Coronary Flow Reserve and Diastolic Dysfunction Pattern In Patients with Dilated Cardiomyopathy

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Summary

Introduction: In patients with nonischemic dilated cardiomyopathy (DCM), decreased coronary flow reserve is associated with increased risk of death and one of the possible mechanisms is the increased left ventricular filling pressures.

Objective: To evaluate the coronary flow reserve (CFR) by transthoracic echocardiography (TTE) and compare it with degrees of diastolic function in patients with DCM.

Methods: We studied 156 patients with DCM (101 men, mean age 53±12 years) and severe systolic dysfunction. Diastolic function was assessed by mitral inflow, pulmonary venous flow and tissue Doppler, and classified as normal (grade 0), impaired relaxation pattern (Grade 1), pseudonormal pattern (Grade 2), reversible restrictive pattern during Valsalva maneuver (Grade 3) and irreversible restrictive pattern during Valsalva maneuver (Grade 4). The CFR was determined by pulsed Doppler in left anterior descending coronary artery and calculated as the ratio of the maximum diastolic velocity during hyperemia (dipyridamole, 0.84 mg/kg) and baseline.

Results: All patients had significant systolic dysfunction, with mean left ventricular ejection fraction of 25.3±5.7%. 86 patients (55%) had grade 0 or 1 diastolic function while 70 patients (45%) had grades II, III or IV of diastolic dysfunction. The feasibility of CFR obtained by TTE was 90.4%. The CFR was significantly higher in patients with diastolic dysfunction 0 or 1 (2.2±0.5) than in patients with diastolic dysfunction grades II, II or IV (1.9±0.5, p<0.001).

Conclusion: CFR is reduced in patients with nonischemic DCM and advanced degrees of diastolic dysfunction. (Arq Bras Cardiol: Imagem cardiovasc. 2015; 28(1):30-35)

Keywords: Cardiomyopathy, Dilated; Fractional Flow Reserve, Myocardial; Ventricular Dysfunction, Left; Heart Failure/Mortality.

Introduction

Coronary flow reserve is often decreased in Dilated Cardiomyopathy (DCM) of nonischemic origin and represents a three times higher relative risk of death and/or development of progressive heart failure[1]. However, the mechanisms responsible for this alteration are not well established. Three reasonable factors, either alone or together, can contribute to this reduction: microvascular dysfunction; myocardial hypertrophy; and increased left ventricular filling pressures[1,2]. Coronary flow reserve is traditionally used to functionally assess coronary artery disease[3]. The calculation of this parameter was only possible through invasive techniques, such as thermodilution, gas clearance, surgical implantation of flowmeters and intracoronary Doppler. Today, with advances in Doppler echocardiography and the advent of ultrasound contrast agents, it is possible to see the epicardial coronary arteries by transthoracic way and, by measuring the flow rate before and after maximal vasodilation, it is possible to calculate the Coronary Flow Velocity Reserve (CFVR)[4-5]. Note that this parameter is being increasingly incorporated into the routine of echocardiography laboratories for evaluating microcirculation in different clinical situations out of the context of obstructive coronary artery disease[6-7]. Echocardiography is a widely available tool and it is useful for diagnostic and prognostic evaluation of patients with DCM[8]. We know in advance that, in these patients, the diastolic function indexes express more faithfully the filling pressures and correlate more with the symptoms of exercise intolerance than left ventricular ejection fraction[9].

Objective

The objective of this study was to compare the CFVR obtained by transthoracic echocardiography categories of diastolic function in patients with DCM of nonischemic origin.

Method

Patients

Patients with nonischemic DCM with severe left ventricular systolic dysfunction (ejection fraction ≤ 35%) and

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angiographically normal coronary arteries on hemodynamic study conducted up to five years from inclusion in the study. Exclusion criteria were: age < 18 years and > 75 years, malignant arrhythmias in the last thirty days, concomitant disease of poor prognosis such as cancer, severe acute myocarditis, aortic valve disease and mitral stenosis, congenital heart disease, advanced atrioventricular block, chronic obstructive pulmonary disease, use of xanthine derivatives in the last 24 hours before the test and patient's refusal to participate in the protocol. The study was approved by the ethics committee and all patients signed the informed consent (IC).

