goals.

Because this was a cross-sectional study, the evaluation of compliance was based on the prescription at the moment prior to the BP measurement. In other words, a prescription regarded as compliant could have the doses of the medications not yet optimized or an insufficient number of medications to achieve the desired BP goal. Also, due to the cross-sectional design of the study, the BP was measured at a single moment, which could have missed an inadequate BP control over time, or a white coat effect.[40] Similarly, another limiting factor may

have been the indication of an appropriate BP control in individuals who in fact had masked hypertension.[41]

It is worth noting that the present study evaluated the medical assistance given to hypertensive patients based on two quality aspects: the prescribed treatment and BP control. However, it is difficult to establish a direct correlation between prescription compliance and BP control, considering that a proper BP control is the result of a rather complex system involving biological, genetic, and socioeconomic factors, as well as cultural and structural sanitary aspects. We also must mention the importance of non-pharmacological measures in BP control. In this study, we did not assess non-pharmacological recommendations, which could have contributed to a better BP control. Furthermore, it can be inferred that possible non-evaluated failures in adherence or the need of a more intensive treatment, with a greater number or higher doses of medications, may be factors that contributed to a better BP control in these individuals. We did not consider the adherence to BP control because the study was aimed at analyzing the effectiveness of the therapy, and not its efficacy. Possibly, the analysis of this set of factors involved in BP control would help to find a better correlation between treatment and BP goals. On the other hand, much has evolved in recent years regarding the optimization of antihypertensive treatment, so that drugs once recommended and widely prescribed are no longer considered to be first-line choices in hypertension treatment, which is why the correlation between prescription compliance and BP control may have failed in this study.

Further studies should be performed to try to elucidate other factors involved in proper BP control, allowing the definition of quality indicators that best correlate with BP control.

Conclusion

The degree of compliance was considered satisfactory. The rates of achievement of the recommended BP goals were compatible with those found in international studies and close to the highest values reported in Brazil. However, the achievement of the goals in 44.9% of the population in primary care, in which most of the patients are classified as having stage 1 and 2 hypertension without target organ damage, indicates that there is a long way to go and that the best investment to improve this parameter may be continuing education of physicians and other professionals involved in caring for hypertensive patients.

Author contributions

Conception and design of the research: Novello MF, Rosa MLG, Jorge AJL, Correia DMS, Martins WA; Acquisition of data: Novello MF, Rosa MLG, Ferreira RT, Nunes IG, Jorge AJL, Correia DMS; Analysis and interpretation of the data: Novello MF, Rosa MLG, Ferreira RT, Nunes IG, Jorge AJL, Martins WA; Statistical analysis: Novello MF, Rosa MLG, Ferreira RT, Nunes IG, Jorge AJL; Writing of the manuscript: Novello MF, Rosa MLG, Jorge AJL, Martins WA; Critical revision of the manuscript for intellectual content: Novello MF, Rosa MLG, Ferreira RT, Nunes IG, Jorge AJL, Correia DMS, Martins WA.

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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Impact of Different Normality Thresholds for 24-hour ABPM at the Primary Health Care Level

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Abstract

Background: Hypertension is an important risk factor for cardiovascular outcomes. Primary health care (PHC) physicians should be prepared to act appropriately in the prevention of cardiovascular risk factors. However, the rates of patients with control of blood pressure (BP) remain low. The impact of the reclassification of high BP by 24-hour ambulatory BP monitoring (ABPM) can lead to different medical decisions in PHC.

Objective: To evaluate the agreement between the BP measured by a conventional method by PHC physicians and by 24-hour ABPM, considering different BP normal thresholds for the 24-hour ABPM according to the V Brazilian ABPM Guidelines and the European Society of Hypertension Guidelines.

Methods: A cross-sectional study including 569 hypertensive patients. The BP was initially measured by the PHC physicians and, later, by 24-hour ABPM. The BP measurements were obtained independently between the two methods. The therapeutic targets for the conventional BP followed the guidelines by the Eighth Joint National Committee (JNC 8), the V ABPM Brazilian Guidelines, and the 2013 European Hypertension Guidelines.

Results: There was an accuracy of 54.8% (95% confidence interval [95%CI] 0.51 – 0.58%) for the BP measured with the conventional method when compared with the 24-hour ABPM, with a sensitivity of 85% (95%CI 80.8 – 88.6%), specificity of 31.9% (95%CI 28.7 – 34.7%), and kappa value of 0.155, when considering the European Hypertension Guidelines. When using more stringent thresholds to characterize the BP as "normal" by ABPM, the accuracy was 45% (95%CI 0.41 – 0.47%) for conventional measurement when compared with 24-hour ABPM, with a sensitivity of 86.7% (95%CI 0.81 – 0.91%), specificity of 29% (95%CI 0.26 – 0.30%), and kappa value of 0.103.

Conclusion: The BP measurements obtained by PHC physicians showed low accuracy when compared with those obtained by 24-hour ABPM, regardless of the threshold set by the different guidelines. (Arq Bras Cardiol. 2017; 108(2):143-148)

Keywords: Hypertension; Risk Factors; Blood Pressure Monitoring, Ambulatory; Primary Health Care; Antihypertensive Agents.

Introduction

Hypertension, a chronic disease with an estimated prevalence of 40–45% in adults, is a recognized public health problem and the main cause of general mortality,[1] for which low rates of control still remain.[2] The hypertensive patient requires periodic medical care associated with adequate pharmacological therapy and lifelong lifestyle changes.[3] The contribution of 24-hour blood pressure (BP) assessment by ambulatory BP monitoring (ABPM) in the diagnosis, monitoring, and prognostic stratification of hypertension is clearly defined in the literature.[4]

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A national study compared the BP classification according to new thresholds established by the VI Brazilian Guideline for Hypertension / V Brazilian Guideline for ABPM, in relation to those previously established by the IV Brazilian Guideline for ABPM.[5] The authors observed that the new thresholds substantially reclassified hypertension, increasing the percentage of hypertensive patients, especially for the variable systolic BP during sleep.[5] When considering different thresholds for 24-hour borderline BP / hypertension and normal BP / borderline BP, and the reclassification of hypertensive patients in regard to their control, it was observed that the samples of patients in the studies were similar in regard to antihypertensive treatment. Regarding the IDACO study, [6] the guidelines from the European Society of Cardiology (ESC) have maintained BP thresholds for the definition of hypertension by 24-hour ABPM as values greater than or equal to 130 mmHg for systolic BP and 80 mmHg for diastolic BP.[7]

Two questions of application in clinical practice regarding the care of the hypertensive patient remain little explored: the applicability and the importance of more

rigorous thresholds as criteria of normality for BP, and the prospective evaluation of the diagnostic accuracy between the different methods of BP measurement.[8] These inquiries arise from a need for prospective studies and elaboration of databases, preferably national ones, to allow a more adequate assessment of the ABPM normality thresholds for the hypertensive population, especially those attended by the primary health care (PHC) system.

This study proposed to evaluate the diagnostic accuracy of BP measurement by the conventional method, performed by PHC physicians, and the agreement of these measures with those obtained by the 24-hour ABPM, set as normality thresholds by the guidelines.

Methods

Delineation and participants

The participants of this cross-sectional study conducted at two health posts included hypertensive patients from Antônio Prado (RS), a city in the south of Brazil with 12,883 inhabitants.[9] All patients were hypertensive, were enrolled in the *Programa de Saúde da Família* (Family Health Program, PSF), took part in regular clinical follow-up at the hypertension outpatient clinic of the city's two *Unidades Básicas de Saúde* (Basic Health Units, UBS), and were on antihypertensive treatment for at least 6 months.

The samples were randomly selected from the total set of hypertensive patients enrolled in the UBSs, through random numbers generated by the program Microsoft Excel 2010. Patients were assessed by their own PHC physicians during routine visits to the hypertension outpatient clinic from January 2013 to October 2014. Patients who had participated in a previous cross-sectional study,[8] which included an assessment with 24-hour ABPM, were contacted by phone and/or letter to participate in this new study. Those who were not able to answer the questionnaire, pregnant women, individuals with a non-sinus rhythm electrocardiogram, residents from outside the coverage area of the UBSs, patients who switched cities or who were not found, and those who did not tolerate the use of ABPM or who presented some technical difficulty in the application of the method were excluded. Thus, out of the total of 639 patients, 28 were excluded from the study due to complications related to technical problems in the reading and failures in the adjustment of the ABPM cuff (18 patients), sleep disorders that prevented adequate BP measurements (8 patients), and intolerance of the equipment due to anxiety (2 patients).

All subjects agreed to participate in the study and signed an informed consent form. The results of the biochemical tests and ABPM performed during the study were delivered to the patients. The project was approved by the Research Ethics Committee (REC) of the IC/FUC - 4278.08.

Measurements performed

The BP was verified by the PHC physicians through three measurements with a mercury sphygmomanometer (the use of a mercury column sphygmomanometer is allowed in the state of Rio Grande do Sul, which follows the guidelines of the Resolution of the Collegiate Board of Directors no. 63, dated November 25, 2011, article 23) with orientation for individualized adjustment of the cuff, with the patients in a seated position and their feet resting on the floor and after a minimum rest period of 5 minutes. The physicians at the health centers were instructed to measure the BP in both arms, taking, as a reference, the highest value obtained after an approximate interval of 3 minutes between measurements. The first measurement was discarded, and the mean of the two subsequent measurements was calculated and recorded on the patient's chart. Then, during the same visit, the patient was referred to a nurse trained for this study who placed the device for the 24-hour ABPM, applied a standardized questionnaire, and obtained the anthropometric measurements. Subsequently, the patient's medical records were reviewed, biochemical exams were requested, and the ABPM report was prepared blindly by the investigating physician. The ABPM device was applied during a normal day of the patient's work activity, excluding days on the weekends and holidays. Based on prognostic evidence, the ABPM was selected as the standard reference for BP measurements and for assessing the diagnostic accuracy of the conventional BP measurement.[10]

The ABPM monitors used in the study were duly validated and calibrated according to international recommendations.[11] The ABPM recorder used was the DMS Brasil model TM 2430 and the model of the mercury sphygmomanometer was the MDF 800. The ABPM was scheduled to record a BP measurement every 15 minutes during the waking period and every 30 minutes during sleep. The schedules were adjusted according to the individualization of the sleep and awakening habits of each patient. The obtaining of data from at least 60 records in the 24-hour period was considered adequate, with at least two records every hour during the sleep period. The parameters assessed by the ABPM were the mean systolic and diastolic BP from the 24-hour, waking, and nocturnal periods. For the conventional measurements, uncontrolled hypertension was defined as the achievement of values ≥ 140/90 mmHg, according to the main hypertension guidelines. For the group of patients aged ≥ 60 years, guidelines from the Eighth Joint National Committee (JNC 8) were also adopted.[1]

Parameters and classification

In order to classify hypertension as uncontrolled, the ABPM criteria of the European Hypertension Guidelines and the Brazilian Hypertension Guidelines from the Brazilian Society of Cardiology were adopted.[12,13] Thus, patients with a mean BP of ≥ 130/80 mmHg in 24 hours, ≥ 135/85 mmHg in the waking period and ≥ 120/70 mmHg for the nocturnal mean BP for the first criterion were considered as having uncontrolled hypertension.[12] Whereas, when the guidelines of the Brazilian Guidelines for Hypertension were observed,[13] the values for BP used in the study were the borderline ones considered normal as cutoff point for the 24-hour averages: >125/75 mmHg, > 130/85 mmHg for the waking period, and > 110/70 mmHg for the mean BP during sleep.[14]

A ≤ 10% reduction in the mean nocturnal BP in relation to the daytime mean in the ABPM was defined as an absence

of nocturnal descent.[3] The white coat syndrome (WCS) was considered to be present when a patient on antihypertensive treatment had high BP, as measured in the clinic environment and/or under surveillance, but controlled BP in other situations.[15] Masked hypertension (MH) was characterized by the presence of a BP that was controlled when obtained with a conventional measurement, but high when obtained with ABPM or in-home measurements.[16] "Masking effect" was the term used when MH was observed in hypertensive patients using antihypertensive treatment. The same values for the normality criteria for 24-hour BP were considered for diabetic and nondiabetic patients.

Laboratory evaluation

In addition to BP measurements by the conventional method and the 24-hour ABPM, the biochemical profile of the patients in this study was evaluated. Laboratory tests included total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, creatinine, blood count, glycosylated hemoglobin (fraction A1c), microalbuminuria, and fasting blood glucose. Anthropometric data, such as body mass, height, waist-hip ratio, and body mass index were also evaluated. The screening questionnaire also included validated instruments for the evaluation of smoking and nicotine dependence (Fagerström test), abusive alcohol consumption (Alcohol Use Disorders Identification Test, AUDIT), and adherence to treatment using the Morisky Medication Adherence Scale.[8]

Statistical methods

Data entry and analysis were performed using the SPSS statistical software, version 21.0. Descriptive statistics were performed with continuous variables (mean and standard deviation) and categorical variables (frequency distribution). The estimated sample size was 398 patients and was based on the previous cross-sectional study conducted at the same site of the current study and on BP control rates of 55% for ABPM and 41% for conventional measurements performed by the PHC physicians for a confidence interval of 95% (95%CI) and 80% power. The sample was considered representative of the PHC service in the city of Antônio Prado (RS) because it was randomly selected at the two health posts with hypertension outpatient clinics, out of a total of 1,216 patients enrolled in this system. The hypertension care units, where the study was conducted, are referential units of the PHC in the city.

The comparison between the subgroups was performed using the chi-square test, Mann-Whitney U test (for continuous variables with non-homogeneous variances), and Student's *t* test (for variables with homogeneous variances). To analyze the agreement between the techniques of BP evaluation, kappa statistics was used. A multivariate analysis was also performed for cardiovascular risk factors and agreement of BP control, according to the 24-hour ABPM compared with conventional BP. P values < 0.05 were considered significant.

Results

Between January 2013 and October 2014, a consecutive sample of 639 hypertensive patients enrolled in the hypertension outpatient clinic of two health posts in the city of Antônio Prado (RS) was selected from a total of 1,216 patients. ABPM was applied in 611 patients who remained in the study after application of the exclusion criteria, shortly after conventional BP measurements by PHC physicians. The final sample comprised 569 patients after exclusion of patients who abandoned the research protocol or who presented inadequate ABPM measurements. No patient required medical care due to the compressive action of the ABPM cuff, whose reported events included: local discomfort (22 patients), mild local erythema (6 patients), and short-term paresthesia in the limb used for placing the cuff (2 patients). Table 1 summarizes the demographic profile and lifestyle of the patients.

In relation to BP measured by the conventional method *versus* 24-hour ABPM, we observed an accuracy of 54.8% (95%CI 0.51 – 0.58%) and, when considering the European Society of Hypertension Guidelines, a sensitivity of 85% (95%CI 80.8 – 88.6%), a specificity of 31.9% (95%CI 28.7 – 34.7%), and a kappa value of 0.155. When more stringent thresholds were used to characterize BP as "normal" by ABPM, we identified an accuracy of 45% (95%CI 0.41 – 0.47%) by the conventional measurement when compared with 24-hour ABPM, in addition to a sensitivity of 86.7% (95%CI 0.81 – 0.91%), a specificity of 29% (95%CI 0.26 – 0.30%), and a kappa value of 0.103 (Table 2).

The prevalence of WCS and the masking effect in treated hypertensive patients was 3.1% and 46.9%, respectively, when considering the European Hypertension Guidelines for ABPM. On the other hand, the prevalence of WCS

Table 1 - Demographic profile and lifestyle of the patients in the sample

Variável	Total (n = 569)*
- Female n (%)	339 (59.6%)
- Age (years)	60.32 +/- 13.58 (20-89)
- White	504 (88.1%)
- BMI **	28.54 +/- 4.57 (19-46)
- Fasting blood glucose (mg/dL)	100 +/- 26.89 (47-279)
- Glycosylated hemoglobin	6.14 +/- 4.52 (2.7–11.2)
- Total cholesterol (mg/dL)	203.9 +/- 40.28 (88-453)
- HDL-cholesterol (mg/dL)	52.73 +/- 12.51 (39.1-66.2)
- LDL-cholesterol (mg/dL)	121.36 +/- 33.78 (14-241)
- Triglycerides (mg/dL)	155.98 +/- 136.55 (35-2446)
- Creatinine (mg/dL)	0.88 +/- 0.27 (0.41-3.09)
- Smoking n (%)	32 (5.6%)
- Alcohol consumption n (%) (> 30 g/day)	174 (30.6%)
- Microalbuminuria > 30 mg/dL n (%)	151 (26.4%)
- Physical activity n (%)	276 (48.5%)
- Physical activity > 150 min/week n (%)	148 (53.6%)

** Standard deviation, percentage and maximum and minimum values; ** body mass index (kg/m2).*

Table 2 – General accuracy for conventional measurement of blood pressure (BP) according to the various normality thresholds for 24-hour ambulatory blood pressure monitoring (ABPM) *

	Accuracy	Sensitivity	Specificity	95%CI	kappa
ABPM 130/80 mmHg* X BP Conventional Method	54.8%	85%	31.9%	0.513-0.580	0.155
ABPM 125/75 mmHg X BP Conventional Method	45%	86.7%	29%	0.418 – 0.475	0.103
ABPM 130/80 mmHg* X BP JNC 8**	51.8%	88.5%	23.8%	0.485 – 0.546	0.111
ABPM 125/75 mmHg X BP JNC 8**	40.6%	89.8%	21.6%	0.377 – 0.428	0.072

** ESC 2013 and Joint 8 ** SBP normal ≤ 150 mmHg. 95%CI: 95% confidence interval; JNC 8: Eighth Joint National Committee.*

and MH was 2% and 56.1%, respectively, according to the different cutoff criteria for ABPM normality. When we considered the JNC 8 recommendations for conventional measurements, the prevalence of WCS and MH presented a slight variation. The prevalences according to the various parameters of ABPM and conventional measurement is shown in Table 3.

Discussion

The present study, including hypertensive patients receiving PHC, showed differences in accuracy and agreement between BP measurements performed by PHC physicians according to the different parameters of normality for 24-hour ABPM, as determined by the European Hypertension Guidelines and by the V Brazilian Guidelines for ABPM, respectively. The main result was the low accuracy of the conventional measures when compared with those obtained by the 24-hour ABPM, regardless of the guideline or cutoff point adopted for normal 24-hour ABPM. Regarding the differences in normality thresholds for 24-hour ABPM, when more stringent BP control targets were used, the accuracy of conventional measurements was even lower.

The vast majority of hypertensive patients are assisted by the PHC system,[17] in which physicians play a relevant role in the search for better results in BP control. In addition, the use of auxiliary methods for BP measurements to assess the adequacy of antihypertensive treatment has not been widely adopted in PHC.[15] In a national study using ABPM, a high degree of reproducibility was observed between casual measurements performed by non-medical professionals and those performed in an environment with a high standard of standardization in BP measurement.[18] However, although casual BP measure is still the standard for hypertension diagnosis and control, its adoption with the rigor of controlled studies is not a reality in the current clinical practice of PHC. Additionally, the 24-hour BP assessment is the reference standard for prognostic evaluation, reduction of false diagnoses, and BP control evaluations.

In another national study with a retrospective analysis of ABPM examinations,[5] the impact of the reclassification of BP control thresholds was evaluated according to the application of the last two Brazilian ABPM Guidelines. With the adoption of the current guidelines, all modified thresholds reclassified the exams significantly. The present study, however, sought to prospectively assess the impact of adopting different thresholds of normality for ABPM in comparison with measures performed by PHC physicians. The results, in terms of accuracy, were similar to those of other studies that indicated a low accuracy of BP obtained by conventional measures compared with that obtained by ABPM,[8] but with unique results when comparing different guidelines for 24-hour mean pressure thresholds.

Current guidelines for hypertension recommend satisfactory BP control for cardiovascular protection in both primary and secondary prevention.[19] The extent of agreement between the classification of controlled and uncontrolled BP, based on conventional measures and compared with 24-hour ABPM, is of strategic importance in PHC. The search for normality thresholds for 24-hour ABPM is based on cardiovascular outcomes,[14] having the IDACO study database as an example of a population benchmark. These results guided the normality targets for ABPM in the different guidelines for hypertension. Thus, the adoption of normality criteria for ABPM as a gold-standard auxiliary method for the control, evaluation and prognostic stratification of hypertension[4] should ideally be supported by a database that reflects population specificities.

The Systolic Blood Pressure Intervention Trial (SPRINT) study[20] presents evidence of benefits for BP control in hypertensive patients with stringent measures for systolic pressure (< 120 mmHg) compared with a more flexible control (< 140 mmHg). Therefore, evidence of reduced outcomes with more stringent cutoff points for BP control may lead to substantial changes in future revisions of hypertension guidelines.[20] Thus, this need is in agreement with the evaluation of the impact on the diagnostic accuracy of usual methods of BP in comparison with the different thresholds of normality for the gold-standard BP evaluation.