Echocardiography

All patients underwent transthoracic echocardiography with commercially available equipment (IE 33, Philips Medical Systems) equipped with broadband sector transducers 2.5-3.5 MHz using second harmonic technology. The diameters of the cavities were measured by M or bidimensional mode obtained by long axis parasternal plane. Ventricular volumes and ejection fraction were calculated by the Simpson's method, as recommended by the American Society of Echocardiography and the Brazilian Guidelines of Echocardiography[10]. Diastolic function was assessed by conventional Doppler of the mitral valve and pulmonary veins and tissue Doppler at the level of the medial and lateral mitral annulus. For quantification purposes, the algorithm for patients with systolic dysfunction[11] was followed (Figure 1), and classified in the following categories: Grade 0 (normal diastolic function); Grade I (impaired relaxation); Grade II (pseudo-normal standard); Grade III (restrictive with reversion to the Valsalva maneuver); and Grade IV (restrictive without reversion to the Valsalva maneuver). All patients underwent stress echocardiography with dipyridamole at a maximum dose of 0.84 mg/kg for ten minutes with discontinuation criteria in case any intolerant symptoms occurred, hypotension characterized by a drop in blood pressure of 30 mmHg, wall motion abnormalities and in the end of the protocol. The coronary flow velocity was determined by two-chamber modified apical window with the pulsed Doppler sample placed in the Medium Distal segment of the Anterior Descending Artery (ADA). For this evaluation, a sector transducer with frequency 5-8 MHz oriented with color flow mapping was used. Ultrasonic contrast agents were used for enhancing the Doppler signal with PESDA (Perfluorocarbon Exposed Sonicated Dextrose and Albumin) or Definity® (Lantheus) available. The spectral curves of flow velocities were obtained with pulsed Doppler with sample volume of 2 mm placed at the medium distal portion of the ADA, both at rest and during infusion of dipyridamole. The maximum velocity of the diastolic component was measured and the mean of at least three beats was determined by selecting the clearer curves. CFVR was calculated by the ratio of the maximum diastolic velocity during hyperemia (dipyridamole 0.84 mg/kg) and the maximum diastolic velocity at baseline (Figure 2).

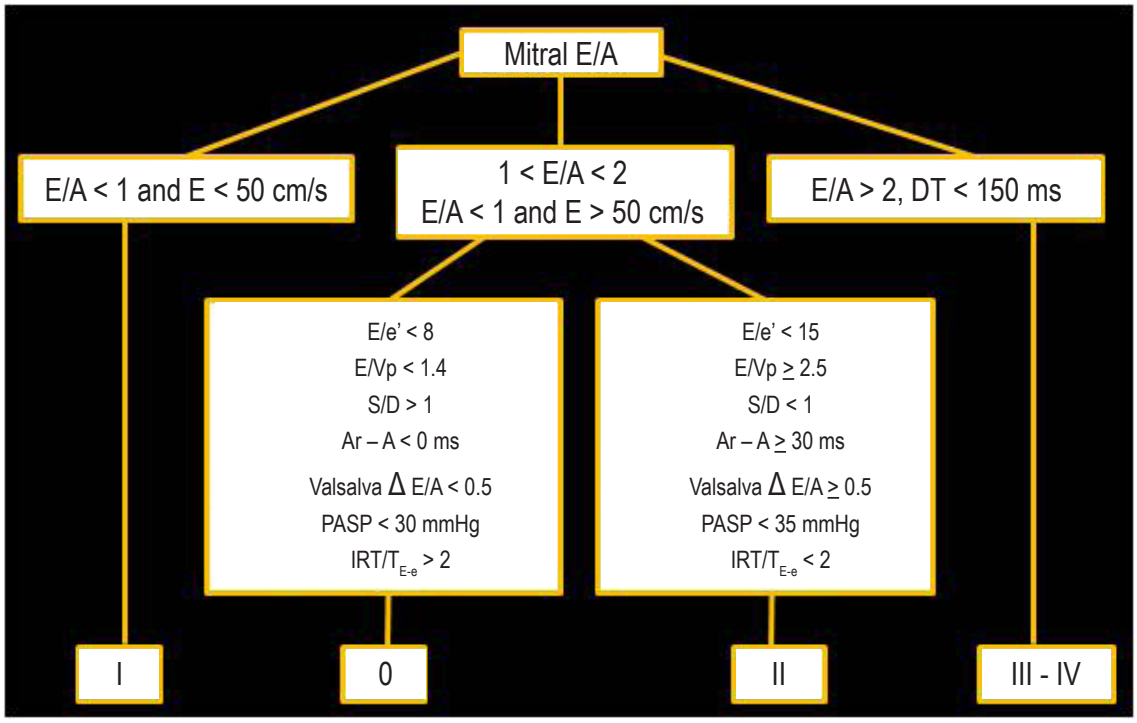

Figure 1 - *Algorithm for diastolic function classification. DT: e-wave deceleration time; Vp: mitral valve propagation velocity; Ar: pulmonary reverse A-wave; IRT: isovolumic relaxation time; PASP: pulmonary artery systolic pressure; T_{E-e}: time difference between the E and e' wave of the mitral ring against QRS. Reproduction authorized by Nagueh et al.[11]*

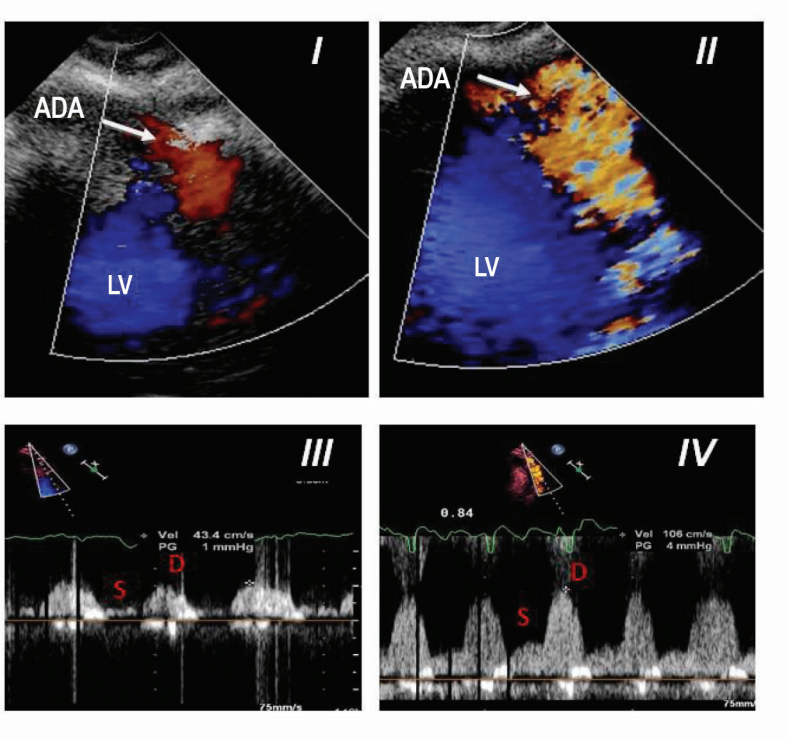

Figure 2 - *Calculation of coronary flow velocity reserve. PANEL I and II: color flow mapping of the anterior descending artery by transthoracic test at rest and after dipyridamole infusion respectively. PANEL III and IV: pulsed Doppler of the anterior descending artery at rest and after dipyridamole infusion respectively. ADA: anterior descending artery. LV: left ventricle. S: systolic coronary flow component. D: diastolic coronary flow component. CFVR: coronary flow velocity reserve.*

$$CFVR = \frac{\text{Maximum diastolic velocity during hyperemia}}{\text{Maximum basal diastolic velocity}}$$

Statistical analysis

Continuous variables were expressed as mean and standard deviation and categorical variables were expressed as proportions. Student's t test was used to compare the CFVR between the two defined groups (Grades 0 and I versus Grades II, III and IV), since the data were normally distributed (verified by the Kolmogorov-Smirnov test). To study the homogeneity of the samples, the Mann-Whitney test was used to compare age, and chi-square test was used for the other variables, all categorical. In this study, $p < 0.05$ was considered statistically significant.

Results

Altogether, 156 patients with nonischemic DCM were studied. Table 1 shows the clinical and echocardiographic characteristics of the study population. Of these, 101 were men with a mean age of 53.22 years ± 12.22. The etiology of CMP was: hypertension (47%), Chagas disease (19%), alcohol (21%) and idiopathic (17%). According to the functional class of the New York Heart Association (NYHA), 24% were in class I, 47% in class II, and 29% in class III. All patients had significant systolic dysfunction with a mean ejection fraction of 25.34 ± 5.77%.