Table 3 – White coat effect and masked hypertension according to the parameters of 24-hour ambulatory blood pressure monitoring (ABPM) and conventional measurement of blood pressure (BP)*

	White Coat Effect	Masked
ABPM 130/80 mmHg* X BP Conventional Method	6.5% (37)	38.7% (220)
ABPM 125/75 mmHg X BP Conventional Method	3.7% (21)	51.3% (292)
ABPM 130/80 mmHg * X BP JNC 8**	5% (28)	43.3% (244)
ABPM 125/75 mmHg X BP JNC 8**	2.8% (16)	56.6% (319)

** ESC 2013 e Joint 8 ** PAS normal ≤ 150 mmHg. JNC 8: Eighth Joint National Committee.*

The adoption of the 24-hour ABPM through a single measurement in our sample may be considered a limitation of the present study. This may imply a limitation in the reproducibility of the measurements, especially when considering the evaluation of the nocturnal decreasing BP pattern. However, to mitigate this potential limitation, precautions were taken, such as the individualization of the sleep and waking period, as well as a rigidity regarding the minimum number of measurements and the quality of the measurements during the 24 hours as criteria for inclusion in the study. These measurements followed the guidelines and recommendations of the Italian Society of Hypertension.[21]

The use of ABPM in PHC, as well as the impact of the reclassification of hypertension according to the different normality thresholds for 24-hour BP, may have implications for decision-making by PHC physicians. Thus, a more significant number of national studies may serve as a reference for the elaboration of future guidelines and indicate BP thresholds for therapeutic definition.

Conclusion

This study evaluated the use of 24-hour ABPM within the scope of the PHC. BP measurements assessed by PHC physicians presented low accuracy when compared with those obtained by 24-hour ABPM, regardless of the threshold used as a normality criterion.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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Which Coronary Lesions Are More Prone to Cause Acute Myocardial Infarction?

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Abstract

Background: According to common belief, most myocardial infarctions (MIs) are due to the rupture of nonsevere, vulnerable plaques with < 70% obstruction. Data from recent trials challenge this belief, suggesting that the risk of coronary occlusion is, in fact, much higher after severe stenosis. The aim of this study was to investigate whether or not acute ST-elevation MIs result from high-grade stenoses by evaluating the presence of coronary collateral circulation (CCC).

Methods: We retrospectively included 207 consecutive patients who had undergone primary percutaneous coronary intervention for acute ST-elevation MI. Collateral blood flow distal to the culprit lesion was assessed by two investigators using the Rentrop scoring system.

Results: Out of the 207 patients included in the study, 153 (73.9%) had coronary collateral vessels (Rentrop 1–3). The Rentrop scores were 0, 1, 2, and 3 in 54 (26.1%), 50 (24.2%), 51 (24.6%), and 52 (25.1%) patients, respectively. Triglycerides, mean platelet volume (MPV), white cell (WBC) count, and neutrophil count were significantly lower in the group with good collateral vessels ($p = 0.013$, $p = 0.002$, $p = 0.003$, and $p = 0.021$, respectively).

Conclusion: More than 70% of the patients with acute MI had CCC with Rentrop scores of 1–3 during primary coronary angiography. This shows that most cases of acute MI in our study originated from underlying high-grade stenoses, challenging the common believe. Higher serum triglycerides levels, greater MPV, and increased WBC and neutrophil counts were independently associated with impaired development of collateral vessels. (Arq Bras Cardiol. 2017; 108(2):149-153)

Keywords: Plaque, Atherosclerotic; Rupture; Myocardial Infarction; Coronary Restenosis; Collateral Circulation.

Introduction

An ST-segment myocardial infarction (STEMI) is the result of an abrupt rupture of a coronary atherosclerotic plaque and subsequent thrombosis. Most myocardial infarctions (MIs) are thought to follow the rupture of vulnerable plaques deemed nonsevere and with less than 70% obstruction.[1-3] This belief has been mostly founded on old studies and, as a result, has been debated in recent years. In these older trials, the time between the angiography and the index case was long; this may be problematic since noncritical lesions may progress to a more severe stenosis with time. Reflecting this issue, Alderman et al. published in 1993 a 5-year, prospective, follow-up study (the CASS trial) in which they suggested that the risk of coronary occlusion was much higher in severe compared with nonsevere stenoses.[4]

Collateral vessels develop distally from the ischemic area to compensate for the decreased blood supply distal to the lesions. These collateral vessels may preserve the myocardial function in the case of severe stenosis. In this study, we used the presence of coronary collateral circulation (CCC) as a marker of severe stenosis. Our hypothesis was that the finding of coronary collaterals distal to the culprit lesion would mean that the lesion responsible for the acute occlusion was already severe prior to the episode of acute MI. The aim of this study was to investigate in patients with an episode of acute STEMI whether this episode originated or not from high-grade stenoses.

Methods

We included retrospectively 207 patients who had undergone primary percutaneous coronary intervention (PCI) due to an acute STEMI at the Dumlupinar University Kutahya Evliya Celebi Education and Research Hospital during a 6 month-period between January 2012 and June 2012. The patients were selected from our catheter laboratory database. At least two physicians double-checked the database to guarantee the accuracy of the data.

The definition of STEMI comprised an ST-segment elevation greater than 1 mm in two or more contiguous precordial leads, or two or more adjacent limb leads, or new or presumed new left bundle-branch block with angina. The culprit lesion was defined as the lesion that received the intervention. Collateral blood flow distal to the culprit lesion was measured by two investigators using the Rentrop grading system:[5]

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Rentrop 0 — No visible filling of collateral vessels;

Rentrop 1 — Filling of collateral vessels without any epicardial filling of the artery to be dilated;

Rentrop 2 — Partial epicardial filling by collateral vessels of the artery to be dilated;

Rentrop 3 — Complete epicardial filling by collateral vessels of the artery to be dilated.

Only patients who had undergone primary PCI for acute STEMI were included in the study. Patients with acute coronary syndromes without ST elevation and those who did not undergo primary PCI were excluded.

The number and percentages of the patients who had CCC according to the Rentrop scoring system were calculated. We then divided the patients into two groups according to the rating of the collateral vessels and the Rentrop scores: patients with collateral vessels deemed "poor" (Rentrop 0–1) were included in group 1 and those with collateral vessels deemed "good" (Rentrop 1–3) were included in group 2.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables are presented as numbers and percentages. The normality of the data was tested with the Kolmogorov-Smirnov test. Numerical predictors were estimated with the Mann-Whitney U test, whereas categorical predictors were estimated with Pearson's chi-square test. Differences were considered statistically significant when $p < 0.05$. The variables with a p value below 0.1 were included in a multiple logistic regression analysis.

Results

Out of the 207 patients included in the study, 138 were males (67%) and 69 were females (33%). The mean age of the patients was 63 ± 11 years. In total, 153 patients (73.9%) presented CCC (Rentrop 1–3). The Rentrop scores were 0, 1, 2, and 3 in 54 (26.1%), 50 (24.2%), 51 (24.6%), and 52 (25.1%) patients, respectively (Table 1). The left anterior descending artery was the most common culprit artery (48.3%), followed by the right coronary artery (30.9%), and the circumflex artery (20.8%). The most common acute STEMI type was inferior MI (52%).

When we grouped the patients according to the adequacy of collateral vessel development as "poor" (Rentrop 0–1) and "good" (Rentrop 2–3), we found no significant differences between these groups in terms of baseline demographic and clinical characteristics. Triglycerides, mean platelet volume (MPV), white cell (WBC) count, and neutrophil count were significantly lower in the group with "good" collateral vessel development ($p = 0.013$, $p = 0.002$, $p = 0.003$ and $p = 0.021$, respectively).

Multiple logistic regression analysis showed that triglycerides levels (odds ratio [OR] 1.005, 95% confidence interval [95%CI] 1.001–1.008), MPV (OR 1.271, 95%CI 1.084–1.490), WBC count (OR 1.142, 95%CI 1.020–1.278), and neutrophil count (OR 1.159, 95%CI 1.040–1.292) were independent predictors of CCC (Table 2).

Discussion

Our study showed that the majority of the acute STEMIs originated from severe stenotic segments of coronary arteries. A total of 73.9% of our patients had coronary collateral vessels, indicating that the majority of the acute MIs originated from previous severe stenotic lesions. This finding challenges the historical belief that acute MI occurs as a result of abrupt rupture of nonsignificant (< 50% obstruction) coronary lesions.

This is a field with many controversies. Older studies supported the idea that coronary occlusion and acute STEMI due to sudden plaque rupture occur from nonsignificant coronary stenotic lesions.[6,7] Little et al.[1] conducted one such study in which they monitored 29 patients after coronary angiography until they presented MI. The mean follow-up time was 706 days. As a result, the initial stenosis was below 70% in 97% of the patients. They concluded that the majority of the cases of MI arose from nonsignificant coronary stenosis.[1] The major limitation of their study was that the time from the initial angiography to the acute MI was so long that nonsignificant coronary lesions could have progressed to high-grade stenosis during follow-up. In another study by Hackett et al.,[8] the authors found that the mean residual stenosis was below 70% in patients with acute MI after successful thrombolytic therapy. In 1993, Alderman et al. reported results of a prospective study showing that severe lesions were more likely to progress to total occlusion than mild ones after a follow-up period of 5 years.[4]

Results of more recent studies dispute these findings. Frobert et al.[9] conducted a study in 156 patients with MI who had spontaneous reflow or reflow after uncomplicated wiring at the first angioplasty. Using quantitative coronary analysis (QCA) programs to measure the severity of the culprit lesion, they found that the severity of the underlying lesion was > 50% in 151 (96%) patients and > 70% in 103 (66%) of them.[9] However, the main disadvantage of this method is that it excludes the presence of thrombus, since the presence of thrombi makes the lesion appear more severe than they really are. Manoharan et al.[10] performed thrombus aspiration after wiring the culprit lesions in patients with STEMI undergoing primary coronary angioplasty. They then measured the severity of the underlying coronary stenosis with QCA and found that only 11% of the culprit stenoses were below 50%.[10]

In our study, we used the presence of CCC and the Rentrop scoring system to assess the severity of the underlying lesions, instead of using thrombolytic application, thrombus aspiration, and recanalization (spontaneous or wiring), as done in other previous studies.

Table 1 – Distribution of the patients according to Rentrop scores

Rentrop score	Number of patients	%
0	54	26,1
1	50	24,2
2	51	24,6
3	52	25,1
1-3	153	73,9

Table 2 – Univariate and multivariate predictors of inadequate coronary collateral circulation (CCC, Rentrop 0 and 1)

Variable	Univariate analysis			Multivariate analysis		
	OR	p	95%CI	OR	p	95%CI
Triglycerides (TG)	(TG)	0.006	1.001-1.008	1.004	0.018	1.001-1.008
Mean platelet volume (MPV)	1.271	0.003	1.084-1.490	1.215	0.021	1.030-1.434
Neutrophil count	1.159	0.007	1.040-1.292			
White cell (WBC) count	1.142	0.022	1.020-1.278	1.142	0.020	1.021-1.278

TG, MPV, and neutrophil and WBC count were analyzed with forward stepwise multiple logistic regression. CI: confidence interval; OR: odds ratio.

In a study similar to ours, Khoo et al.[11] investigated the development of collateral vessels using the Rentrop grading system in 159 patients with acute MI. Of all patients, 95 (60%) had collateral vessels.[11] Their study supports our findings and was the first trial using CCC as a surrogate marker for underlying lesion severity. Our study is the second trial using this method but our sample size is larger than that in the study by Khoo et al. [11]

Collateral vessels are vascular connections from one coronary vessel to other high-grade, stenotic vessels.[12] This is an adaptation to ischemia. Although the exact mechanism for this occurrence is unknown, it has been suggested to be through the release of some growth factors in response to ischemia.[13] Collateral vessels have some beneficial effects, including reduced infarct size, preservation of ejection function, and reduction of postinfarction complications like rupture and aneurysm.[14-16] While coronary collaterals may supply enough blood flow during rest, they may not supply sufficient flow during exercise.[17]

The degree of collateral development varies among patients. It is not clear why some patients have a Rentrop score of 3 for collateral vessels, while others have a Rentrop 1 score. Several factors and markers have been identified as contributors to the development of coronary collateral vessels. The severity of the underlying coronary stenosis, proximal location of the lesion, symptom duration, and slow heart rates are described as clinical factors that influence the development of collaterals.[18-20] Granulocyte-monocyte–colony stimulating factor (GM-CSF) and granulocyte-colony stimulating factor (G-CSF), physical exercise, and external counterpulsation have also been found to positively affect the development of collaterals, whereas aging, obesity, and levels of uric acid and C-reactive protein have been found to have negative effects.[21-28]

We found in our study that higher levels of serum triglycerides, greater MPV, and increased WBC and neutrophil counts were independently associated with impairment of collateral vessel development. Akın et al.[29] reported that the level of serum triglycerides and ratio of neutrophil / lymphocyte (N/L) were independently associated with poor CCC development after multivariate regression analysis. MPV and WBC count were not different between the groups with poor and good CCC in their study. In our study, we did not find any significant association between N/L ratio and CCC, expect for the neutrophil count.

The association between MPV and CCC is unclear. Ege et al.[30] reported that MPV levels were significantly higher in patients with poor CCC and coronary artery disease (CAD). In contrast, Duran et al. reported that elevated MPV levels were independent predictors of a good CCC development in patients with acute coronary syndrome.[31] While Kadı et al. found that levels of high-density cholesterol (HDL-C) were associated with good CCC development,[32] we found that serum triglycerides level was positively associated with CCC development.

The presence of coronary collateral vessels may imply that the underlying stenosis is severe. In our study, we regarded patients with Rentrop 1–3 coronary collateral vessel development as having underlying high-grade ischemia causing stenosis. Our use of collateral vessel development as a surrogate marker of ischemia may reflect more reliably the physiological reality than methods to measure the anatomical calculation of lesion severity used in previous studies.

Study limitations

Collateral vessels of small caliber may not have been visible during coronary angiography. With that, we may have underestimated the presence of coronary collateral vessels.

The Rentrop scoring system is a subjective method to evaluate collateral vessel development. Coronary flow index is a better method for this evaluation, as it is a more objective and sensitive technique to determine the development of CCC. However, while it may evaluate CCC more accurately than Rentrop, it is an invasive technique and not easy to incorporate into routine clinical practice.

Conclusion

Most cases of acute myocardial ischemia originated from underlying high-grade stenoses, contrary to older belief. More than 70% of the patients with acute MI had CCC with Rentrop scores of 1–3 during primary coronary angioplasty. Higher serum triglycerides level, greater MPV, and increased WBC and neutrophil counts were independently associated with impairment of collateral vessel development.

Author contributions

Conception and design of the research, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Sen T; Acquisition of data: Sen T, Astarcioglu MA, Beton

O, Asarcikli LD, Kilit C; Analysis and interpretation of the data: Sen T, Astarcioglu MA, Beton O; Statistical analysis: Sen T, Beton O.

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.

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Original Article

Serotoninergic Modulation of Basal Cardiovascular Responses and Responses Induced by Isotonic Extracellular Volume Expansion in Rats

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Abstract

Background: **Isotonic blood volume expansion (BVE) induced alterations of sympathetic and parasympathetic activity in the heart and blood vessels, which can be modulated by serotonergic pathways.**

Objective: **To evaluate the effect of saline or serotonergic agonist (DOI) administration in the hypothalamic paraventricular nucleus (PVN) on cardiovascular responses after BVE.**

Methods: **We recorded pulsatile blood pressure through the femoral artery to obtain the mean arterial pressure (MAP), systolic (SBP) and diastolic blood pressure (DBP), heart rate (HR) and the sympathetic-vagal ratio (LF/HF) of Wistar rats before and after they received bilateral microinjections of saline or DOI into the PVN, followed by BVE.**

Results: **No significant differences were observed in the values of the studied variables in the different treatments from the control group. However, when animals are treated with DOI followed by BVE there is a significant increase in relation to the BE control group in all the studied variables: MBP (114.42±7.85 vs 101.34±9.17); SBP (147.23±14.31 vs 129.39±10.70); DBP (98.01 ±4.91 vs 87.31±8.61); HR (421.02±43.32 vs 356.35±41.99); and LF/HF ratio (2.32±0.80 vs 0.27±0.32).**

Discussion: **The present study showed that the induction of isotonic BVE did not promote alterations in MAP, HR and LF/HF ratio. On the other hand, the injection of DOI into PVN of the hypothalamus followed by isotonic BVE resulted in a significant increase of all variables.**

Conclusion: **These results suggest that serotonin induced a neuromodulation in the PVN level, which promotes an inhibition of the baroreflex response to BVE. Therefore, the present study suggests the involvement of the serotonergic system in the modulation of vagal reflex response at PVN in the normotensive rats. (Arq Bras Cardiol. 2017; 108(2):154-160)**

Keywords: **Serotonin; Serotonin Agents; Rats; Hypotalamic Paraventricular Nucleus; Arterial Pressure; Extracellular Fluid.**

Introduction

Isotonic blood volume expansion (BVE) induces the activation of several areas of the brain that are important in cardiovascular and neuroendocrine adjustments.[1,2] BVE activates baroreflex, which promotes hypotension and bradycardia through the excitation of two neural pathways. Hypotension involves excitatory projections of the nucleus of the solitary tract (NST) to the caudal ventrolateral area of the medulla oblongata, and when activated, promotes inhibition of the rostral ventrolateral area of the medulla oblongata, sympathetic-inhibitory pathway, which results in the decrease of sympathetic tone to the heart, reduction of total peripheral resistance, and increase of venous capacitance. Bradycardia involves an excitatory projection of the NST to parasympathetic preganglionic neurons in the dorsal motor nucleus of the vagus and nucleus ambiguous, leading to an increase of vagal efferent in the heart.[3,4]

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BVE also promotes an increase in the plasma concentrations of oxytocin (Oxt), mainly synthesized in the paraventricular nucleus (PVN) and in the supraoptic nucleus of the hypothalamus (SON).[4] Evidence that Oxt acts as an important neuromodulator of the autonomic control of the circulation stemmed from studies in which projections of the PVN to the NST were observed and reinforced by the observation that manipulations in PVN's oxytocinergic system resulted in deep alterations in cardiovascular responses to stress and peptidergic stimuli.[5-8]

The participation of serotonergic mechanisms (5-HT) in PVN responses has also been studied, especially 5-HT action on 5-HT_{1A} and 5-HT_{2A} receptors. Authors have demonstrated the presence of 5-HT_{1A} and 5-HT_{2A} receptors and their respective mRNA in PVN. Moreover, researchers have verified the co-expression of 5-HT_{1A} and 5-HT_{2A} receptors in PVN regions, and a sub-population of these neurons presented double marking, 5-HT_{2A}/Oxt, showing evidence of 5-HT participation in the activation of these receptors in PVN.[9,10] Raphe dorsal nucleus afference to PVN regions and the significant density of 5-HT receptors in these hypothalamic nuclei have been described by several authors, and these results show that neuroendocrine responses to volume alterations may be modulated by 5-HT activating 5-HT_{1A} and/or 5-HT_{2A} receptors in the PVN.[11,12]

Based on the neuro-anatomical evidence of PVN oxytocinergic projections to NST and in works that have demonstrated serotonin neuromodulation over Oxt secretion, which is increased during isotonic BVE, we aim to evaluate serotonergic neuromodulation over 5-HT_2 receptors in cardiovascular responses of the PVN in basal conditions or induced by BVE.

Methods

Animals

Thirteen male Wistar rats, weighing between 250-300 g in the beginning of the experiments were obtained and kept in the vivarium *Biotério da Disciplina de Fisiologia* at the University *Universidade Federal do Triângulo Mineiro* (UFTM), acclimatized to the controlled room temperature of 23 ± 2°C, with a light-dark cycle of 12h (light – 7 a.m. to 7 p.m.), with food and water *ad libitum*. These animals were divided into two groups: Control (N=8), and DOI (N=5). All experiments were done between 8 a.m. and 1 p.m., and were previously approved by the Ethics Committee on Animal Experimentation (CEUAUFTM) under protocol number 273.

Habituation of the animals to experimental procedures

To decrease the influence of stress promoting factors at the time of experiments, the rats were handled daily and trained, for seven days, with the maneuvers used in the experimental protocol, such as: cleaning of the cannula and soft massage in the supra-pubic region for at least one week before the experiment.

Experimental protocol

Cannulas in the PVN

The rats were anaesthetized with tribromoethanol (150mg/kg) and fixed to a stereotaxic device (*Insight Equipamentos – model ETX3/99, São Paulo, Brazil)*. Two anthropometric points of the skull – bregma (union point of sagittal and coronal sutures) and lambda (union point of sagittal and lambdoid sutures) – were used as a reference to level the animals' heads in the horizontal plane. The the bregma, we determined the points for the bilateral introduction of the cannula in the rats's PVN. In these points, we made trepanations of the skull bones with a spherical drill, by opening two orifices of approximately 1.5 mm in diameter. In the PVN, stainless steel cannulas (12 x 0.55 mm d.i) were bilaterally positioned in the brain per the coordinates: 1.2 mm caudal to bregma; 0.5 mm lateral to the median line; and 5.0 mm under the dura-meter, according to the coordinates from the Atlas by Paxinos and Watson.[13] The cannulas were positioned 2 mm above the PVN, and fixed to the skull with screws and acrylic dental resin. Metal chucks (0.3 mm d.i) were used to obliterate the cannulas. The rats received prophylactic injections of penicillin (20,000 units, i.m.). During the six days of recovery, before cannulation of the veins and femoral arteries, the rats were handled and trained daily for the procedure and cleaning of the chucks to reduce possible influences of stress responses due to animal manipulation.