To analyze the data, we divided the patients into two groups: Group A, those with normal diastolic function and diastolic dysfunction grade I (86 patients, 21 without normal diastolic function and 65 with diastolic dysfunction grade I); and Group B, those with diastolic dysfunction grades II, III and IV (70 patients, 44 with diastolic dysfunction grade II, 18 grade III and 8 grade IV). There was no statistical significance between the two groups as for age, sex and medication used. In Group A, 27 patients were in NYHA class I; 40 in class II; and 19 in class III. In Group B, 11 patients were in NYHA class I; 33 in class II; and 26 in class III. Regarding the etiology there was a higher prevalence of Chagas disease in group B. CFVR was significantly higher in the patients of group A (2.2 ± 0.52) than in those of group B (1.8 ± 0.49) $p < 0.001$. The feasibility of determining CFVR was higher in group A than in group B (94% versus 84%, respectively, $p < 0.05$). In group A, 5 patients presented symptoms (arrhythmia, hypotension or malaise) during dipyridamole infusion leading to interruption of the test; while in group B, 11 patients had symptoms.

Discussion

Our study showed that CFVR is lower in patients with nonischemic DCM with more advanced degrees of diastolic

Table 1 – Clinical and echocardiographic characteristics

Clinical data	Group A (DD grades 0-I) N = 86	Group B (DD grades II-III-IV) N = 70	P value
Age (years)	54.4 ± 12.1	51.7 ± 12.4	0.17
Male	55 (64%)	46 (65%)	0.82
Etiology			
Hypertensive	46 (53%)	28 (40%)	0.09
Idiopathic	13 (15%)	13 (18%)	0.57
Chagas disease	11 (12%)	18 (27%)	0.04
Alcoholic	19 (22%)	14 (20%)	0.75
Medication in use			
ACEI/ARB	83 (96%)	64 (91%)	0.19
Diuretic	76 (88%)	60 (86%)	0.62
Betablocker	80 (93%)	64 (92%)	0.71
Digital	34 (40%)	30 (43%)	0.67
Echocardiographic data			
LV ejection fraction (%)	27.67 ± 5.69	22.51 ± 4.49	<0.01
EDV (mL)	222 ± 74.94	250.50 ± 76.78	0.02
ESV (mL)	162.15 ± 61.50	194.57 ± 59.88	0.03
LA (mm)	42.58 ± 6.07	48.12 ± 6.32	<0.01
Basal ADA velocity cm/s	38.82 ± 10.87	40.07 ± 11.01	0.50
ADA peak velocity cm/s	83.47 ± 20.60	72.84 ± 18.38	<0.01
CFVR	2.2 ± 0.52	1.8 ± 0.49	<0.01

ACEI: angiotensin-converting enzyme inhibitors I; ARB: angiotensin II receptor blockers: EDV: end-diastolic volume; ESV: end systolic volume; LA: left atrium; ADA: anterior descending artery; CFVR: coronary flow velocity reserve.

dysfunction. This finding supports the hypothesis that in DCM, reduced CFR is related to increased wall stress, and myocardial ischemia, especially in the subendocardial layers, may be responsible for clinical deterioration and ventricular function.

Vanderheyden et al.[12] evaluated patients with idiopathic DCM and demonstrated that CFVR obtained by transesophageal echocardiography correlated negatively with invasive hemodynamic parameters such as right atrial pressure, end-diastolic pressure of the left ventricle and pulmonary capillary pressure. This reserve was reduced by an increase in basal coronary flow, rather than a reduction in hyperemic flow. In this study, basal coronary flow velocity was higher in patients in the control group and correlated positively with left ventricular meridional diastolic stress, signaling the recovery of microcirculation with persistent vasodilation against higher metabolic demand. In the same vein, the study by Dini et al.[13] showed a strong correlation of CFVR obtained by transthoracic echocardiography with plasma levels of atrial natriuretic peptide, a neurohormonal peptide that also reflects conditions of increased filling pressures.