Cannulation of femoral veins and arteries

For the cardiovascular record of the conscious animals, on the day before the experiment, the animals were anaesthetized with tribromoethanol (150 mg/kg) for the implantation of polyethylene catheters (PE-50 and PE-10) in the abdominal aorta through the femoral artery to record the BP, and in the femoral vein to perform the BVE. After implantation, the cannulas were properly filled with a physiological solution and subcutaneously exteriorized in the posterior region of the neck. Before starting to record, the cannulas were heparinized (heparin 2% in physiological solution) to avoid the formation of clots.

Cardiovascular records

After 24 hours of surgical recovery, the cannulas were washed with heparinized saline solution (0.1 mL of heparin sodium 25000 UI, Liquemine®, Roche, Rio de Janeiro, Brazil, dissolved in 20 mL of saline 0.9%). The arterial catheter was connected to a PA transducer (P23Db, Gould-Statham), and the signs of pulsatile BP were recorded in basal conditions for 30 minutes, and the signal was converted by an analogue-digital board (CODAS, with a sample frequency – 4 kHz, Di220 Dataq Instruments, Inc., Akron, OH, USA). During the experimental procedure, MBP and HR were derived from the pulsatile BP. During the recording, the animals stayed in a room with noise control, at a temperature of 27°C. After positioning of the animals and connection to the equipment, there was a 15-minute adaptation period before recording began. After adaptation of the animals and adequation of signal caption, we began the continuous recording of pulsatile BP for 30 minutes to obtain basal values of BP and HR.

Microinjections of saline or drug in the brain

Thirty minutes after recording began, saline (1.0 μg/200 ηL; n=8 animals) or serotoninergic dimethoxy-4-iodoamphetamine hydrochloride (DOI – 1.0 μg/200 ηL; n=5 animals) dissolved in physiological saline solution were bilaterally injected in the PVN of the rats using a Hamilton syringe (5 μL) connected by a PE-10 polyethylene tube to an injection needle introduced into the brain by the guide cannula, previously fixed to the brain. During and after the intracerebroventricular microinjections, animal records were done in a period of 30 minutes.

Blood volume expansion (BVE)

Sixty minutes after beginning the recording, some animals underwent BVE, performed through intravenous infusion (femoral vein) of isotonic NaCL (0.15 M) in a volume of 2 ml/100 g of body weight during 60 seconds. During and after BVE, animal records were done in a 15-minute period.

Recording of pulsatile BP

On the day of the experiment, between 8 and 9 a.m., the animals were weighed and the arterial cannula was connected to a pressure transducer; basal pulsatile BP was recorded for 30 minutes. After this period, the animals received microinjections of DOI in the PVN (1.0 μg/200 ηL; n=5 animals) or the same volume of vehicle (isotonic saline; n=8 animals). After 30 minutes, the animals underwent isotonic BVE (NaCl 0.15 M/ 2 ml100 g weight), and the

pressure was continuously recorded for another 15 minutes (Figure 1) (supplementary figure). After 75 minutes of recording, the animals were euthanized with thiopental sodium (100 mg/Kg) and their brains were removed and fixed in 10% formalin for a few days. Cross sections (40 μm thick) were done in the points of PVN injection with a freezing microtome (MICROM, model HM 5000 M). Histologic sections, assembled onto slides, were stained by the Nissl method and analysed for PVN injection points according to the Atlas by Paxinos and Watson.[13]

Study of the variability of BP and HR

Pulsatile BP was processed by a specific software that determined, beat-by-beat, SBP and HR values. HR, SBP, and DBP variability was also evaluated in the frequency domain, with the autoregressive spectral analysis method.[14,15]

Pulse Intervals (IP), SBP, and DBP time series, collected during 30 basal minutes, were divided into serial segments of 300 beats, and all successive segments overlapped in 50% with the previous segment (Welch method). Using stationary segments of the time series, autoregressive parameters were estimated through the Levinson-Durbin method, and the model order was chosen according to Akaike's criterion.[15] After that, over each individual stationary segment of 300 beats, spectral decomposition was done. Normalization of values minimizes interference of the total potency over the components; normalization procedure was done by diving the potency of the low frequency component (LF – 0,15-0,4 Hz) or the high frequency component (HF – 0,04-0,15 Hz) by the total spectral potency, from which we subtracted the potency of the very low frequency band (VLF – 0,01-0,20 Hz), and then multiplied the result by 100.[15] Spectral parameters obtained for each individual stationary segment of 300 beats were measured, and mean result values for the 30 basal minutes were collected for each animal. Quotient between LF and HF (LF/HF ratio) was used to express the sympathetic-vagal balance.[16]

Statistical analysis

Statistical analysis was done through the software R, version 3.3.0. The obtained results were presented as mean ± standard deviation of the mean. To confirm that all continuous variables were normally distributed, we used the Kolmogorov-Smirnov test, and afterwards, to evaluate the effects of groups and evaluations in relation to SBP, DBP, MBP, HR, and LF/HF variables we used the two-way ANOVA with measurements, and Bonferroni's method of multiple comparisons. Significance level was set at 5%.

Results

Table 1 shows the results (mean ± standard deviation of the mean) of the cardiovascular variables of the control group animals (C) and of the DOI group animals (D). No significant differences were observed in the control group between the values obtained in basal period (Cb), after microinjection with saline (Cm), and saline followed by isotonic BVE (Ce) in the variables MBP, SBP, and DBP. DOI microinjection (Dm) and DOI followed by BVE (De) significantly increased MBP (Figure 2), SBP, and DBP in relation to the control group (Ce) (114.42±7.85 vs 101.34±9.17; 147.23±14.31 vs 129.39±10.70; and 98.01±4.91 vs 87.31±8.61, respectively).

Animals in the control group presented significant difference in basal HR values (Cb), with microinjection of saline (Cm) and saline followed by BVE, in relation the DOI group with the same treatments (Db, Dm, and De) (354.14±29.53 vs 399.40±25.09; 356.14±32.09 vs 405.08±41.09 and 356.35±41.99 vs 421.02±43.32, respectively). DOI microinjection (Dm), and DOI followed by BVE (De), increased the LF/HF ratio in relation to control animals who received saline microinjection (Cm) and saline followed by isotonic BVE (Ce) (2.45±0.82 vs 0.55±0.22 and 2.32±0.80 vs 0.27±0.32, respectively).

All p values obtained from statistical analysis of the studied variables are depicted in Table 2 (supplementary data).

Discussion

Our study showed that isotonic BVE did not promote alterations in MBP, SBP, and DBP, or in HR and sympathetic-vagal ratio (LF/HF). As previously shown by other authors,

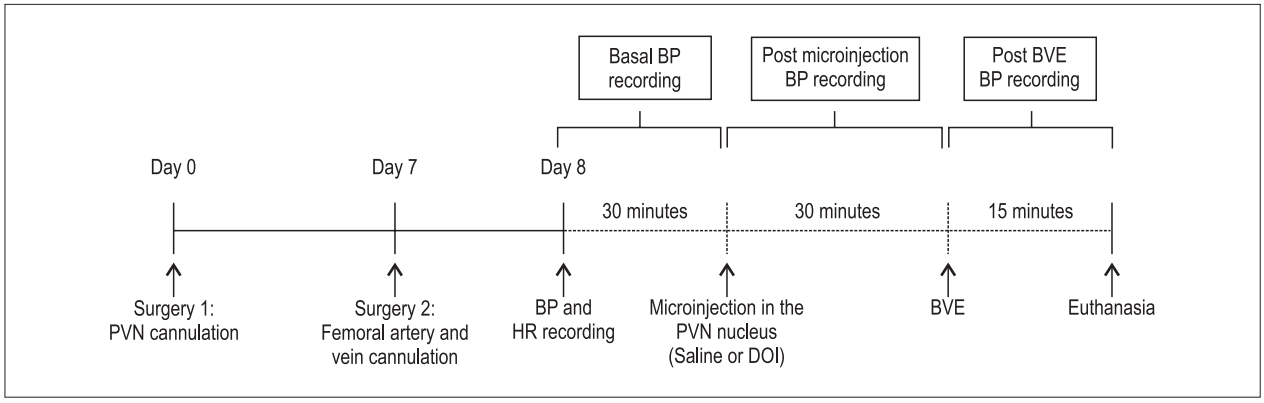

Figure 1 – *Representative scheme of the seven days of experimental protocol of the groups Control and Serotoninergic Agonist (DOI). PVN: paraventricular nuclei of the hypothalamus; BP, pulsatile BP; HR, BVE HR, extracellular volume expansion with isotonic saline (supplementary figure).*

Table 1 – Mean values (± standard deviation of the mean) of mean blood pressure (MBP), systolic blood pressure (SBP), and diastolic blood pressure (DBP), heart rate (HR), low frequency component (LF), and high frequency component (HF) of the animals of the basal control groups (Cb), post saline microinjection in the paraventricular nuclei of the hypothalamus (Cm), control after expansion of the extracellular volume (Ce), and those treated with DOI, in the basal state (Db), after DOI microinjection in the paraventricular nuclei of the hypothalamus (Dm), and after expansion of the extracellular volume (De)

Variables	Cb	Cm	Ce	Db	Dm	De
MBP (mmHg)	100.83 ± 7.98	99.79 ± 7.24	101.34 ± 9.17	105.65 ± 2.25	108.79 ± 9.31	114.42 ± 7.85$^{\#\,\lambda}$
SBP (mmHg)	130.28 ± 7.62	129.66 ± 6.49	129.39 ± 10.70	136.05 ± 2.74	141.11 ± 14.95	147.23 ± 14.31$^{\&*}$
DBP (mmHg)	86.10 ± 8.53	84.86 ± 7.97	87.31 ± 8.61	90.46 ± 3.63	92.63 ± 6.50	98.01 ± 4.91$^{+\,\%}$
HR (bpm))	354.14 ± 29.53	356.14 ± 32.09	356.35 ± 41.99	399.40 ± 25.09$^{\$}$	405.08 ± 41.09$^{\alpha}$	421.02 ± 43.32$^{\beta}$
LF/HF ratio	0.36 ± 0.20	0.55 ± 0.22	0.27 ± 0.32	0.67 ± 0.68	2.45 ± 0.82**	2.32 ± 0.80$^{\#\#}$

$^{\#}$p=0.018 vs MBP Ce; $^{\lambda}$p=0.016 vs MBP Db; $^{\&}$p=0.010 vs SBP Ce; *p=0.035 vs SBP Db;$^{+}$p=0.047 vs DBP Ce; $^{\%}$p=0.022 vs DBP Db;$^{\$}$p=0.034 vs HR Cb; $^{\alpha}$p=0.033 vs HR Cm; $^{\beta}$p=0.010 vs HR Ce; **p=0.001 vs LF/HF ratio Cm and Db; $^{\#\#}$p=0.001 vs LF/HF Ce eDb.

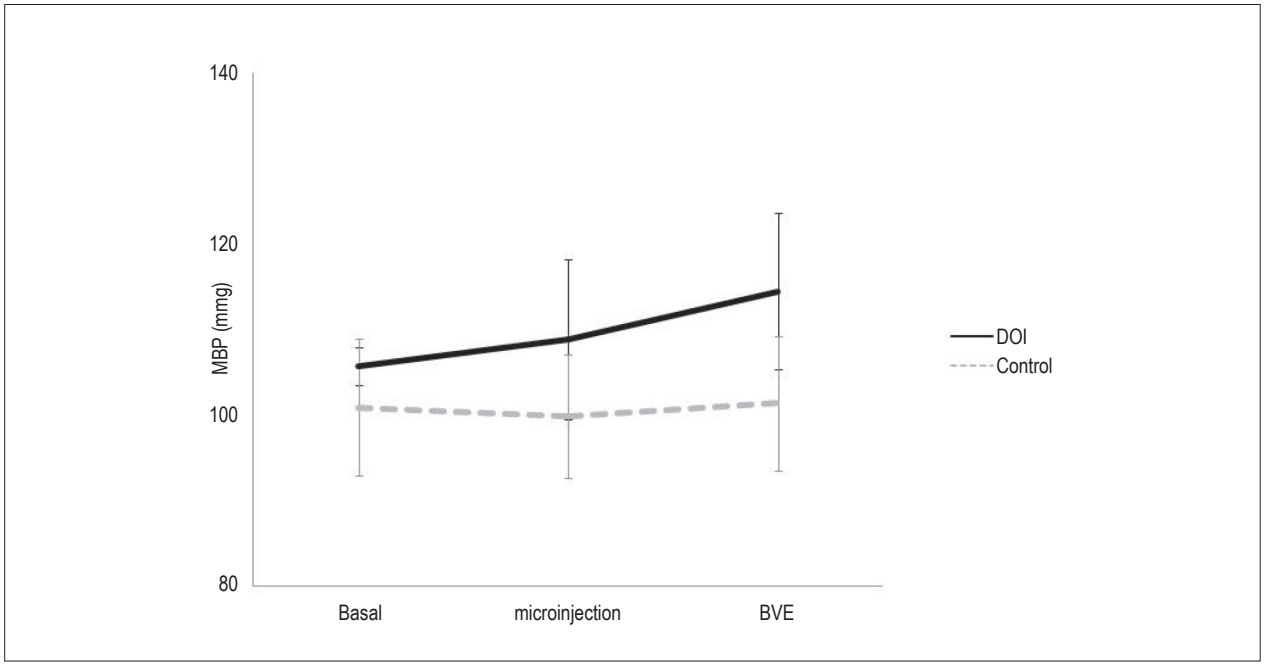

Figure 2 – *Mean values (± standard deviation of the mean) of the MBP of the basal control group animals (Cb), control after microinjection of saline (Cm), control after extracellular volume expansion (Ce) and those treated with DOI, in the basal state (Db), after DOI microinjection (Dm), and after extracellular volume expansion (De). $^{\#}$p=0.018 vs MBP Ce; $^{\lambda}$p=0.016 vs MBP Db.*

acute BVE induces a series of hemodynamic events, including an increase in central venous pressure, right atrial pressure, central and peripheral blood volume, cardiac debit, and systolic volume. On the other hand, HR decreases significantly, and total peripheral resistance decreases slightly during volume overload, while MBP remains unaltered.[17] These findings differ from those obtained by Godino et al., 2005, who performed BVE through infusion of a great intra atrial volume for one minute and observed a reduction not only in HR, but also in MBP. This hypotension can be mediated by a quick and pronounced release of oxytocin and atrial natriuretic peptide, which have a diuretic and vasodilatory effect.[18] Moreover, these peptides are involved in the baroreflex control of the HR, facilitating vagal response in the increase of reflex bradycardia during baroreceptor discharge.[19-23]

In the present work, the animals who received intracerebroventricular microinjection of the serotonergic agonist DOI in the PVN, followed by BVE, presented a significant increase in MBP, SBP, DBP, HR, and LF/HF, suggesting that the serotonergic agonist DOI leads to the inhibition of Oxt secretion as a response to BVE, when it is bilaterally microinjected into the PVN, or even that is exerts a neuromodulation in the PVN level, which then promotes an inhibition in the baroreflex response to BVE.

Table 2 – p values obtained after comparisons between the groups Control (n=8) and DOI (dimethoxy-4-iodoamphetamine) (n=5) of the studies variables: mean blood pressure (MBP), systolic blood pressure (SBP), and diastolic blood pressure (DBP), heart rate (HR), low frequency component (LF), and high frequency component (HF) of the animals of the basal control groups (Cb), post saline microinjection in the paraventricular nuclei of the hypothalamus (Cm), control after expansion of the extracellular volume (Ce), and those treated with DOI, in the basal state (Db), after DOI microinjection in the paraventricular nuclei of the hypothalamus (Dm), and after expansion of the extracellular volume (De). Variance analysis with repeated measurements and Bonferroni's multiple comparison method were employed in this study. Significance level was set at p<0.05

Comparisons	MBP	SBP	DBP	HR	LF/HF
Cb vs Cm	0.827	0.937	0.568	0.987	0.704
Cb vsCe	0.828	0.930	0.568	0.988	0.755
Cm vs Ce	0.820	0.934	0.560	0.980	0.704
Db vs Dm	0.293	0.234	0.418	0.730	0.001
Db vs De	0.016	0.035	0.022	0.503	0.001
Dm vs De	0.096	0.230	0.075	0.500	0.711
Cb vs Db	0.287	0.316	0.308	0.034	0.290
Cm vs Dm	0.077	0.076	0.110	0.033	0.001
Ce vs De	0.018	0.010	0.047	0.010	0.001

Intravenous administration of 8-OHDPAT (5-HT_{1A} receptor agonist) or DOI (5-HT_{2A} receptor agonist) promotes an increase in plasma concentrations of Oxt. Both responses are significantly attenuated when the animals receive intravenous pre-treatment with antagonists of these receptor, suggesting that this increase occurs by the serotoninergic activation of these receptors, instead of stimulation by interneurons.[11,12,24,25] 5-HT_{2A} receptors stimulation in the central nervous system can induce an increase in BP, partly through the increase in vasoconstrictor sympathetic activity due to sympathetic premotor neuron activation in the rostral ventrolateral medulla oblongata, and also through vasopressin release.[26]

PVN is reciprocally connected to several other areas of the brain involved in the cardiovascular function control.[27] PVN also contains pre-autonomic neurons, which directly and indirectly project to sympathetic preganglionic neurons inside the spinal cord mediolateral cell column, via the rostral ventrolateral medulla oblongata.[28]

Several studies have reported the contribution of PVN parvocellular neurons in the compensatory autonomic response during physical training for volume overload, suggesting that the volume overload stimulates vagal cardiac receptors, especially by the activation of PVN parvocellular neurons, which successively induces the inhibition of the sympathetic nervous activity.[29-35] Several works have suggested that the increase in neuron activity in the PVN is associated to sympathetic excitation during cardiac collapse.[36-38] Moreover, some works have found that an altered GABAergic mechanism in the PVN may be involved in the regulation of the sympathetic afferent in the cardiac collapse, and that alterations in the inhibitory mechanism can contribute to an increase in sympathetic activity.[39-40]

This is the first study to explore serotoninergic neuromodulation via 5-HT_{2A} receptors in the PVN level about cardiovascular responses to isotonic BVE, which proved to be inhibitory. However, it is noteworthy that further, more in depth studies are necessary to check if this neuromodulation directly affects sympathetic and/or baroreflex activity or if it is accompanied by neuroendocrine alterations, especially concerning Oxt, arginine, vasopressin, and atrial natriuretic peptide secretion.

Conclusion

The present work provides evidence that serotonin performs neuromodulation in the PVN level, which promotes an inhibition of the baroreflex response to BVE. Thus, this work suggests the serotoninergic involvement in the neuromodulation in the PVN level in the vagal reflex response in normotensive rats.

Author contributions

Conception and design of the research and Statistical analysis: Semionatto IF, Capitelli CS, Chriguer RS; Acquisition of data and Analysis and interpretation of the data: Semionatto IF, Alves AC, Capitelli CS, Chriguer RS; Writing of the manuscript: Semionatto IF, Raminelli AO, Capitelli CS, Chriguer RS; Critical revision of the manuscript for intellectual content: Capitelli CS, Chriguer RS

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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Non-Invasive Ventilation in Patients with Heart Failure: A Systematic Review and Meta-Analysis

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Abstract

Non-invasive ventilation (NIV) may perfect respiratory and cardiac performance in patients with heart failure (HF).

The objective of the study to establish, through systematic review and meta-analysis, NIV influence on functional capacity of HF patients.

A systematic review with meta-analysis of randomized studies was carried out through research of databases of Cochrane Library, SciELO, Pubmed and PEDro, using the key-words: heart failure, non-invasive ventilation, exercise tolerance; and the free terms: bi-level positive airway pressure (BIPAP), continuous positive airway pressure (CPAP), and functional capacity (terms were searched for in English and Portuguese) using the Boolean operators AND and OR. Methodological quality was ensured through PEDro scale. Weighted averages and a 95% confidence interval (CI) were calculated. The meta-analysis was done thorugh the software Review Manager, version 5.3 (Cochrane Collaboration).

Four randomized clinical trials were included. Individual studies suggest NIV improved functional capacity. NIV resulted in improvement in the distance of the six-minute walk test (6MWT) (68.7m 95%CI: 52.6 to 84.9) in comparison to the control group.

We conclude that the NIV is an intervention that promotes important effects in the improvement of functional capacity of HF patients. However, there is a gap in literature on which are the most adequate parameters for the application of this technique.

Introduction

HF is a clinical syndrome in which the heart has difficulty pumping blood, generating functional limitation with important cardiovascular, hemodynamic and metabolic alterations.[1-3] HF patients have reduced FC, which may limit their performance of daily life activities (DLA) and reduce quality of life (QL).[4-6] These alterations contribute to the increase of symptoms and to exercise intolerance, progressively reducing FC.[7]

Cardiac rehabilitation programs are being more and more recommended for this population, with the objective of minimizing the consequences of HF and improving the patient's QL. Cardiac rehabilitation is defined as a non-pharmacological treatment with an emphasis on the practice of physical exercise.[8]

Currently, some resources used in physical therapy are complementing a cardiac rehabilitation program for patients who initially cannot tolerate exercising. NIV with administration of CPAP is one of the utilized techniques. NIV may improve cardiac and respiratory performances of HF patients, considering it enhances oxygenation and pulmonary mechanics, so it can also improve FC.[7]

Traditionally, NIV has been used in respiratory insufficiency situations and in HF patients with the objective of reversing pulmonary edema and respiratory failure situations. The use of NIV and its effect on exercise tolerance have only recently started to be investigated, but there are controversies surrounding its efficacy and use in clinical practice. Systematic review with meta-analysis can solve conflict issues of individual studies and provide more reliable estimates of the efficacy of NIV use in HF patients. The aim of this work was to carry out a systematic review with meta-analysis about the use of NIV to improve FC in HF patients.

Methods

A systematic review was realized, observing the criteria established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[9]

Eligibility criteria

We included random clinical trials (RCT) that tested the use of NIV in patients over 18 years old, of both genders, with HF and without associated restrictive or obstructive pulmonary disease.

Evaluation measurements were: tolerance to effort; duration of exercise; perceived exertion; spirometry; lactatemia.

Data source and research

Article research was done with databases from PubMed, *Cochrane Library*, SciELO and Physiotherapy Evidence Database (PEDro). In this research we included original articles published in English, Spanish and Portuguese up to August of 2015.

The initial search strategy consisted of four key-words (study design, participants, interventions, and result

Keywords

Heart Failure; Noninvasive Ventilation; Exercise Tolerance; Review; Meta-Analysis.

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measurements). The utilized key-words were described from search terms Medical Subject Headings (MeSH) and Health Science Descriptors (DeCS) where, for the study design, we included: randomized clinical trial and controlled study. The group of participants used words referent to the disease such as HF, cardiac dysfunction or ventricular dysfunction. The key-words that were used for intervention were: NIV and exercise tolerance. The terms used for result measurements were: 6MWT, ergometry, ergospirometry, spirometry.

An experienced reviewer carried out the search and initial selection to identify the titles and abstracts of potentially relevant studies. Each abstract was assessed independently by two reviewers. If at least one of the reviewers considered a reference to be eligible, the article was obtained in its entirety. Both reviewers would then independently analyse the articles to select the ones to be included in the review. When there was a disagreement, the decision was made by the authors' consensus. A manual tracking of citations of the selected articles was also performed.

Methodological quality assessment of the studies

The quality of the studies was assessed using the PEDro scale – the most widely used in the area of rehabilitation. This scale is based on the Delphi list,[10] in order to measure the internal validity through the presence or absence of methodological criteria.[11] The PEDro scale is made up of the following criteria: 1) specification of inclusion criteria (non-scored item); 2) random allocation; 3) confidential allocation; 4) group similarities in the initial or basal phase; 5) masking of subjects; 6) masking of the therapist; 7) masking of the assessor; 8) measurement of at least one primary outcome in at least 85% of the allocated subjects; 9) analysis of intention to treat; 10) comparison between groups of at least one primary outcome; 11) reports of variability measurements and parameter estimates of at least one primary variable. For each defined criterion in the scale, one point (1) is attributed to the presence of evidence quality indicator, and zero (0) is attributed to the absence of these indicators.[11]

Statistical evaluation

Meta-analysis was done due to the similarity between studies in regards to the chosen intervention, patients' characteristics, and the variable distance covered in the 6MWT. Combined effect estimates were expressed as the mean difference between the groups. Statistical heterogeneity among the studies was assessed with Cochrane's Q test, and inconsistence test I^2, in which values above 25% and 50% were considered indicative of moderate and high heterogeneity, respectively. Calculations were done using a fixed effect model, due to the low heterogeneity. An α value of 0.05 was considered significant. Analysis was done using the Review Manager, version 5.3 (*Cochrane Collaboration*).

Results

We initially identified a total of 37 articles in the selected database research, 21 at PubMed, nine at SciELO, and seven at the Cochrane Library. After careful examination, 30 articles were excluded by title and/or abstract, and three by duplicate. The four remaining articles met the inclusion criteria and were selected, in their entirety, for reading (Figure 1).

Study methodological quality analysis

Methodological quality analysis of the studies that met the inclusion criteria was done by two researchers in an independent way, in which a mean value of 6.2 was found using the PEDro scale (Table 1).

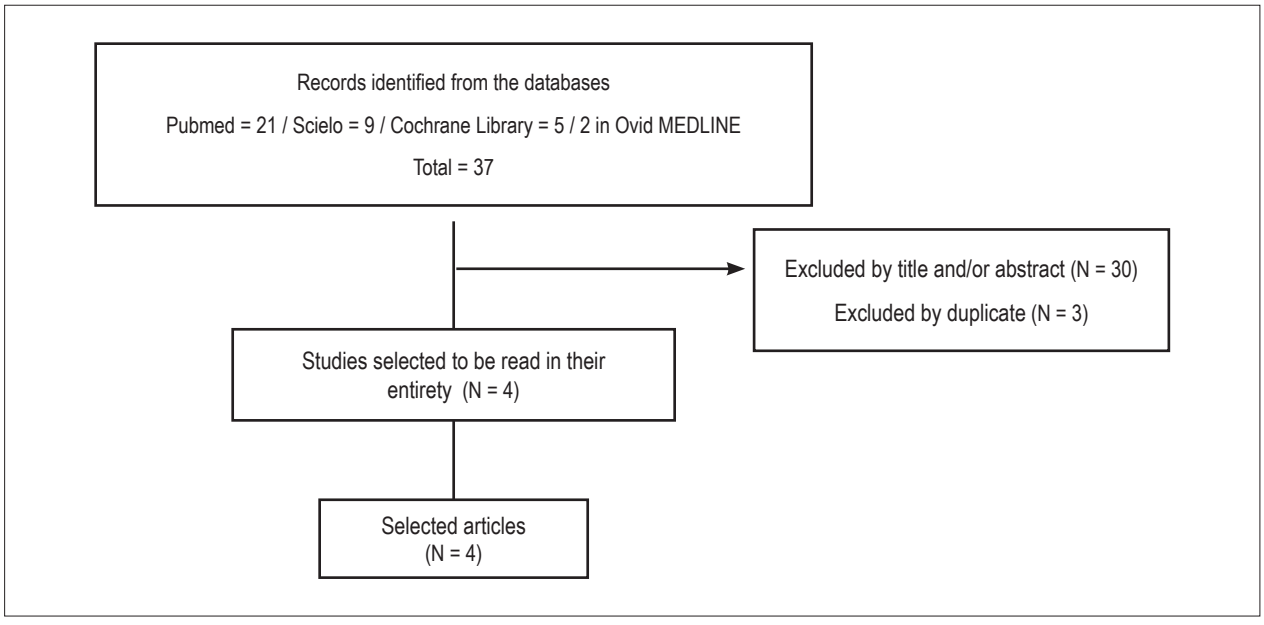

Figure 1 – *Flowchart of the article selection process.*

Table 1 – Quality assessment of studies through PEDro scale

	O'Donnell et al.[12]	Wittmer et al.[14]	Chermont et al.[13]	Lima et al.[7]
1		✓		✓
2	✓	✓	✓	✓
3				✓
4		✓		✓
5				
6				
7		✓	✓	
8	✓	✓	✓	✓
9				
10	✓	✓	✓	✓
11	✓	✓	✓	✓
Total:	4	6	5	6
				Mean: 6,2

Study characteristics

The four studies evaluated the impact of NIV in exercise tolerance of HF patients. Participants from all selected studies suffered from HF.[7,12-14] The period of study publication was from 1999 to 2011, and the studied population size varied between 12[7,12,13] and 22[14] patients, amounting to 58 studied individuals. Mean age of participants varied between 46[7] and 61[12] years of age. The four studies were done with a population made up of both genders.[7,12-14] In three of the studies, participants belonged to functional class II to III according to the NYHA,[7,13,14] and in one study, functional class varied between II to IV.[12]

Three of the studies used the 6MWT as an indicator of functional capacity of HF individuals,[7,13,14] and only one study used the exercise test on a cycle ergometer[12] as an evaluation tool.

Non-invasive ventilation support characteristics

As an interface for NIV application, two studies[13,14] chose the nasal mask, one study[7] used the facial mask, and another opted for the oral mask.[12]

Three of the studies opted for CPAP,[7,13,14] and one of them used CPAP and support pressure (SP).[12] Wittmer et al.[14] used CPAP of 8 cmH_2O; Chermont et al.[13] used a pressure of 3 cmH_2O for 10 minutes in the CPAP group, progressing to 4 to 6 cmH_2O, while in the placebo group, a pressure of 0 to 1 cmH_2O was fixed. Lima et al.[7] applied a pressure of 10 cmH_2O, whereas O'Donnell et al.[12] used CPAP and SP with positive end-expiratory pressure (PEEP) of 4.8 cm of H_2O, comparing it to a control that used only 1 cmH_2O.

The four selected articles that took part in the review used a control group and assessed the use of ventilator support in FC of HF patients.[7,12-14] Two of them used CPAP in one single session before the exercises;[7,13] one article used CPAP for 14 days;[14] and only one article used both ventilatory support models (CPAP and SP) during the exercise.[12]

Characteristics of the included RCTs and of the intervention are described in Tables 2 and 3.

NIV effects on FC and pulmonary function

All works evaluated NIV impact on FC of HF patients, and all studies found, after the use of NIV,[7,12-14] an increase in exercise tolerance.

Chermont et al.[13] observed an increase in tolerance to physical exercise with a longer distance covered in the 6MWT in HF patients, when they were submitted to 30 minutes of CPAP at 6 cmH_2O before the test.

These results confirmed the findings of Wittmer et al.[14] in their prospective randomized blind clinical trial, in which 22 patients (12 men and 10 women) were randomly divided to do 30 minutes of treatment with CPAP, respiratory exercises, and walking exercises (CPAP group), or respiratory exercise and walking exercise (control group) for 14 days. Through the 6MWT evaluation, one day before the treatment (day 0) and on the 4th, 9th, and 14th days of treatment, the authors observed that patients in the CPAP group showed progressive improvement in the distance covered during 6MWT, reaching approximately 28% of base values at the end of the treatment, whereas the control group showed no significant changes. Despite having found an improvement in the distance covered, the authors were not able to determine with certainty if this positive outcome was due to an improvement on pulmonary function or to hemodynamic alterations.

In the study by O'Donnell et al.,[12] the total time of exercise increased significantly during exercise with SP ($p = 0.004$), but only slightly with the use of CPAP ($p = 0.079$) in comparison to the control.

According to Lima et al.,[7] there was significant improvement in the distance covered during 6MWT after the use of CPAP in only one application session of 30 minutes.

Table 2 – Characteristics of studies included in the review

Study	Participants	Evaluation	Methods of evaluation			Results		
			Duration of exercise	Aerobic capacity	Dyspnea	Duration of exercise	Aerobic capacity	Dyspnea
O'Donnell et al.[12]	12 patients Men (11) Women (1) LVEF 35% FC/II/IV NYHA	Duration of exercise dyspnea	Time in minutes	No	BORG Scale	10.1±1.5 PS p < 0.01 8.7±1.1 CPAP p = 0.08 7.2 ± 1.0 control	No	p > 0.005
Wittmer et al. [14]	22 patients Men (12) Women (10) LVEF 45% FC/II/III NYHA	Aerobic capacity	No	6MWT	No	No	↑6MWT (p<0.05)	No
Chermont et al.[13]	12 patients Men (8) Women (4) LVEF 45% FC/II/III NYHA	Aerobic capacity	No	6MWT	No	No	↑6MWT (p<0.05)	No
Lima et al.[7]	12 patients Men (8) Women (4) LVEF 35% FCII/III NYHA	Aerobic capacity	No	6MWT	BORG Scale	No	↑6MWT (p<0.05)	P: 0.009

6MWT: six-minute walk test; SP: support pressure; CPAP: continuous positive airway pressure; NYHA: New York Heart Association.

Table 3 – Characteristics of interventions of studies included in the review

Study	Intervention time	Application time	Respiratory exercises	PEEP	NIVS (CPAP) Before exercise	NIVS (CPAP/SP) During exercise
O'Donnell et al.[12]	Session (1)	During exercise	No	PS/CPAP 4.8 cmH_2O Control 1 cmH_2O	No	Yes
Wittmer et al.[14]	Session (14)	30 minutes	3 x 10 repetitions SE/ DB/IH	CPAP 8 cmH_2O	Yes	No
Chermont et al.[13]	Session (1)	30 minutes	No	CPAP 4-6 cmH_2O Control 0-1 cmH_2O	Yes	No
Lima et al.[7]	Session (1)	30 minutes	No	CPAP 10 cmH_2O	Yes	No

NIVS: non-invasive ventilatory support; PEEP: positive end-expiratory pressure; SP: support pressure; CPAP: continuous positive airway pressure; SE: short expiration; DB: deep breath; IH: inspiratory hiccups.

Of the four studies we found, three evaluated pulmonary function.[12-14] In the study by O'Donnell et al.[12] basal parameters of pulmonary function were within normal limits, except for a small reduction in forced vital capacity (FVC) and a reduction of the expiratory reserve volume (ERV). However, during exercise, patients presented significant increases in the end-expiratory lung volume. Even though the study by Chermont et al.[13] cites that the patients were submitted to pulmonary function tests, it did not describe the results. Wittmer et al.[14] observed an increase in FVC in patients treated with CPAP, reaching a maximum value or 16% of the basal value on the 9th day of treatment, in comparison to the control group. In the same way, FEV1 values increased progressively, reaching a maximum value of 14% on the 14th day of treatment.

NIV effects on lactate concentration

Only the study by Lima et al.[7] evaluated the lactate concentration in HF patients after the 6MWT with previous application of CPAP. The patients who were submitted to NIV obtained a lower lactate concentration at the end of the test in comparison to controls.

NIV effects on the duration of exercise

Patients who used CPAP before the 6MWT walked a longer distance in meters than those in the control group.[7,13] The use of CPAP, added to the respiratory exercises and walking exercises, also induced a significant increase in the covered distance during the 6MWT in comparison to a control group that did only respiratory and walking exercises.[14] The use of SP in association to exercise on a cycle ergometer, in comparison to CPAP and placebo, was more effective in the evaluation of permanence time in the exercise on a cycle ergometer, and in the evaluation of subjective perceived exertion through the BORG scale.[12] There were also differences in the use of CPAP in comparison to the placebo. CPAP mode increased the duration of the exercise, with a smaller effort rate by the BORG scale.

Three studies evaluated the 6MWT. Of these, two evaluated the effect of one NIV session, while the third evaluated the effect of 14 sessions of NIV. The meta-analysis of the three showed (Figure 2) a significant difference in the 6MWT distance (68.7 m 95% CI: 52.6 to 84.9; N=58) for participants of the NIV group compared to controls. When combining only the two studies that used NIV in one single session, meta-analysis showed (Figure 2) a significant difference in the 6MWT distance (65.2 m 95% CI: 38.8 a 91.7; N=36) for participants in the NIV group in comparison to controls.

Discussion

This systematic review had the objective of identifying the scientific evidence on the impact of NIV on HF patients' FC. The results indicate a significant improvement on tolerance to exercise in HF patients after NIV intervention, in comparison to the control group.

NIV is being used as an important tool in the treatment of HF patients for the improvement of ventilatory efficiency during exercise.[15,16] This fact may be associated to factors such as improvement in oxygenation, attenuation of the metaboreflex, improvement in the ventilation/perfusion ratio (V/Q), airway patency and consequent reduction of ventilatory work and fatigue.[7,12,17]

HF patients present decreased tolerance to effort associated to an increase of dyspnea and muscle fatigue.[18] Previous use of CPAP increased the distance patients covered during the 6MWT and prolonged duration of exercise on the cycle ergometer when used simultaneously with exercises.[7,12-14]

Evaluation of HF patients is extremely relevant; thus, cardiopulmonary exercise testing (CPET) is the reference standard and the most specific test for ventilatory evaluation during physical exercise – it not only measures FC, which is directly linked to the severity of HF, it can also evaluate the patient's oxygen consumption (VO2). However, since the cardiopulmonary test is complex and costly, the 6MWT proves to be an efficacious tool in FC evaluation.[19]

The 6MWT can be related to daily physical activities, and so it is a submaximal test of simple execution and low cost. The 6MWT is an excellent option, able to assess FC, and working as a predictor of mortality in this population.[17-19] Moreover, studies report that the distance covered in the test is associated to the functional classification of the NYHA.[20-24]

The 6MWT has been used in three studies to evaluate the distance covered by the patients.[7,13,14] Lima et al.[7] found significant differences in the distance covered during the 6MWT in patients submitted to NIV with CPAP, in comparison to the control group. The study's results

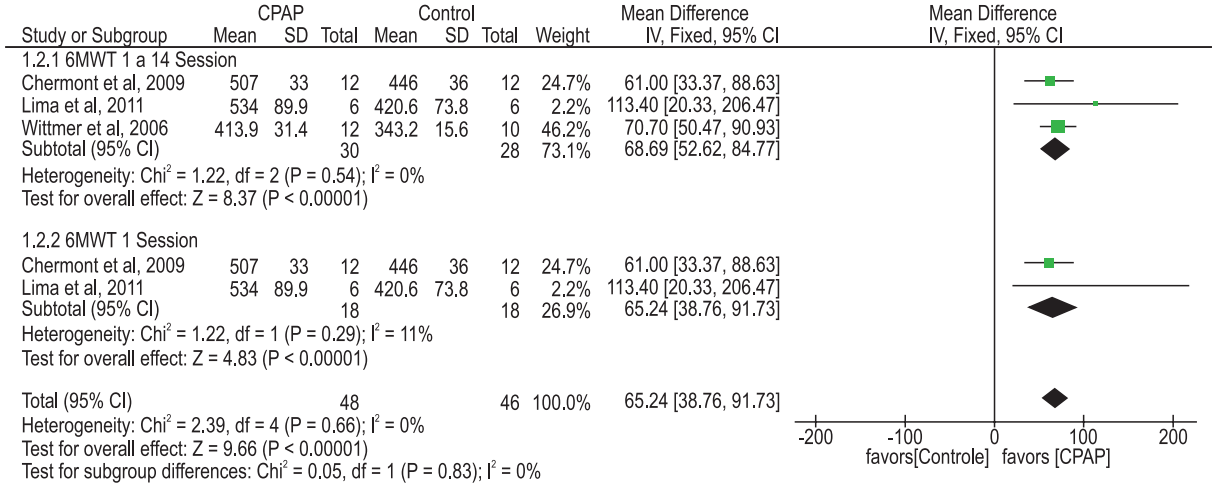

FIG. 2. Alteration in 6MWT – CPAP versus Controle

Figure 2 – *CPAP versus Control: 6MWT. Review Manager (RevMan). Version 5.2 The Cochrane Collaboration, 2013.*

corroborate the work done by Chermont et al.[13] in which NIV promoted an increase in the distance covered (NIV: 507 m; placebo: 446 m; p = 0.001) by patients with increased tolerance to exercise.

Previous CPAP administration in HF decreases respiratory discomfort in patients, generating lower cardiac work during exercise.[12,25] Smaller quantities of lactate have also been attributed to the use of CPAP in patients after the 6MWT.[7]

NIV is an important instrument used to perfect the treatment of patients, with significant improvement in the performance of physical activities.[26] Pulmonary function may be decreased in HF, having a direct relationship with the reduction in FC and in the performance of DLAs. [27,28] Wittmer et al.[14] have demonstrated that treatment with CPAP progressively increased FVC and FEV1 in HF patients when compared to the control group. This improvement may have occurred due to the increase in functional residual capacity and opening of collapsed alveoli. [7,12-14]

In the study by Wittimer et al.[14] a clinical implication in relation to FVC was observed as a component of the outcome associated to FC after repercussion of NIV application. The CPAP group showed progressive increase of FVC, reaching a maximum of 16% of the basal value on the 9th day of treatment, with no additional improvement on the 14th day of treatment. VEF1 values increased progressively and reached a maximum of 14% on the 14th day of treatment with CPAP, with no significant changes in the control group. The authors concluded that the treatment with CPAP, for two weeks, increased pulmonary function of HF patients, consequently improving tolerance to activities.

The increase in respiratory work in HF is associated to a decreased diaphragm perfusion. Due to this event, patients who are decompensated by the disease evolve with muscle fatigue in lower limbs, caused by an increase in peripheral vascular resistance.[12,25] Obtainment of lower resistance to airflow in the airways with administration of positive pressure,[7,12,19] and reduction in respiratory discomfort or fatigue in lower limbs [7,12-14] are factors that can also explain the improvement in FC with the use of NIV associated to exercise.