Myocardial hypertrophy may reduce coronary flow reserve by mechanisms such as inappropriate vascular growth for increased cardiac mass and compression of intramural vessels by increased extravascular resistance. In a previous study, we showed that, in our series, mass index was not significantly associated with events in the univariate analysis[14]. In these patients, the increase in mass is determined mainly by dilation with the sarcomeres arranged in series, leading to increased myocardial thickness. In this situation, hypertrophy is a compensatory mechanism to reduce wall stress. According to our data, CFVR reduction occurred primarily through reduction of hyperemic flow, an indicator of microvascular dysfunction. These findings are consistent with the study of Neglia et al.[1], which evaluated patients with idiopathic DCM using positron emission tomography (PET). He demonstrated that the reduction of myocardial flow was a predictor of poor prognosis regardless of the degree of left ventricular functional impairment. In the follow-up, the basal coronary flow was not statistically different between patients with and without events, while hyperemic flow with dipyridamole, and consequently the flow reserve, was significantly lower in those patients who developed the progressive form of the disease.

Although the basal flow velocity of our patients has shown a slightly higher average, it was not statistically significant between the two groups concerning diastolic function. These results support the hypothesis that repetitive myocardial ischemia and chronic myocardial hypoperfusion assigned

to microvascular dysfunction have a pathophysiological role responsible for the progression of ventricular dilatation and dysfunction. According to Cecchi et al.[15], microvascular dysfunction may represent a common pathway leading to disease progression in various heart diseases, including aortic stenosis and hypertensive heart disease. The mechanisms responsible for microvascular dysfunction in this group of patients are: decreased microvessel density; increased intercapillary space; interstitial and perivascular fibrosis; medial hypertrophy with arteriolar remodeling; and endothelial dysfunction[16-18].

All our patients had severe systolic dysfunction, and unlike most previous studies that mainly addressed individuals with idiopathic etiology, our series was composed of a large number of patients with Chagas' disease[19], that is, we included patients in advanced stages of the disease, when it is not possible to identify the possible trigger in the reciprocal interaction mechanism between myocardial flow depression and myocardial function. The study by Neglia et al.[1] evaluated patients with minor severity, left ventricular ejection fraction < 50% and functional status class I (NYHA), which made it possible to determine the independent predictive power of CFVR in disease progression. Our data are also consistent in identifying other determinants of severe diastolic dysfunction, including ejection fraction and left atrial size. In these patients, the left atrial size chronically reflects not only diastolic dysfunction, but also the impact of mitral regurgitation. These parameters present great variability under the influence of loads, specifically.

A recent study[14] that assessed the prognostic value of myocardial flow reserve using contrast echocardiography in patients with nonischemic DCM, demonstrated in a multivariate analysis that β reserve and left atrial diameter were independent predictors of death and cardiac transplantation. However, in the incremental risk model, the β reserved added information on clinical variables, ejection fraction and left atrial diameter. Finally, the CFVR had a slightly smaller feasibility in patients with a more severe diastolic function. This group includes the most serious patients most likely to develop heart rhythm disorders and intolerance to dipyridamole infusion.

Limitation

Our series consisted of patients with DCM with heterogeneous etiology that may represent a bias by itself. In the evaluation of diastolic function we did not use any variables with continuous spectrum, which add greater robustness in terms of correlation due to the high incidence of arrhythmias and conduction changes presented by the patients, and we thought it would be good to categorize it, rather than relying on a single parameter.

Conclusion

CFVR obtained by transthoracic echocardiography is a feasible method in the evaluation of patients with DCM of nonischemic origin. CFVR is lower in advanced stages of diastolic dysfunction, identifying, in this group of patients, those at higher risk of developing progressive heart failure.

Authors' contribution

Research creation and design: Sbano JC, Tsutsui JM; Data acquisition: Lima MF, Lima MM; Analysis and interpretation of data: Lima MF, Lima MM; Statistical analysis: Lima MF; Funding: Mathias Jr W, Sbano JC; Manuscript drafting: Lima MF, Mathias Jr W, Tsutsui JM; Critical revision of the manuscript as for important intellectual content: Mathias Jr W, Tsutsui JM.

Potential Conflicts of Interest

No relevant conflicts of interest.