Patients who used non-invasive ventilatory support (NIVS) increased their FC when they used a PEEP superior to 4 cmH_2O. Studies that compared the use of a lower value PEEP or placebo mode proved it to be inefficacious when compared to a higher level PEEP.[12,13,29]

Enlargement of the cardiac area generates a volume overload in cardiac cavities. NIV decreasesthis volume overload, momentarily, with an increase in cardiac contractility, which occurs with the advent of transmural pressure reduction.[7,30,31] Moreover, NIV favors a pressure condition, which promotes an improvement in gas exchange by simple recruitment and stabilizes alveolar units.[32]

Despite the positive results, patient care and monitoring are necessary during NIV application. The decrease in cardiac debit and hypoperfusion seem to challenge the use of this technique. However, the positive intrathoracic pressure offered by NIV influences the patient's hemodynamic condition, with the decrease of cardiac preload and afterload due to the reduced transmural pressure.[33]

Tkacova et al.[34] observed, after treatment with CPAP during three months, a significant decrease in atrial natriuretic peptide (ANP) in the plasma of HF patients. Patients submitted to CPAP had a decrease in pulse pressure correlated to an increase in the ejection fraction originated by the reduction of the transmural pressure.[35]

The presence of biases in these studies leads to conclusions that systematically tend not to be completely reliable.[36] All selected studies presented high risk of biases in regards to allocation confidentiality, which is extremely important. O'Donnell et al.[12] for instance, presented uncertain risk of masking, one of the factors that may significantly alter the study's result.

Conclusion

This systematic review with meta-analysis showed that NIV is an effective method for the improvement of exercise tolerance in HF patients. However, there is a gap in literature regarding which are parameters that are the most adequate for the application of this technique, and that promote the best results in FC performance. Further research is necessary to determine a standardization regarding NIV application, so that this technique can contribute, more efficiently, to the treatment of HF patients.

Author contributions

Conception and design of the research and Acquisition of data: Bittencourt HS, Reis HFC, Gomes Neto M; Analysis and interpretation of the data and Statistical analysis: Bittencourt HS, Gomes Neto M; Obtaining financing: Gomes Neto M; Writing of the manuscript: Bittencourt HS, Reis HFC, Lima MS; Critical revision of the manuscript for intellectual content: Reis HFC, Lima MS, Gomes Neto M.

Potential Conflict of Interest

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

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Reprocessing of Medical Products in Electrophysiology

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Electrophysiological procedures use high-cost multipolar electrode catheters which can be reprocessed. The reuse thereof has been performed by electrophysiology services in Europe, United States, Latin America and also in our midst. In fact, prior studies have proved that there is an actual cost decrease[1,2] and have also attested to the safety and efficacy of such practice,[3-12] observing rates of complication and therapeutic results similar to the ones obtained with first-use electrophysiology devices. The growing concern with sustainability and no waste, associated with the efficacy and safety already demonstrated, increasingly stimulate the practice of reprocessing single-use medical devices throughout the world.

The American Society of Cardiac Arrhythmias issued a favorable opinion to the reprocessing of electrophysiological devices to the FDA - Food And Drug Adminstration[13] as did the GAO - Government Accountability Office, a federal oversight entity of the United States.[14]

In Brazil, the reprocessing of such products was regulated by the National Health Surveillance Agency (ANVISA), through a Resolution by the Collegiate Board (RDC) 156[15] and Special Resolution (RE) 2605,[16] both published in 2006. The RDC 156 establishes that the authorization of reprocessing single-use medical devices, should be at the time of registration in Brazil.[15] Despite the fact that most of the manufacturers labeled their products as single-use, ANVISA demands the submission of documents that substantiate the reasons for not reprocessing. Once the manufacturer's arguments are proved and accepted, the words "Reprocessing Forbidden" must be included in the label of that certain product. Also, RE 2605[16] lists 66 materials classified as materials whose reprocessing is invariably forbidden. We stress that said list does not contain any product used in the electrophysiological procedures routine.

In 2013, ANVISA issued Technical Note No. 001/2013[17] reiterating the validity of the reprocessing rules published in 2006, in reply to the users' recurrent doubts and demands for clarifications, as per the following excerpt from the resolution: "*demands and questions regarding the correct interpretation to be given to the contents of the labels of product for a single use, available in the market, has become increasingly frequent*". Currently, in spite of this notice, doubts still persist with regard to the understanding of the rules in force. Due to that, we have made a detailed analysis of the labels of materials routinely used here in electrophysiology procedures, with the purpose of assessing possible incongruences that justify misunderstandings and interpretation errors.

For such analysis, we analyzed the contents of the labels of materials used in electrophysiological procedures, written in Portuguese, available in ANVISA's database http://www.anvisa.gov.br/scriptsweb/correlato/correlato_rotulagem.htm. We included labels from 7 manufacturers that registered products intended for electrophysiology with ANVISA. Once the website had been accessed, we typed the name of the manufacturers in field "*Supplier's Name*", obtaining a complete list of medical products each manufacturer. Afterwards, we chose only the labels of the products used in electrophysiological procedures. The labels were then printed out, numbered and grouped according to their similarity with regard to physical characteristics and technical applicability, classified as: 1) fixed-curve diagnostic catheter; 2) deflectable-curve diagnostic catheter; 3) circular catheter or high-density mapping catheter; 4) non-irrigated ablation catheter; 5) irrigated ablation catheter; 6) introducers and sheaths; 7) transseptal needle; and 8) intracardiac echocardiography catheter. Labels and/or records with more than one kind of product were attached more than once, that is, one for each of the products to which they corresponded, according to the applicability and characteristic thereof.

The products were then classified into 5 groups:

1) G1 – reprocessing permitted;

2) G2 – reprocessing forbidden;

3) G3 – irregular condition, for not complying with the labeling recommendations set forth in RDC 156;

4) G4 – conflicting information; and

5) G5 – no label in ANVISA's database.

This classification was based on the RDC 156, which recommends that the labels should contain only the words: "Reprocessing Forbidden" or "The manufacturer recommends single use" [15]. Thus, the products whose labels did not contain the expression "Reprocessing Forbidden" were defined as G1, and they may or may not contain the words "The manufacturer recommends single use". In G2, the products whose labels carried the expression "Reprocessing Forbidden" were included, in spite of the presence of any other word or information. In G3, labels with expressions "Single Use", "Product for Single Use", "Do Not Re-Sterilize", "Discard after using" and "Destroy after using" were included, even if accompanied by expression "The manufacturer recommends single use", given that, pursuant to Technical Note No. 001/2013,[17] these sentences are considered to not be in conformity with the rules of the regulatory agency. The products that had 2 or more labels, with recommendations differing from one another and/or irregular, were classified as G4. And lastly, the products not in ANVISA's database were classified as G5.

Keywords

Recycling; Electrophysiologic Techniques / cardiac; Catheter Ablation; Cost Savings.

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The products included in G1 and G2 were considered to have their labels in conformity with ANVISA's rules, while those classified as G3, G4 and G5 were considered to not be in conformity.

For each group of products with the same applicability and characteristic, and whose labels were in conformity with ANVISA (G1 and G2), it was also assessed whether they were uniform with regard to reprocessing prohibition or not.

Lastly, physical labels were compared by sampling with the labels in ANVISA's database, to assess whether the information contained in both sources matched.

The labeling research was made from July 25, to August 25, 2016 and identified 121 products used in electrophysiological procedures, registered with ANVISA's database, totaling 116 labels (Table 1). Forty-five labels (37.2%) were classified as reprocessing permitted (G1); 41 (33.9%) as reprocessing forbidden (G2); 28 (23.1%) were irregular (G3); 3 (2.5%) had two or more labels with conflicting information (G4) and lastly, four products (3.3%) did not have labels in ANVISA's database (G5). We were then able to note that 86 (71.1%) labels were in conformity, whereas 34 (28.9%) were not in conformity with RDC 156.

The analysis of sub-groups of products with similar characteristics and the same applicability, included in G1 and G2 (labels in conformity with RDC 156), showed that only the intracardiac echocardiography catheter was uniform with regard to the reprocessing recommendations. In this specific case, all six existing types had in their labels the words "The manufacturer recommends single use", which characterizes, therefore, a reprocessing permission. Other products did not have parity in the contents of their labels (Table 1).

Three products were classified as G4, of which one was a fixed-curve diagnostic catheter, one was a deflectable-curve diagnostic catheter and another a non-irrigated ablation catheter with bidirectional curve, all of which were from different manufacturers. The three products had more than one label catalogued in ANVISA's database, under the same registration number and with different recommendations. For the fixed-curve diagnostic catheter (ANVISA registration 10192030102), three labels were found, with the following information: "Reprocessing Forbidden", "The manufacturer recommends single use" and "Product for Single Use", which, pursuant to the RDC 156, mean, respectively, reprocessing forbidden, reprocessing allowed and irregular information. The deflectable-curve diagnostic catheter (ANVISA registration 10341350368) and the ablation catheter (ANIVISA registration 10332340206), for their turn, had two labels, with the following words: "Reprocessing Forbidden" and "The manufacturer recommends single use", which are contradictory instructions.

Lastly, nine physical labels of products used in electrophysiology (Table 2) were analyzed. In six of them, no reprocessing information was found. Upon assessing these six labels in ANVISA's database, we were able to ascertain that one of them contained the expression "The manufacturer recommends single use"; three of them contained the words "Reprocessing Forbidden", and in the other one, the information was not in conformity with RDC 156. In addition, one product (transseptal introducer sheath, registered with ANVISA under No. 10332340208) did not have a label in ANVISA's database.

As we were able to note in this analysis, in spite of the fact that the reprocessing of materials used in electrophysiological procedures is allowed and regulated by ANVISA, there are important incongruences in the labels, in a number of products that is not trifling, which may generate mistaken interpretations by the users, and consequently the improper reprocessing of said materials.

The contents of 34 labels (28.9%) from ANVISA's database, which are not in conformity with RDC 156, require urgent adaptation.

We consider it to be extremely important for this information, defined upon the registration of the product, to be clear and

Table 1 – Labels of medical products grouped according to similarity of characteristics and applicability

Medical products in electrophysiology	In conformity with RDC 156		Not in conformity with RDC 156			Total
	G1	G2	G3	G4	G5	
Transseptal needle	1 (20%)	4 (80%)	0	0	0	5
Non-irrigated Ablation Catheter	7 (36.8%)	4 (21%)	7 (36.8%)	1 (5.3%)	0	19
Irrigated ablation catheter	9 (33.3%)	15 (55.5%)	3 (11.1%)	0	0	27
Deflectable-curve diagnostic catheter	9 (50%)	4 (22.2%)	3 (16.7%)	1 (5.5%)	1 (5.5%)	18
Fixed-curve diagnostic catheter	2 (22.2%)	4 (44.4%)	1 (11.1%)	1 (11.1%)	1 (11.1%)	9
High-density mapping circular catheter	7 (58.3%)	2 (16.7%)	2 (16.7%)	0	1 (8.3%)	12
Introducers and sheaths	4 (16%)	8 (32%)	12 (48%)	0	1 (4%)	25
Intracardiac echocardiography catheter	6 (100%)	0	0	0	0	6
Total	45 (37.1%)	41 (33.9%)	28 (23.1%)	3 (2.5%)	4 (3.3%)	121 (100%)

G1: reprocessing permitted; G2: reprocessing forbidden; G3: irregular in relation to the recommendations in RDC 156; G4: conflicting information; G5: labels absent from ANVISA's database.

Table 2 – Comparative analysis of physical labels vs. labels in ANVISA's database

Product	ANVISA Registration	Physical Label	Label in the Website
Non-irrigated Ablation Catheter	10332340098	The manufacturer recommends single-use	The manufacturer recommends single-use
Deflectable Diagnostic Catheter	10332340161	The manufacturer recommends single use	The manufacturer recommends single use
Circular Catheter	10332340332	No expression	Product for a single use
Irrigated Ablation Catheter	10332340361	No expression	The manufacturer recommends single use
Deflectable introducer	10332340207	No expression	Product for a single use Reprocessing forbidden Destroy after using
Non-irrigated Ablation Catheter	10332340226	The manufacturer recommends single use	The manufacturer recommends single use
Transseptal Needle	10332340151	No expression	Product for a single use Reprocessing forbidden Destroy after using
Hemostatic Introducer	10332340107	No expression	Product for a single use Reprocessing forbidden Destroy after using
Transseptal Introducer	10332340208	No expression	Not found

irrefutable, thus making sure a quick and correct indentification of medical products with regard to the use thereof. In this regard, the labels should contain a single expression, clearly defining the situation of each medical product: "reprocessing forbidden" or "reprocessing allowed". We are also of the opinion that the criteria used to classify the product must be standardized and ensure the equity of information contained in the physical labels and in ANVISA's database.

Also, it is our opinion that the technical information submitted to ANVISA by the manufacturers, in justification of the prohibition of reprocessing a certain product, upon the registration thereof, must be accessible to the users for them to be aware of it.

For these reasons, the Brazilian Society of Cardiac Arrhythmias (SOBRAC) met with the suppliers of electrophysiological products available in the domestic market and suggested an immediate review of the information contained in the labels, so as to adapt them to ANVISA's standards and make the information unequivocal.

In summary, after the conduction of this research, it was possible to reach the following conclusions and suggestions:

1) The reprocessing and reuse of medical products in electrophysiology is permitted in Brazil and regulated by ANVISA, through RDC 156;

2) A thorough analysis of the labels found inconsistencies that could entail misinterpretations and improper decisions by the users with regard to the compliance with RDC 156, even if unintentional.

3) In the current scenario, while these incongruences are not rectified, it is necessary for the healthcare services that reprocess such products to make a stringent and systematic assessment of both product labels: the physical one and the one in ANVISA's database, with the purpose of identifying the ones that are not in conformity with the RDC 156, as well as those that contain differing instructions, thus avoiding mistakes in the compliance with ANVISA's orders.

Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Kuniyoshi RR, Sternick EB, Nadalin E, Hachul DT; Acquisition of data: Kuniyoshi RR; Analysis and interpretation of the data: Kuniyoshi RR, Sternick EB, Hachul DT; Writing of the manuscript: Kuniyoshi RR, Sternick EB.

Potential Conflict of Interest

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

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Case 1/2017 – 26-Year-old Male with Rapidly Progressive Heart Failure

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The patient was a 26-year-old male, from the town of Medina, Minas Gerais state, coming from the city of Barueri, São Paulo state, hospitalized due to dyspnea and edema (April 19, 2013).

At the age of 24 years (July 18, 2011), he was referred to InCor complaining of dyspnea on heavy exertion for 2 months. Before that, he never had any cardiovascular symptom, and, after beginning specific medication, his clinical findings improved. The patient denied other cardiovascular symptoms, diabetes mellitus, arterial hypertension, dyslipidemia, smoking. He reported using illicit drugs (amphetamines and marijuana) and abusive alcohol consumption on weekends (20 beer cans). He reported prophylaxis for rheumatic fever with monthly use of benzathine penicillin from the age of 12 years to 17 years.

The clinical and laboratory assessments prior to referral revealed cardiopathy with ventricular dilatation.

His serology for Chagas disease was negative, and coronary angiography was normal. The echocardiogram revealed left ventricular systolic and diastolic diameters of 60 mm and 44 mm, respectively, and left ventricular ejection fraction of 51%.

The physical examination on July 18, 2011, showed: weight, 99.7 kg; height, 1.70 m; body mass index, 31.14 kg/m^2; heart rate, 60 bpm; blood pressure, 116/70 mm Hg; and normal pulmonary auscultation. Cardiac auscultation revealed the presence of third cardiac sound and systolic murmur (++/6+) over the mitral area, apex beat palpated on the precordium (left 5th intercostal space), displaced 2 cm from the left midclavicular line, with extension of 2 digital pulps. The examination of the abdomen and lower limbs was normal, and there was no jugular venous distention.

Keywords

Heart Failure; Cardiomyopathy, Dilated; Street Drugs; Atrial Flutter.

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The electrocardiogram (ECG) on July 14, 2011, revealed atrial flutter with high-degree atrioventricular block, mean heart rate of 40 bpm, QRS duration of 100 ms, SÂQRS -30º, probable antero-superior divisional block (ASDB) and final conduction disorder (rsr') on V_1 and V_2 (Figure 1).

His chest X-ray showed pulmonary fields and hila, aorta and cardiac area within the normal range.

The laboratory tests (July 14, 2011) revealed: hemoglobin, 17.9 g/dL; red blood cell count, 51%; leukocytes, 7640/mm^3; creatinine, 1.3 mg/dL; sodium, 137 mEq/L; potassium, 4.7 mEq/L; total cholesterol, 189 mg/dL; HDL-C, 45 mg/dL; LDL-C, 117 mg/dL; triglycerides, 136 mg/dL; AST, 28 U/L; ALT, 44 U/L; TSH, 1.38 UI/mL; free T4, 1.03 ng/dL; TP(INR), 1.2; APTT(rel), 1.01; normal urinalysis; negative serology for Chagas disease.

The following drugs were prescribed: daily acetylsalicylic acid 300 mg, carvedilol 12.5 mg, losartan 25 mg, spironolactone 25 mg, and furosemide 40 mg.

The new echocardiogram (Sept 2011) revealed left ventricular dimensions of 53x40 mm, ejection fraction of 48%, septal thickness and posterior wall of 11 mm, left atrial diameter of 34 mm, and diffuse left ventricular hypokinesia (Table1).

The 24-hour Holter showed persistent atrial fibrillation, with mean heart rate of 62 bpm, longest pause of 3.2s, 330 ventricular extrasystoles (14 VE/h), 1 paired extrasystole and 1 ventricular tachycardia with 3 beats.

Acetylsalicylic acid was replaced with warfarin, and electric cardioversion was programed 3 weeks after effective anticoagulation.

The first cardioversion was performed on December 13, 2011, with relapse of atrial fibrillation minutes after, and very low heart rate.

The transesophageal echocardiogram (December 4, 2012) revealed: aorta, 44 mm; left atrium, 47 mm; ventricular septum and posterior wall, 11 mm; left ventricle (systole/diastole), 56/49 mm; ejection fraction, 27%; biatrial and biventricular enlargement, with moderate mitral and marked tricuspid valve regurgitation; aortic ectasia and no intracavitary thrombus (Table 1) (Figure 2).

New electric cardioversion was performed on the following day (December 5, 2012), with atrial fibrillation recurrence few minutes later.

On April 19, 2013, the patient sought urgent medical care, reporting worsening of the dyspnea in the previous 4 months, with progression to occurrence at rest, orthopnea, abdominal volume enlargement and lower limb edema. In addition, he reported dry cough in the preceding week and marked worsening of dyspnea in the past two days.

The physical examination revealed: dyspnea; heart rate, 100 bpm; blood pressure, 100/80 mm Hg. The pulmonary

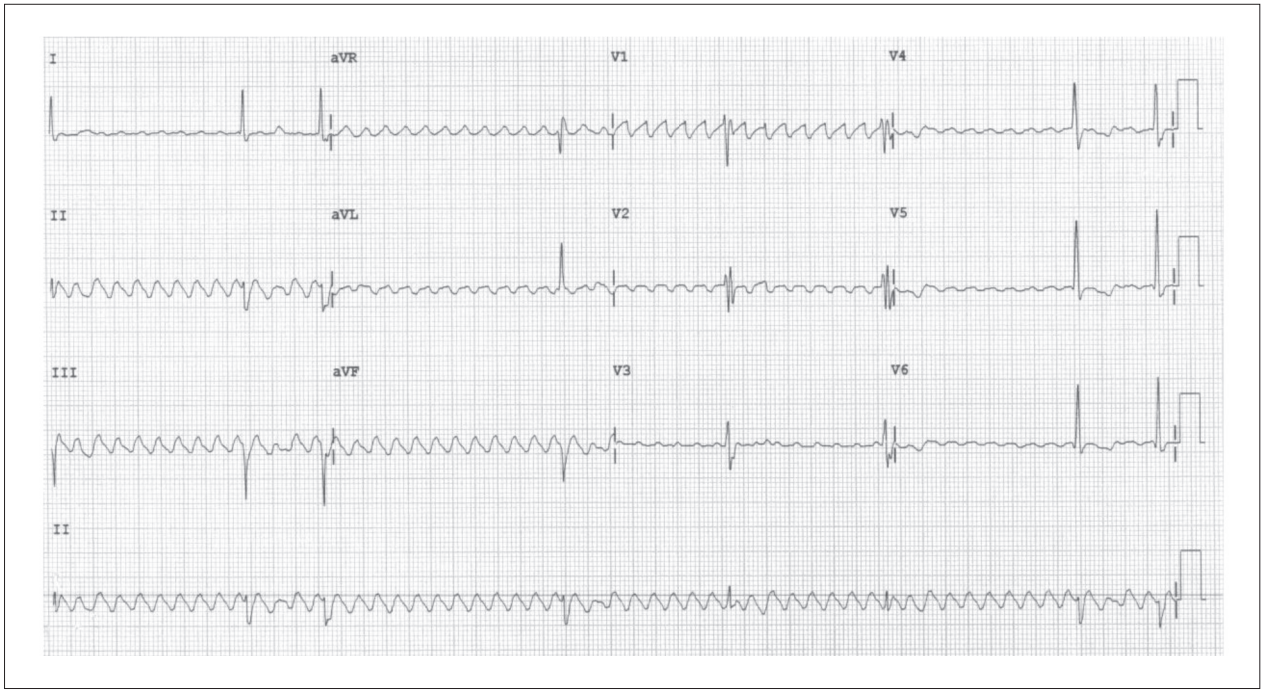

Figure 1 – *Electrocardiogram: atrial flutter with high-degree atrioventricular block, antero-superior divisional block, and right bundle-branch conduction disorder.*

Table 1 – Echocardiographic evolution

	September 2011	December 2012	April 2013
Aortic sinus (mm)	41	44	45
Left atrium (mm)	34	47	50
RV (mm)	-	40	55
Ventricular septum (mm)	11	11	11
LV posterior wall (mm)	11	11	8
LVDD (mm)	53	56	66
LVSD (mm)	40	49	-
Ejection fraction (%)	48	27	20
Mass index (g/m²)	100	112	125
LV motility	Mild reduction	Marked reduction	Marked hypokinesia
RV motility	Mild reduction	Moderate reduction	Moderate hypokinesia
Mitral valve	Normal	Mild/moderate regurgitation	Moderate regurgitation
Tricuspid valve	Normal	Marked regurgitation	Marked regurgitation
Aortic valve	Normal	Normal	Normal
Right atrium	-	Enlarged	Enlarged

RV: right ventricle; LV: left ventricle; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter.

auscultation evidenced rales on the bases. The cardiac auscultation revealed irregular heart rhythm, systolic murmur (+++/6+) over the mitral and tricuspid areas. The liver was palpated 3 cm from the right costal margin, and there was lower limb edema (++++/4+).

The cough was attributed to heart failure (HF) because there was neither fever, nor leukocytosis nor images suggesting pneumonia on chest X-ray, which showed global cardiomegaly and a rectified middle arch (Figure 3). Intravenous furosemide and dobutamine, 5 μg/kg/min, were administered.

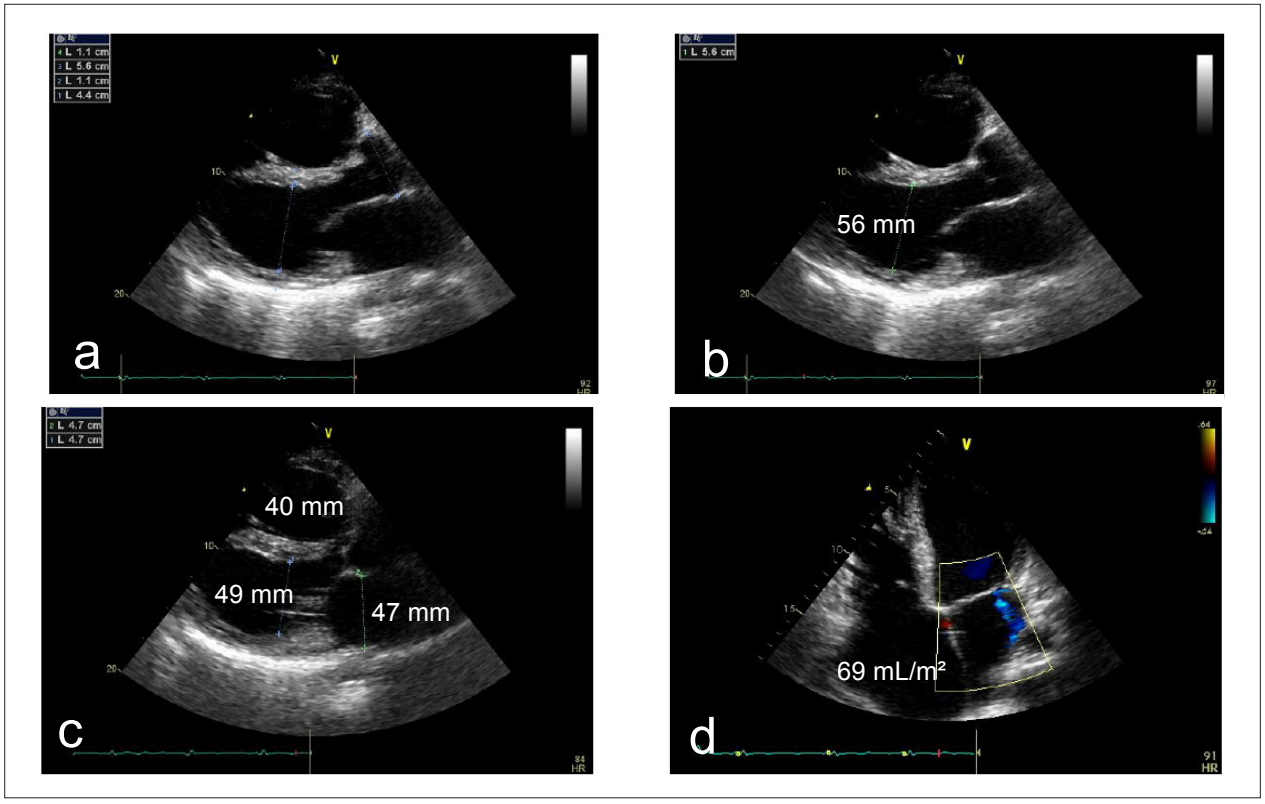

Figure 2 – *Transthoracic echocardiogram, longitudinal parasternal view (a, b, c) and four-chamber view (d) of the left ventricle. Note the enlarged atria and right ventricle.*

The laboratory tests (Table 2) evidenced kidney function deterioration and marked increase in the levels of brain natriuretic peptide (BNP) and C-reactive protein (CRP).

New electric cardioversion was indicated, as was a new transesophageal echocardiogram to rule intracavitary thrombi out.

The cough worsened, then with purulent sputum, and the association of tazobactam, piperacillin and azithromycin was introduced.

On April 26, 2013, the echocardiogram showed biatrial and biventricular enlargement, marked left ventricular and moderate right ventricular dysfunction, moderate mitral and marked tricuspid regurgitation, and no intracavitary thrombus (Table 1) (Figure 4).

Right after the exam, the patient had a decrease in his consciousness level and arterial hypotension, requiring orotracheal intubation for respiratory support and increased doses of vasoactive amines.

On April 26, 2013, he had hyperthermia (38.6°C). Vancomycin was introduced, and the new chest X-ray was unaltered (Figure 5).

Despite the administration of increasing doses of vasoactive amines, on April 27, 2013, the patient had shock and cardiac arrest, which was reversed. On the afternoon of that same day, he had hypotension and bradycardia, and an irreversible asystolic cardiac arrest.

Clinical aspects

The patient was a 26-year-old male, reporting prophylaxis for rheumatic fever from the age of 12 years to 17 years, who, at the age of 24 years, developed dyspnea on heavy exertion, which improved with medication. However, after two years, dyspnea worsening and edema occurred (April 19, 2013).

The clinical and laboratory assessments before the referral revealed cardiopathy with ventricular dilatation. The echocardiogram evidenced left ventricular systolic and diastolic diameters of 60 mm and 44 mm, respectively, and ejection fraction of 51%. His serology for Chagas disease was negative, and his coronary angiography, normal. On physical examination, a third cardiac sound and a systolic murmur (++/6+) over the mitral area were heard. The ECG showed atrial flutter, atrioventricular block with probable ASDB, and heart rate of 40 bpm.

Over the following two years, the cardiopathy with ventricular dilatation evolved. Because the patient had a history of prophylaxis for rheumatic fever, rheumatic cardiopathy was considered as a possible etiology. However, the progressive and rapid course of our patient's illness is not commonly seen in patients without valvular damage consequent upon the acute event of rheumatic fever. The previous echocardiogram revealed left ventricular systolic and diastolic diameters of 60 mm and 44 mm, respectively, and ejection fraction of 51%. In September 2011, the patient showed: left ventricular dimensions of 53x40 mm; ejection

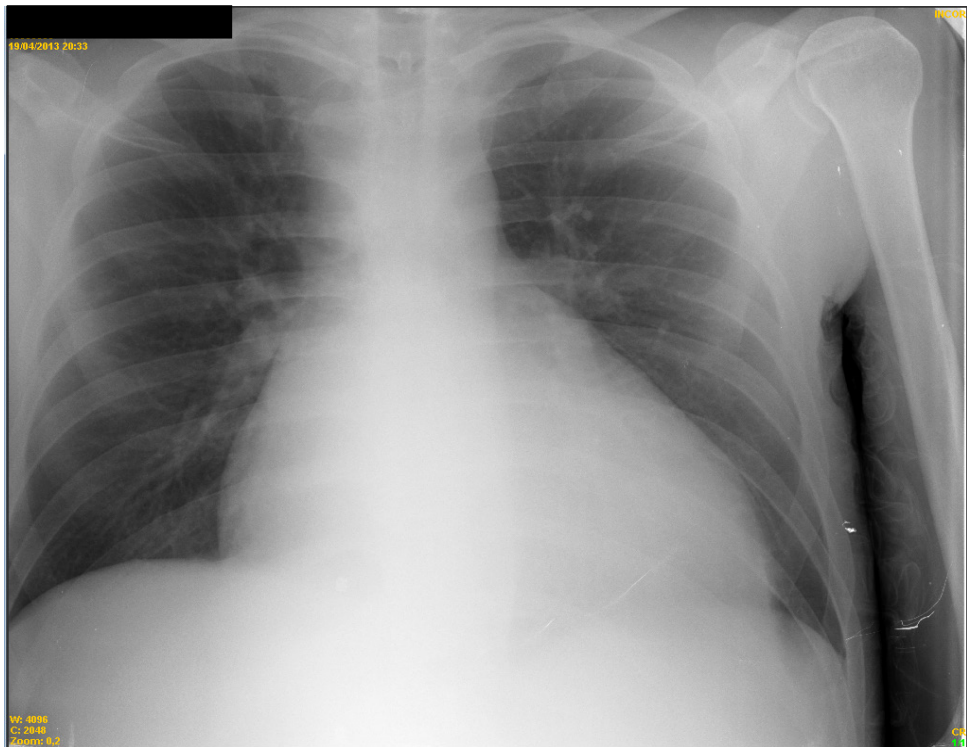

Figure 3 – *Chest X-ray (posteroanterior). Marked cardiomegaly, rectified middle arch and free pulmonary fields.*

fraction of 48%; septal and posterior wall thickness of 11 mm; left atrial diameter of 34 mm; and diffuse left ventricular hypokinesia without valvular damage.[1] Therefore, other etiologies of dilated cardiomyopathy (DCMP) had to be considered for this case.

Dilated cardiomyopathy is a progressive primary myocardial disease of unknown cause, characterized by a reduction in left ventricular or biventricular contractility.[2] Approximately one in every three cases of congestive HF originates from DCMP.[3] In addition to left ventricular or biventricular dilatation, it is characterized by contractile dysfunction, which results in congestive HF. Patients with DCMP have an increase in myocardial mass and in interstitial collagen,[4] known as remodeling myocardial, which eventually leads to HF. Reversing that process to reduce morbidity and mortality remains a major challenge in health care practice.[5] Our patient had echocardiographic changes compatible with DCMP and clinical findings of HF. On December 4, 2012, the transesophageal echocardiogram showed: aorta, 44 mm; left atrium, 47 mm; interventricular septum and posterior wall, 11 mm; left ventricle (systole/diastole), 56/49 mm; ejection fraction, 27%; biatrial and biventricular enlargement; and moderate mitral and marked tricuspid valvular regurgitation. On April 19, 2013, the patient sought medical care complaining of dyspnea worsening in the last 4 months, with progression to dyspnea at rest, orthopnea, increased abdominal volume and lower limb edema. The physical examination revealed congestive HF with pulmonary congestion, hepatomegaly, edema and bilateral atrioventricular valvular regurgitation.

Currently, DCMP accounts for around 10,000 deaths and 46,000 hospitalizations per year in the United States. In addition, DCMP is the major indication for cardiac transplantation.[6] Although many cases lack an evident cause, DCMP either has a family origin or results from myocardial lesions produced by several known or unknown toxic, metabolic or infectious agents. It can be a late consequence of acute viral myocarditis, possibly partially mediated by immune mechanisms. It can occur at any age, being most often clinically apparent in the third or fourth decade of life. Reversible forms of DCMP may be found in cases of alcohol abuse, pregnancy, thyroid disease, cocaine use, and uncontrolled chronic tachycardia.[3] The distribution of the DCMP causes is as follows: idiopathic, 50% of the cases; secondary to myocarditis, 9%; secondary to ischemic heart disease, 7%; consequent to infiltrative disease (amyloidosis and sarcoidosis), 5%; peripartum cardiomyopathy, 4%; secondary to systemic arterial hypertension, 4%; associated with human immunodeficiency virus (HIV) infection, 4%; post-connective tissue disease, 3%; substance abuse, 3%; doxorubicin use, 1%; and the other 10% comprise Chagas disease, Lyme disease, genetic causes, left ventricular non-compaction, and tachycardia-mediated cardiopathy.

Rheumatic fever remains the major cause of acquired cardiopathy in many regions, such as South America, Africa

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Table 2 – Test results of the last admission

	April 19	April 23	April 26	April 27
Platelets/mm^3	163000	135000	146000	22000
Red blood cell count (%)	51	44	44	53
Hemoglobin (g/dL)	16.4	14.4	14.2	16.2
Leukocytes/mm^3	6280	6160	6910	10820
Neutrophils (%)	67	69	76	73
Segmented (%)	65	-	-	66
Cholesterol (mg/dL)	189	-	-	-
HDL-C (mg/dL)	45	-	-	-
LDL-C (mg/dL)	117	-	-	-
Triglycerides (mg/dL)	136	-	-	-
TSH (mIU/l)	-	3.79	-	-
Free T4 (µg/dL)	-	1.50	-	-
PT(INR)	2.6	2.4	2.0	
APTT (rel)	1.16	1.17	1.12	
Urea (mg/dL)	46	38	45	62
Creatinine (mg/dL)	1.33	1.60	1.60	3.07
GF (mL/min/1.73 m²)	69	56	56	26
Sodium (mEq/L)	140	141	138	143
Potassium (mEq/L)	4.2	4.0	3.7	5.2
AST (U/L)	86	-	539	2808
ALT (U/L)	84	-	205	983
Gamma GT (U/L)	93	-	-	104
APh (U/L)	57	-	-	69
Total bilirubin (mg/dL)	2.67	-	-	6.98
Direct bilirubin (mg/dL)	0.69	-	-	4.70
Total proteins (g/dL)	7.3	-	-	-
Albumin (g/dL)	3.5	-	-	-
Lactate (mg/dL)	-	62	-	122
BNP (pg/mL)	3540	2968	-	-
CRP (mg/L)	7.83	12.29	25.84	28.82
Arterial blood gas analysis				
pH	-	-	-	7.10
pO_2 (mm Hg)	-	-	-	36.5
O_2 saturation (%)	-	-	-	50
pCO_2 (mm Hg)	-	-	-	43.6
HCO_3 (mEq/L)	-	-	-	13.1
BE (mEq/L)	-	-	-	(-) 16.7

HDL: high-density lipoproteins; LDL: low-density lipoproteins; TSH: thyroid stimulating hormone; PT: prothrombin time; APTT: activated partial prothrombin time; GF: glomerular filtration; AST: aspartate aminotransferase; ALT: alanine aminotransferase; APh: alkaline phosphatase; BNP: brain natriuretic peptide; CRP: C-reactive protein; BE: base excess.

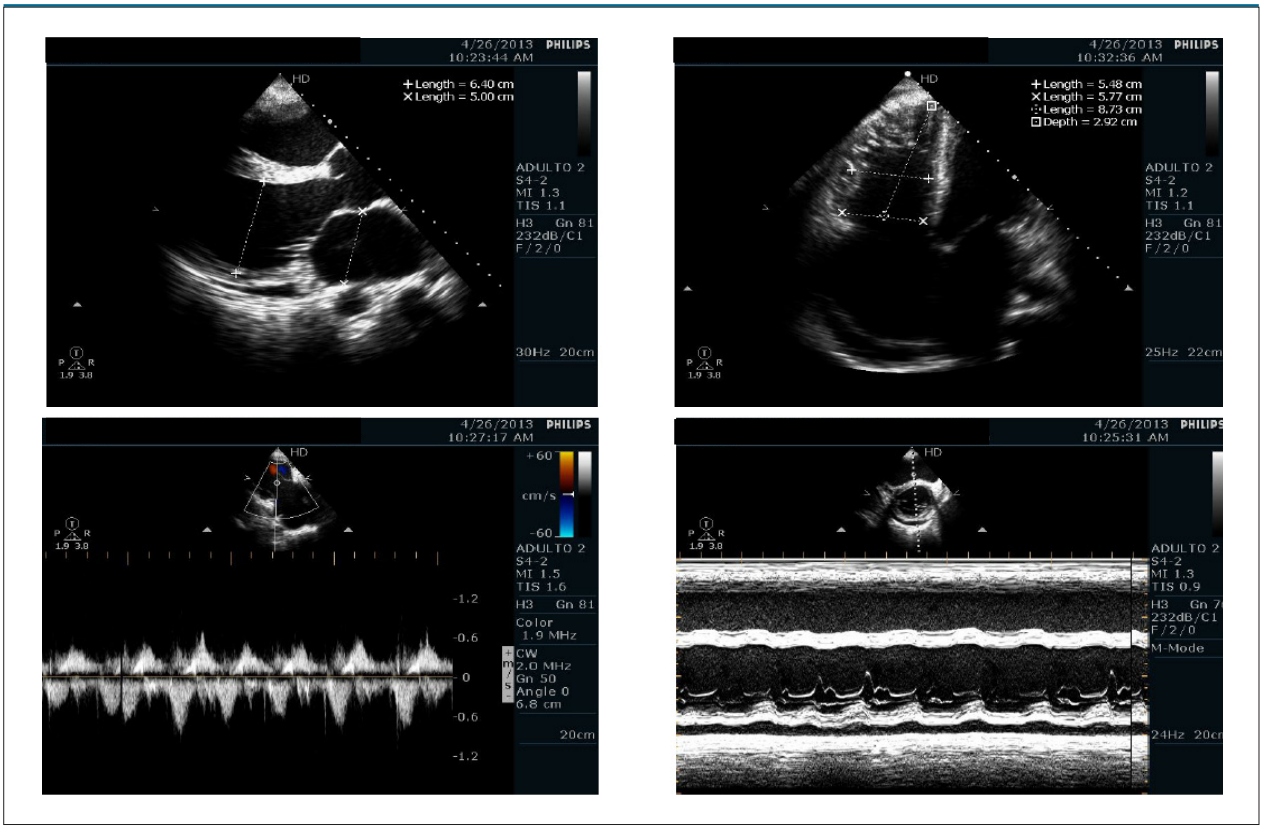

Figure 4 – *Transthoracic echocardiogram (April 2013): biventricular and biatrial enlargement.*

and India. It is frequently asymptomatic, especially rheumatic myocarditis. The most common clinical manifestations are arthritis and fever. Rheumatic fever and acute rheumatic myocarditis are under-represented in medical literature because they are rare in the United States and Europe.[7]

Although the first episode of acute rheumatic fever can lead to persistent valvular lesions, rheumatic cardiopathy most often results from cumulative valvular damage attributed to recurring acute rheumatic fever episodes, which can even be silent (no clinical symptoms). This makes its identification challenging. Rheumatic cardiopathy almost always affects the left-sided heart valves. Direct damage of right-sided heart valves is rare; they are usually affected as a result of the malfunction of the left-sided valves. In addition, narrowing of the mitral valve can develop, with blood flow obstruction, due to fusion of the leaflets or reduction in their mobility due to calcification.[8] Left ventricular dilatation and HF have been mainly observed in patients with severe valvular heart disease. Although myocarditis is a common postmortem examination finding, the major cause of left ventricular dilatation and HF seems to be severe mitral regurgitation with or without aortic regurgitation.[9] The ECG findings can include any degree of heart block, such as atrioventricular dissociation. The chest X-ray can show cardiomegaly. The echocardiography allows assessing the intensity of the valvular lesion, pericardial effusion, ventricular and atrial dilatation, and ventricular dysfunction.[10] Therefore, rheumatic fever does not seem to be the most likely cause for this cardiopathy with dilatation and rapid and progressive aggravation. In addition, the clinical and image findings in this case are not those of rheumatic cardiopathy.