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Academic Association

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References

1. Neglia D, Michelassi C, Trivieri MG,Sambuceti G, Giorgetti A, Pratali L, et al. Prognostic role of myocardial blood flow impairment in idiopathic left ventricular dysfunction. Circulation. 2002;105(2):186-93.
2. Rigo F, Gherardi S, Galderisi M, Pratali L, Cortigiani L, Sicari R, et al. The prognostic impact of coronary flow- reserve assessed by Doppler echocardiography in non-ischaemic dilated cardiomyopathy. Eur Heart J. 2006; 27(11):1319-23.
3. Gould KL, Kirkeeide RL, Buchi M Coronary flow reserve as a physiology measure of stenosis severity. J Am Coll Cardiol. 1990;15(2):459-74.
4. Matsumura Y, Hozumi T, Watanabe H , Fujimoto K, Sugioka K, Takemoto Y, et al.Cut off value of coronary flow velocity reserve by transthoracic Doppler echocardiography for diagnosis of significant left anterior descending artery stenosis in patients with coronary risk factors. Am J Cardiol 2003;92(12):1389-93.
5. Dimitrow PP. Transthoracic Doppler echocardiography – noninvasive diagnosatic window for coronary flow reserve assessment. Cardiovasc Ultrasound. 2003,1:4.
6. Rigo, F Coronary flow reserve in stress-echo lab. From pathophysiologic toy to diagnostic tool. CardiovascUltrasound 2005;3:8.
7. Camici PG, Crea F Coronary microvascular dysfunction. N Engl J Med.2007;356(8):830-40.
8. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiati TG, et al. ACC/AHA Guidelines for the diagnosis and management of heart failure in adults. J Am Coll Cardiol. 2009; 53(15):1343-82.
9. Lapu-Bula R, Robert A, De Kock M, D'Hondt AM, Detry JM, Melin JÁ, et al.. Risk stratification in patients with dilated cardiomyopathy: contribution of Doppler-derived left ventricular filling. J Am Cardiol. 1998;82(6):779-85.

10. Lang RM, Bierig M, Devereux A, Flechskamse FA, Foster E, Pellikka PA, et al.. Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography Recommendations for Chamber Quantification: A report from the American Society of Echocardiography´s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18(12):1440-63.

11. Nagueh SF, Appleton CP, Gillebert TC,Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr. 2009;22(12):107-33.

12. Vanderheyden M, Bartunek J, Verstreken S, Mortier L, Oh JK, Smiseth OA, et al. Non invasive assessment of coronary flow reserve in idiopathic dilated cardiomyopathy: hemodynamic correlations. Eur J Echocardiogr .2005;6(1):47-53.

13. Dini FL, Ghiadoni L, Conti U, Stea F, Buralli S, Taddei S, et al. Coronary flow reserve in idiopathic dilated cardiomyopathy: Relation with left ventricular wall stess, natriuretic peptides, and endothelial dysfunction. J Am Soc Echocardiogr. 2009;22(4):354-36.

14. Lima M, Mathias J W, Tsutsui J, Sbano JC, de la Cruz VY, Abduch MC, Lima MS, et al. Prognostic value of coronary and microvascular flow reserve in patients with nonischemic dilated cardiomyopathy. J Am Soc Echocardiogr. 2013;26(3):278-87.

15. Cecchi F, Olivotto I, Gistri R,Lorenzoni R, Chiriatti G, Camici PG. Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. N Engl J Med. 2003;349(11):1027-35.

16. Brilla CG, Janicki JS ,Weber KT. Impaired diastolic function and coronary reserve in genetic hypertension. Role of interstitial fibrosis and medial thickening of intramyocardial coronary arteries. Circ Res. 1991;69(1):107-15.

17. Tsagalou EP, Anastasiou-Nana M, Agapitos E, Gika A, Drakos SQ, Terrovitis JV, et al. Depressed coronary flow reserve is associated with decreased myocardial capillary density in patients with heart failure due to idiopathic dilated cardiomyopathy. J Am Coll Cardiol 2008;52(17):1391-8.

18. Fang ZY, Marwick TH. Vascular dysfunction and heart failure: epiphenomenon or etiologic agent? Am Heart J. 2002;143(3):383-90.

19. Nunes MCP, Barbosa MM, Ribeiro AL, Amorin Fenelon LM, Rocha MO. Predictors of mortality in patients with dilated cardiomyopathy: relevance of Chagas disease as an etiological factor. Rev Esp Cardiol. 2010;63(7):788-97.