Sarcoidosis, another cause of cardiopathy with dilatation, can be considered in this case. Sarcoidosis is a granulomatous, non-caseous, heterogeneous disorder of unknown etiology, which can affect any organ. The heart involvement can be isolated or precede that of other organs (such as lung), or even occur simultaneously with that.[11] The clinical manifestations of cardiac sarcoidosis depend on the location and extension of the granulomatous inflammation. Other cardiac manifestations comprise conduction disorders, ventricular and supraventricular arrhythmias, pericarditis and valvular dysfunction. In addition, the involvement of papillary muscles can lead to acute symptoms like those of hypertrophic cardiomyopathy with asymmetric septal hypertrophy, caused, however, by edema and not by hypertrophy of myocytes. The likelihood of heart disease caused by sarcoidosis should be considered for a healthy young or middle-aged individual with cardiac symptoms or a patient with known sarcoidosis who develop arrhythmias, conduction disorder or HF. That is an important etiology for our case, who had rapid and progressive worsening, arrhythmia, ventricular dilatation and clinical findings of HF, with no family history of genetic disease, and normal results of the other tests for heart disease.[12,13]

(Rogério Silva de Paula, MD, and Ivna Lobo Camilo, MD)

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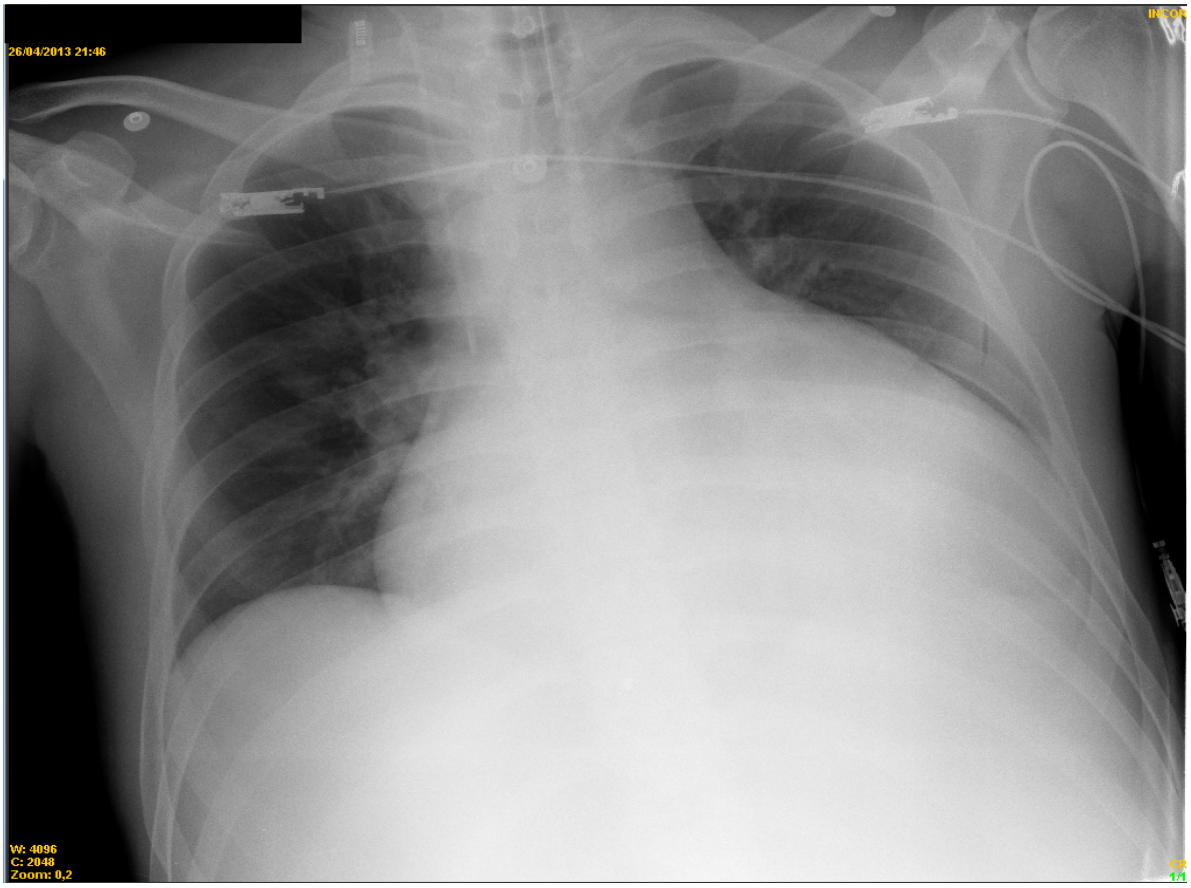

Figure 5 – *Chest X-ray (anteroposterior - bed). Marked cardiomegaly and free pulmonary fields.*

Diagnostic hypothesis: Heart failure secondary to cardiopathy due to sarcoidosis.

(Rogério Silva de Paula, MD, and Ivna Lobo Camilo, MD)

Postmortem examination

The heart weighed 680g and showed dilatation of the four chambers (Figure 6). The epicardial surface was smooth with sparse opaque whitish plaques. Its longitudinal section at the ventricular plane showed diffuse thinning of the ventricular walls and yellowish color due to focal adipose substitution in the right ventricular myocardium, mainly in the inlet, apex, diaphragmatic face and free wall of the subpulmonary infundibulum (Figures 6 and 7). There was no cavitary thrombus. The microscopic exam of the myocardium revealed, in addition to adipose infiltration of the right ventricle, focal fibrosis and lymphohistiocytic infiltrates, and signs of previous damage to cardiomyocytes (Figures 8 and 9). All ventricular walls showed hypertrophy of cardiomyocytes. The histological sections of the septal myocardium showed thickening of the wall and muscle arteries due to hypertrophy of the tunica media (Figure 9B).

The other organs revealed signs of chronic passive pulmonary and liver congestion due to congestive HF with terminal shock. In addition, there were thromboembolism of the small branches of the pulmonary bases, alveolar hemorrhage, serous ascites (3200 mL) and pericardial effusion (120 mL). Other signs of terminal heart failure included focal acute tubular necrosis, edema of renal tubular cells and cerebral edema.

Anatomopathological diagnosis: Arrhythmogenic right ventricular cardiomyopathy (arrhythmogenic right ventricular dysplasia), congestive heart failure and morphological signs of terminal shock.

Cause of death: Cardiogenic shock

(Laís Costa Marques, medical student, and Vera Demarchi Aiello, MD)

Comments

The entity initially described as arrhythmogenic right ventricular "dysplasia" is currently known as arrhythmogenic right ventricular cardiomyopathy (ARVC), according to the European Society of Cardiology's position statement on cardiomyopathies.[14]

Its diagnosis is based on major and minor criteria, which comprise clinical, electrophysiological, hemodynamic and anatomopathological findings.

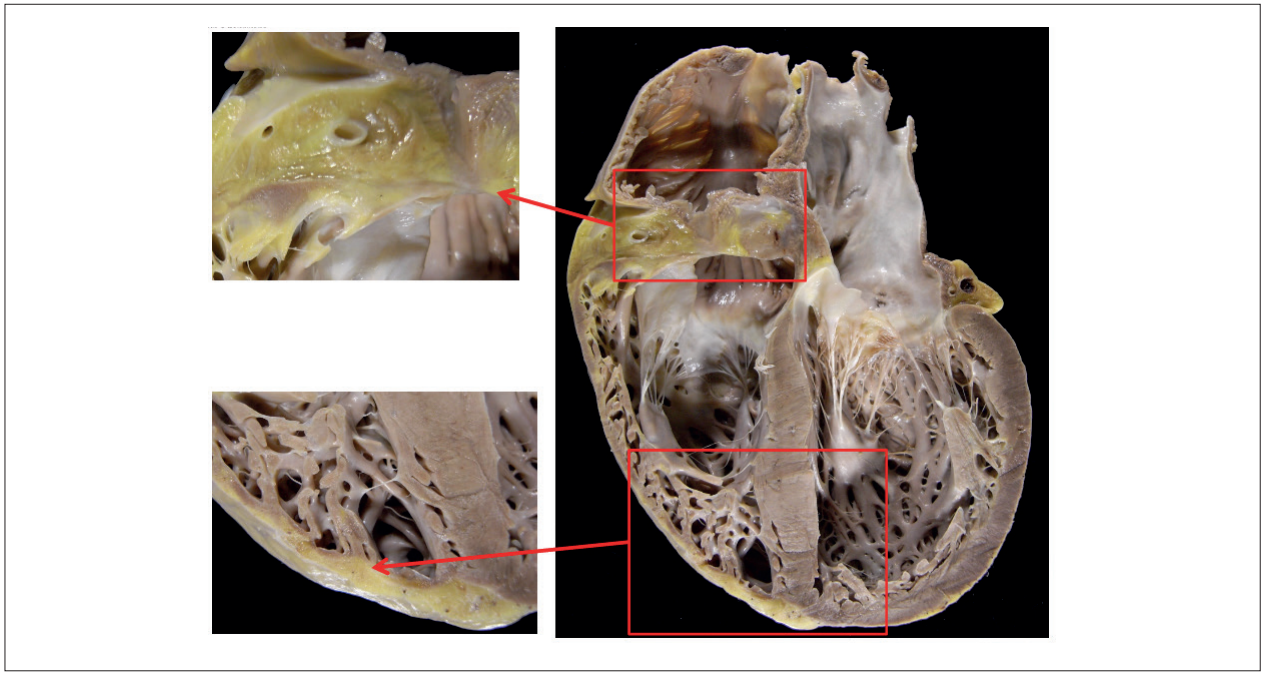

Figure 6 - *Gross aspect of the heart (four-chamber section). Significant fatty infiltration of the myocardium at the right ventricular base and apex, better evidenced in the magnifications (left panels). In addition, note global cardiomegaly with thinning of cardiac walls and biventricular dilatation.*

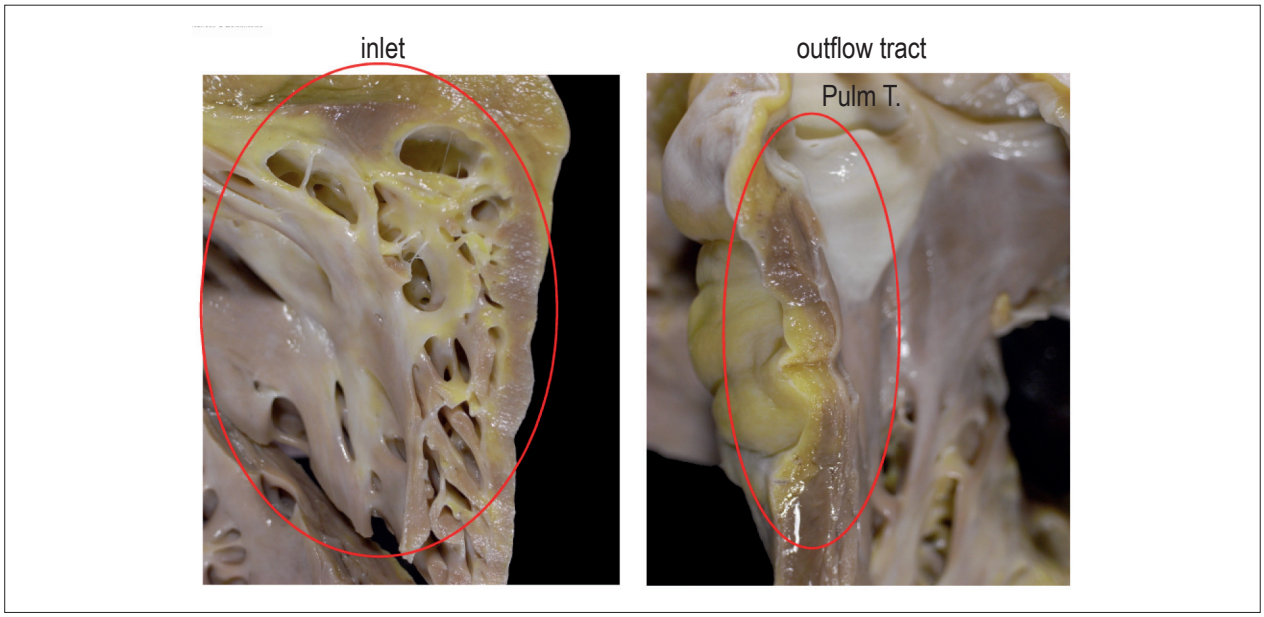

Figure 7 - *Gross aspect of the heart, longitudinal section of the right ventricular inlet and outflow tract. Both show focal fibrofatty replacement in the myocardial. Pulm T. – pulmonary trunk.*

In the case here described, the diagnosis of ARVC was not clinically established. From the anatomopathological viewpoint, however, both the gross and microscopic findings are typical, with adipose infiltration, and focal fibrosis and inflammation. Usually, the right ventricular involvement predominates, with little or no left ventricular involvement. In addition, global cardiomegaly is not usually found.

Phenotypic overlapping (global dilatation associated with fibrofatty replacement in the myocardium) might have hindered establishing the diagnosis during the patient's hospitalization.

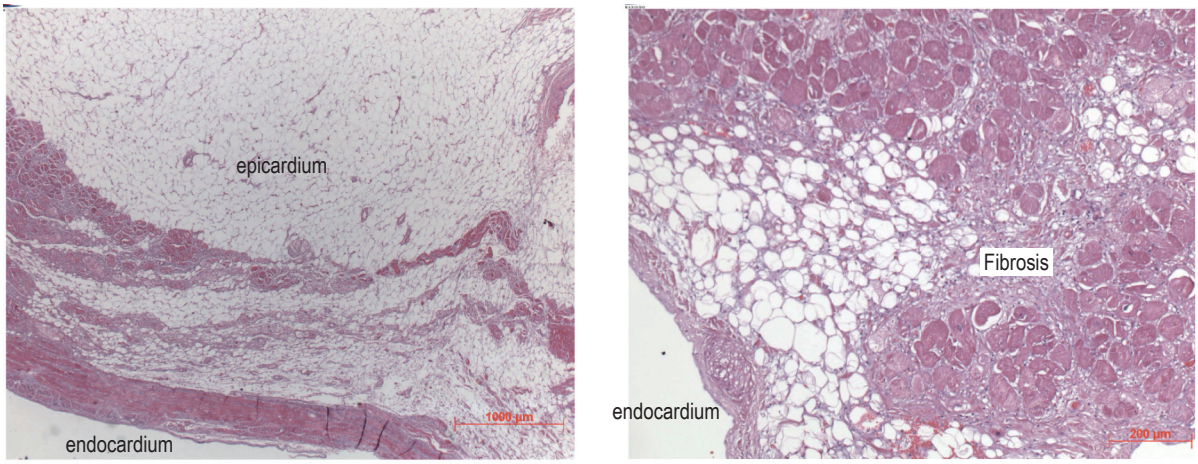

Figure 8 - *Microscopic sections of the right ventricular wall. Left panel: replacement of the muscle tissue with fibrofatty tissue. Right panel: the fibrotic component is better evidenced. Hematoxylin-Eosin objective magnifications, X 2.5 left and X 10 right, respectively.*

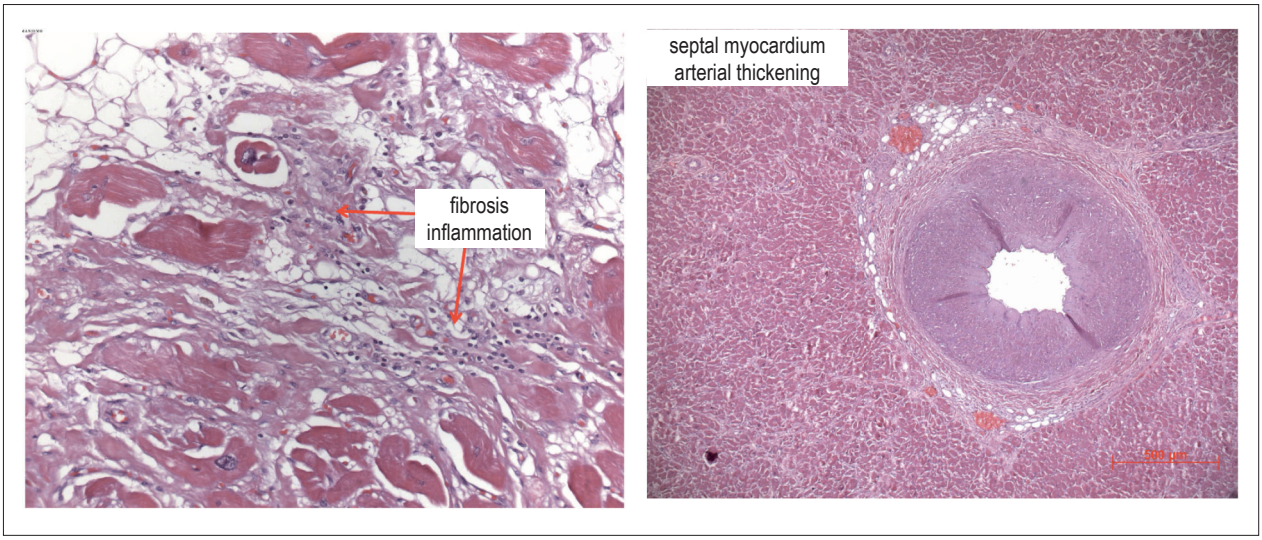

Figure 9 – *Microscopic sections of the right ventricular wall left panel and of the ventricular septum right panel. Left panel focal lympho-histiocytic inflammatory infiltrate and fibrosis between the cardiomyocytes. In addition to the fibrotic component, fatty tissue can be seen in the left upper corner of the image. Right panel arterial thickening in the septal myocardium due to hypertrophy of the tunica media. Hematoxylin-Eosin objective magnifications, X 20 left and X 5 right, respectively.*

The diagnostic criteria for ARVC established by a task force and published in 1994 were divided into major and minor. Those criteria include the presence of global and segment structural changes of the right ventricle, histological and ECG changes, arrhythmias and genetic factors. In 2010, a review of those criteria was published to help to identify ARVC and to diagnose it in the patients' family members.[15] The diagnosis of ARVC requires the association of two major criteria, or one major criterion and two minor criteria, or even four minor criteria.

In the case here reported, in vivo endomyocardial biopsy was not performed, but ARVC was morphologically confirmed on postmortem examination, with the typical finding of myocardial areas of fibrofatty replacement in the right ventricular wall and of thickened arteries in the ventricular septum (previously described in this disease).[16]

Left ventricular involvement in ARVC has been reported in a study of 42 hearts from postmortem examination or from receptors of heart transplantation. That study has reported that approximately 50% of the specimens had gross involvement of the left ventricle, while 75% evidenced histological involvement. In addition to fibrofatty replacement in the myocardium in the sub-epicardial or middle-mural region, there was dilatation of that chamber

in all cases with grossly evident disease, which was marked in 25% of them.[17]

Pathogenesis and genetics

The ARVC consists in fibrofatty replacement in the myocardium. Myocardial atrophy is progressive and absent at birth. The myocardial process results from the death of cardiomyocytes beginning at birth.[18] Postmortem studies have reported evidence of apoptosis in that cardiomyopathy.[19] In addition, that same mechanism has been detected in biopsies (in vivo).[20]

The fibrofatty replacement occurs gradually from the epicardium towards the endocardium, becoming transmural. Consequently, there is weakening of the right ventricular free wall, causing dilatation and aneurysms, characteristically located between the inferior, apical and infundibular walls, forming the triangle of dysplasia.[18]

In addition to weakening the wall, those changes in association with the inflammatory factor hinder and delay the intraventricular electrical conduction, resulting in late potentials, epsilon wave and right bundle-branch block. Therefore, a ventricular arrhythmia can install due to reentry phenomenon.[18]

Two pathogenetic theories have been described.[21] The first says the disease has a genetic component, and that the disorder in myocardial development begins in the intrauterine period.

Genetic studies[22] have evidenced two types of inheritance for the ARVC phenotype. The first type is autosomal dominant inheritance with variable penetrance, while the second is represented by recessive forms associated with skin diseases. Ten genetic loci have been detected, but only five genes with mutations. The first ARVC-related gene was found in the Naxos disease, a rare recessive syndrome related to a mutation in the desmosomal protein called plakoglobin. That syndrome, however, has been characterized as the variant 2 of ARVC. The first form of autosomal dominant mutation in that variant was found in the gene that decodes the cardiac ryanodine receptor (RyR2), the receptor that accounts for calcium homeostasis and coordinates the excitation-contraction mechanism of cardiomyocytes. The mutations change the calcium-channel closing mechanism, and, thus, a high sympathetic stimulation via emotional or physical stress can increase excessively intracellular calcium, leading to severe arrhythmias. In addition to ARVC, mutations in the gene that decodes RyR2 can cause two other diseases: catecholaminergic polymorphic ventricular tachycardia and familial polymorphic ventricular tachycardia. The discovery of ARVC variant 2 is considered essential to unveil the pathogeneses of ARVC. Another recent discovery by the research team of Rampazzo[22] has been in ARVC variant 1: the mutation of the genes that decode TGF-beta3. This cytokine stimulates the proliferation of mesenchymal cells. *In vitro* experiments have shown that the mutations in the genes that encode TGF-beta3 can cause myocardial fibrosis.

In addition, a theory speculates whether ARVC results from a previous infection (myocarditis, pericarditis). The theory considers a viral etiology that could be aggravated by an auto-immune reaction. The auto-immune or viral reaction could explain the inflammatory phenomenon, which would not occur due to only apoptosis of cardiomyocytes. That theory[21] could explain left ventricular involvement and atrial rhythm disorders. The viral etiology has been suspected in a study[23] with detection of viral genome in the myocardium of some patients with ARVC. Such theory, however, has been refuted in another study[24] that advocates that the viruses are innocent bystanders, and that tissue degradation favors viral colonization.

Adipose infiltration by itself does not characterize ARVC, because some hearts have a certain amount of fat in the anterior and apical walls of the right ventricle and do not show degenerative changes in cardiomyocytes. Thus, to establish the diagnosis of ARVC one must identify the fibrous tissue replacement pattern associated with myocardial degeneration.[18]

Although ARVC is clinically recognized as a cause of cardiac sudden death in the young[25] during physical exercise, there is a subgroup, in which our patient is included, with biventricular failure, unfavorable outcome and indication for heart transplantation.

Cardiac magnetic resonance is useful to identify ARVC morphologically, and even to establish its prognosis.[26]

(Laís Costa Marques, medical student, and Vera Demarchi Aiello, MD)

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Rare Association of two Genetic Causes of Sudden Death in a Young Survivor

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Introduction

Sudden cardiac arrest (SCA) in young adults is frequently caused by inherited cardiac diseases, particularly cardiomyopathies and ion channelopathies.[1] Genetic testing can be essential in the follow-up of survivors and today´s genetic diagnostics may include the parallel analysis of several SCA related genes, most commonly those associated with ion channelopathies and hypertrophic cardiomyopathy (HC). We present the case of a young survivor of SCA, carrier of double heterozygosity for mutations in the *SNC5A* and *MYBPC3* genes, illustrating the complexity of genotype-phenotype associations and the difficulties of decisions regarding therapeutic interventions in inherited cardiac diseases.

Case Report

A healthy 19-year-old man suffered SCA while playing football. His girlfriend (a medical student) carried out cardiopulmonary resuscitation until the arrival of the ambulance. Polymorphic ventricular tachycardia degenerating into ventricular fibrillation (VF) was documented (Figure 1A) and defibrillation was successfully performed (Figure 1B). At subsequent hospital admission, the electrocardiogram (ECG) showed sinus rhythm (95 bpm), with a PR interval of 0.26-0.28 sec and a QTc interval of 0.45 sec. (Figure 1C). The echocardiographic study (echo) was normal and reversible causes of SCA including ionic, infectious and toxic were excluded. The patient had a normal clinical exam and no personal history of severe illness. He took no medication. There was no family history of cardiac disease or sudden death. Thoracic X-ray, cardiac magnetic resonance, exercise test (treadmill) and coronary angiography were normal.

Electrophysiological study (EPS) showed a prolonged HV interval (80 ms) and ventricular stimulation (600 ms cycle – 250-220-220 at RV apex) induced polymorphic VT with no pulse (successfully terminated by external cardioversion). A provocative test for Brugada syndrome (BrS) was postponed.

After written informed consent, genetic screening was performed on a panel of 9 genes: *MYBPC3, MYH7, MYL2, SCN5A, TNNI3, TNNT2, KCNQ1, KCNH2* and *LQT5*. The entire coding regions were tested by PCR and direct sequencing. We found the mutation c.3622G>T; p.Glu1208* in the *SCN5A* gene (NM_198056.2), that was already described in BrS. Additionally, another sequent variant, c.446C>A; p.Ala149Asp, in the *MYBPC3* gene (NM_000256.3) was detected (Figure 2B). This alteration was reported as a rare sarcomeric gene variant in a single case of the offspring cohort of the Framingham Heart Study, including 1,637 unrelated individuals.[2] Although this single individual did not show alteration of the left ventricle wall thickness, only one wall segment was measured, without any further detailed information, thus HC cannot be excluded. Besides, no information was given whether the index case of this family was also harboring this sequence variant in *MYBPC3*.

The p.Ala149Asp mutation in *MYBPC3* affects an evolutionarily conserved amino acid and it was absent in 100 age-matched Portuguese control samples. Regarding the various in-silico mutation prediction programs, PolyPhen2 (http://genetics.bwh.harvard.edu/pph2/) predicted this alteration as possibly damaging with a score of 0.65 (sensitivity: 0.87, specificity: 0.91). The SNPs&Go program (http://snps.biofold.org/snps-and-go//snps-and-go.html) predicted this variant as disease associated variation (0.696).

Subsequent family analysis showed that the patient´s father was carrier of both *SCN5A* and *MYBPC3* mutations (Figure 2A). The father was submitted to EPS with provocative test with flecainide. This test showed negative results. The sister of our index patient was harboring the *SCN5A* mutation solely. Because of the young age, we decided not to perform provocative tests or EPS.

A cardioverter defibrillator (ICD) was implanted in the index patient. Provocative pharmacological tests were systematically refused by the patient thereafter. Serial ECGs during hospitalization showed normal patterns except for mild PR prolongation that persisted also during ambulatory follow up. Family screening (parents and sister) revealed normal clinics, ECG and echo studies.

Discussion

In the patient presented herein, the persistent prolonged PR interval on serial ECGs that is explained by a prolonged H-V interval during EPS, the induction of sustained polymorphic VT during EPS (that had to be terminated by an external DC shock) and the identification of a pathogenic non-sense mutation in *SCN5A* gene (already described as causing an

Keywords

Death, Sudden Cardiac; Cardiomyopathy, Hypertrophic, Familial; Adolescent; Brugada Syndrome.

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Case Report

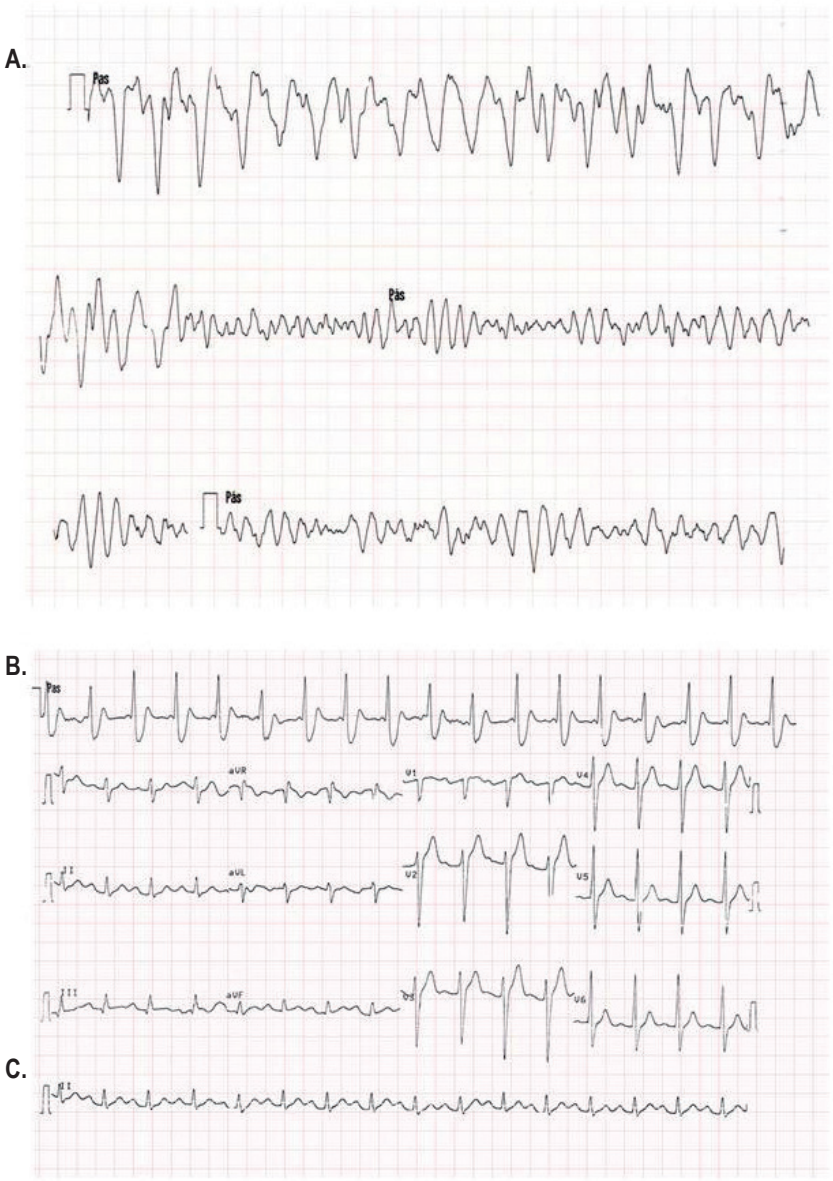

Figure 1 – *A: Polymorphic ventricular tachycardia degenerating into ventricular fibrillation (rhythm strips in sequence); B: Rhythm strip after defibrillation; C: ECG at hospital admission (PR interval: 0.26-0.28 sec; QTc: 0.45 sec).*

important reduction in sodium currents – INa)[3] favored the diagnosis of a loss-of-function sodium channelopathy like BrS or progressive cardiac conduction disease. These inherited conditions may overlap and can coexist in the same family and even in the same individual and it was suggested that they may indeed represent different aspects of the same disease and not separate entities. However, with no BrS sign on ECG and as the patient refused a provocative test, a clear diagnosis of BrS was not confirmed.[4]

Disease penetrance and expressivity are highly variable in these diseases and the causal role of *SCN5A* mutations in BrS is not yet clearly established. The patient´s father, although with the same mutation, was healthy and a provocative test for BrS was negative. The young sister of the patient had also a normal phenotype although invasive tests were not performed. Additionally, both the patient and the father are carriers of a missense mutation in the *MYBPC3* gene, one common mutated gene in HC, an autosomal-dominant inherited disease that may cause ventricular arrhythmias and SCA mainly in the young. The identified mutation supported the probability of pathogenicity. In HC carriers of a mutant gene, the phenotype may develop late in life particularly with

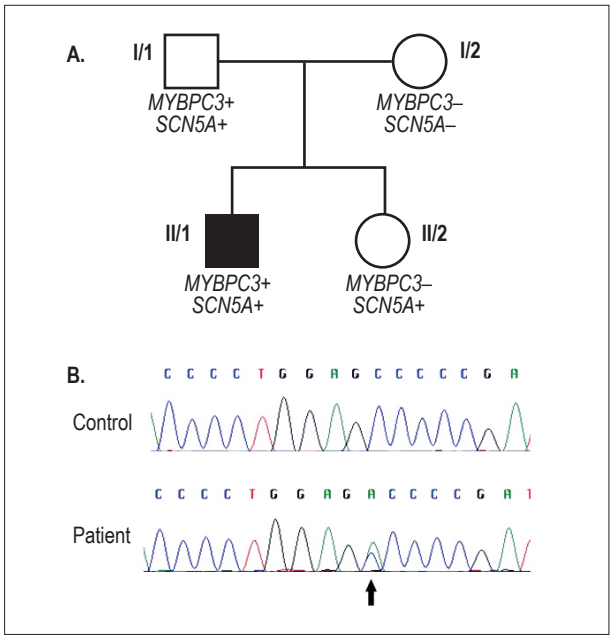

Figure 2 – *A: Pedigree of the family. MYBPC3+: harboring the MYBPC3 mutation, SCN5A+: harboring the SCN5A mutation; B: the MYBPC3 mutation p.Ala149Asp. Upper lane: healthy individual; lower lane: index patient.*

MYBPC3 gene mutations. However, under the "appropriate" trigger, like strenuous exercise as was the case with our patient, sudden death may be the first manifestation of the disease. To our knowledge, this is the first report on *SCN5A* and *MYBPC3* double mutations.

Genetic tools and protocols are evolving fast.[5] The new era of genetic testing, with the easy possibility of screening a large number of genes, like next generation sequencing, is greatly enhancing the perspectives of a genetic diagnosis in inherited cardiomyopathies in a fast and cost-efficient way. However, it is also increasing the complexity of interpretation namely in the context of a limited or even absent phenotype, thus caution should be kept when considering clinical decisions.

Author contributions

Conception and design of the research: Brito D; Acquisition of data and Critical revision of the manuscript for intellectual content: Brito D, Magalhães A, Cortez-Dias N, Miltenberger-Miltenyi G; Analysis and interpretation of the data: Brito D, Cortez-Dias N, Miltenberger-Miltenyi G; Writing of the manuscript: Brito D, Miltenberger-Miltenyi G.

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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Dysphagia Caused by Right-Sided Aortic Arch and Lusorian Artery

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This case report describes a 75-year-old male patient presenting with persistent cough. His chest X-ray showed a right-sided paratracheal opacification. A thoracic CT (Figure 1 and Video 1) was subsequently performed to better characterize the radiographic findings. The exam revealed a Neuhauser Vascular Anomaly, that pertains a right-sided aortic arch and lusorian artery.

The lusorian artery is also known as an aberrant right subclavian artery. It is an anatomical variant in which the brachiocephalic artery is absent. Thus, from the aortic arch there are 4 originating arteries: the right and left common carotid arteries and the right and left subclavian arteries. The lusorian artery prevalence varies from 0.16 to 0.8%, depending on the country. The anomaly is clinically asymptomatic in more than 90% of the cases. Most symptoms arise in individuals at advanced ages, probably related to atherosclerotic phenomena. The most frequent symptoms are dysphagia, dyspnea, retro-sternal pain, coughing and weight loss. The lusorian artery and the right-sided aortic arch coexist in 9.2% of the cases.

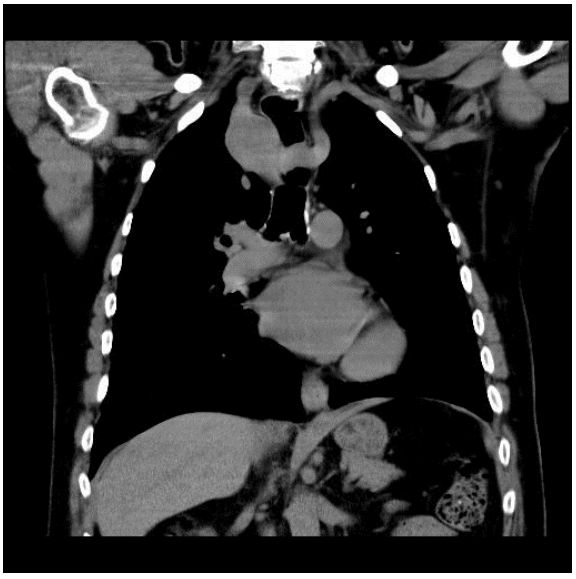

Figure 1 – *Neuhauser vascular anomaly.*

Author contributions

Conception and design of the research, Acquisition of data and Analysis and interpretation of the data: Gil J, Marmelo B, Moreira D; Writing of the manuscript: Gil J; Critical revision of the manuscript for intellectual content: Moreira D, Santos LF, Cabral JC.

Keywords

Deglutation Disorders / complications; Aorta, Thoracic; Cough; Subclavian Artery Syndrome.

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Study Association

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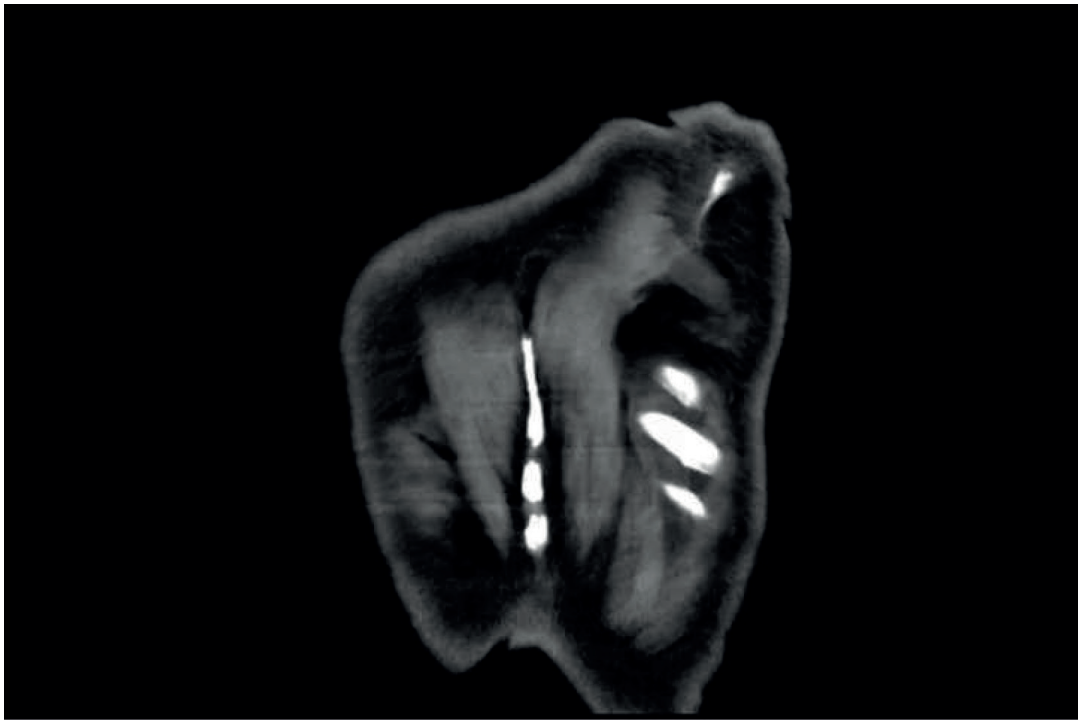

Video 1 – *Watch the videos here: http://www.arquivosonline.com.br/2017/english/10802/video_ing.asp*

Fibrinogen and Atherosclerosis

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To the Editor,

I have read with great interest the article entitled "Early Markers of Atherosclerotic Disease in Individuals with Excess Weight and Dyslipidemia" by Menti et al.[1] recently published in *Arquivos Brasileiros de Cardiologia* 2016; 106: 457-63. The investigators reported that fibrinogen is associated with subclinical atherosclerosis in individuals with excess weight.[1]

Several studies have shown that high serum levels of fibrinogen are strongly associated with coronary artery disease.[2,3] High serum levels of fibrinogen may contribute to vascular disease by increasing blood viscosity, stimulating fibrin formation, or increasing platelet-platelet interaction.[2,3]

Catena et al.[4] reported that plasma homocysteine (Hcy) levels were directly correlated with age, waist circumference, fasting glucose, triglyceride, uric acid, and fibrinogen levels, and inversely correlated with creatinine clearance and high-density lipoprotein cholesterol, vitamin B12, and folate levels. Low vitamin B12 concentration and hyperhomocysteinemia are common, and might affect serum fibrinogen levels.

25-hydroxyvitamin D [25(OH)D] deficiency with increased risks of cardiovascular disease and venous thromboembolism may relate to adverse hemostatic and inflammatory responses. Blondon et al.[5] reported that low levels of serum [25(OH)D] were cross-sectionally associated with higher levels of interleukin-6, homocysteine, total tissue factor pathway inhibitor and plasminogen activator inhibitor-1.

In light of these findings, it might be beneficial to evaluate serum levels of vitamin B12, Hcy, and [25(OH)D] because of their close association with fibrinogen levels.

Keywords

Fibrinogen; Coronary Artery Disease; Obesity; Dyslipidemias.

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Reply

We were honored by your interest in our article entitled *"Early Markers of Atherosclerotic Disease in Individuals with Excess Weight and Dyslipidemia"* published in *Arquivos Brasileiros de Cardiologia*.

The finding of high fibrinogen levels in patients with atherosclerotic disease has generated a large volume of clinical evidences in the past few decades, and has been considered a risk marker for cardiovascular events. High fibrinogen levels are also known to promote atherosclerotic disease by increasing blood viscosity, stimulating fibrin formation and increasing platelet aggregation. In the setting of an inflammatory status such as that seen in individuals with excess weight, the higher hepatic production of fibrinogen regulated by inflammatory cytokines may be an important link in the progression of the atherosclerotic disease in its different subclinical and clinical stages. Our study had a small sample size, however large enough to bring this association to light.[1]

As regards the assessment of serum levels of vitamin B12 and vitamin D, in a recent study with a small sample, Baser et al[2] observed the association of vitamin D deficiency with high fibrinogen levels and pro-oxidative serum markers. Vitamin B12 deficiency, by hyperhomocysteinemia induction, also plays a role in the development of cardiovascular disease. Every 5-mcmol/L increase above 10 mcmol/L in serum levels of homocystein is associated with a 20% increase in the risks of circulatory disorders.[3]

Although the assessment of changes in endothelial function in patients with vitamin B12 and vitamin D deficiency had not been included in this study, it is a promising research field. In a study with a small sample assessing endothelial function using flow-mediated brachial artery dilatation in patients with vitamin B12 deficiency, increased dilatation after proper vitamin B12 replacement was observed.[4] A similar finding was observed in a sample of individuals undergoing hemodialysis after vitamin D replacement.[5]

We thank Dr. Cerit's remarks and are satisfied to stimulate discussion regarding this important field of clinical cardiology, which has been a frequent concern in daily practice, in view of the growing incidence of obesity among our society.

Eduardo Menti

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