Association between myocardial mechanical dispersion and ventricular arrhythmogenicity in Chagas cardiomyopathy.

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Abstract

Endemic Chagas diseaseis a major health concernin LatinAmerica. Ventricular arrhythmias (VA) is a hallmark of Chagas cardiomyopathy (ChC) associated with worse prognosis. To verify if there is an association between myocardial mechanical dispersion and ventricular arrhythmogenicity in CCM. This is a cross-sectional study involving 77 patients with CCM. Global longitudinal strain (GLS) and MD were evaluated by echocardiogram, derived from the speckle tracking technique. Myocardial MD was measured from the onset of the Q / R wave on electrocardiogram to the peak longitudinal strain in 16 segments of the left ventricle. Frequency and complexity of ventricular extrasystoles (VES) were assessed by dynamic electrocardiography. The density and complexity of VES and the presence of non-sustained ventricular tachycardias (NSVTs) increase as MD increases. In logistic regression, MD was the only variable associated with the presence of VES in pairs and bigeminy. In the univariate analysis, both MD and GLS were associated with the presence of NSVT (both, $p < 0.01$), and MD was independently associated with NSVT (OR 1.04, 95% CI: 1.004–1.201, $p = 0.031$). In Chagas cardiomyopathy, MD is associated with a higher density and complexity of ventricular extrasystoles, including NSVT.

Introduction

Chagas disease is an important public health problem in Latin America, affecting about eight million people[1,2], with a significant medical-social impact, even today. Its clinical evolution is quite variable, and several patients may remain asymptomatic for a long time. However, about 20% to 30% of infected patients develop the cardiac form of the disease, which is manifested by the presence of several types of conduction disorders such as cardiac insufficiency, arrhythmias, thromboembolism and sudden death, this being the main cause of death in this form of the disease [3,4,5].

Chagas cardiomyopathy is the most important manifestation of Chagas disease [4,6]. It is characterized by the presence of a dilated ventricular cavity, associated with systolic dysfunction. It has some important peculiarities, which distinguish it from heart diseases of other etiologies [7]. Among them, the following are highlighted: high and complex arrhythmogenicity, high frequency of sudden death, worse diagnosis, its continuous inflammatory and fibrosing nature and denervation of the intrinsic nervous system of the heart.[8,9,10,11,12].

The mechanism of ventricular arrythmia in this condition is related to inflammatory myocarditis[3,13,14,15,16], which creates the substrate for arrhythmogenicity [13,17,18]. Previous studies have shown that fibrosis is present in patients with Chagas cardiomyopathy and that the extension of the fibrosis in myocardial magnetic resonance imaging is correlated to the risk for arrythmias [19]. In addition to this fibrotic substrate, electric dispersion is caused by areas of slow conduction, leading to electric instability [20, 21]. Myocardial fibrosis and the areas of slow conduction result in mechanical changes, both in length and function. Thus, regional differences in electrical properties may cause heterogeneity of myocardial contraction, a condition known as mechanical dispersion [22, 23].

Bidimensional strain is an excellent tool for the assessment of global and segmental ventricular function [24]. Myocardial MD by strain is a sensitive measure of heterogeneity of ventricular contraction and, in recent studies, it has been shown to predict ventricular arrhythmias in patients with idiopathic dilated cardiomyopathy [25] and after the myocardial infarction [23]. There are few studies in the literature relating mechanical dispersion to myocardial fibrosis [26] and the method is still little studied in patients with Chagas cardiomyopathy [27], despite its high arrhythmogenicity.

In this study, we support the hypothesis that the higher the mechanical dispersion, the higher the arrhythmogenicity in CCM. Thus, our objective is to verify whether the myocardial MD is associated with the density and complexity of ventricular arrhythmia of this condition.

Methods

This cross-sectional study included patients with CCM selected at *Centro de Referência e Treinamento para Tratamento de Doenças Infecciosas e Parasitárias* (Reference and Training Center for the Treatment of Infectious and Parasitic Diseases) of *Universidade Federal de Minas Gerais* (Federal University of Minas Gerais) from March 2016 to August 2017. Groups have not been compared. The correlation among mechanical dispersion, echocardiographic variables (LVEF; LVDd, LVSd, E/e' ratio and GLS) and frequency and complexity of ventricular extrasystoles, which were recorded on the dynamic electrocardiography has been studied. Then they have been divided in quartiles, according to the value of mechanical dispersion and the correlation analysis was performed with echocardiographic variables and variables in arrhythmogenicity.

Inclusion criteria of the study were patients being over 18 years old, positive serology for *Trypanosoma cruzi* with at least two out of the three different techniques available (indirect immunofluorescence reaction, indirect hemagglutination and enzyme-linked immunosorbent assay (ELISA), being carriers of chronic Chagas cardiomyopathy, defined by the presence of increased left ventricle diastolic diameter (LVDd) (LVDd > 58 mm in men and LVDd > 52 mm in women [28]) and depressed LVEF (LVEF< 52% in men and < 54 in women [28]). Exclusion criteria were refusal to sign the written consent term, make use of implantable cardioverter defibrillator (ICD) or pacemaker, atrial fibrillation or flutter, left bundle branch block and the presence of systemic diseases such as systemic arterial hypertension, coronary artery disease, rheumatic diseases, diabetes mellitus or glucose intolerance, renal insufficiency, chronic pulmonary obstructive disease, hydroelectrolytic disorders or significant anemia.

All patients were submitted to a medical examination, electrocardiogram, conventional echocardiography through the speckle tracking technique and two 24-hour dynamic electrocardiograms. All participants signed the written informed consent. The research project was evaluated and approved by the Research Ethics Committee of *Universidade Federal de Minas Gerais* (CAAE: 48354315.8.3001.5091).

Electrocardiographic Evaluation

The 12-lead electrocardiogram was recorded on a Hewlett Packard, model 1504, to select patients from the left bundle branch block (LBBB), atrial fibrillation and flutter who were excluded from the study [29].

Dynamic Electrocardiography (Holter System)

The 24-hour electrocardiographic monitoring was performed using a 3-channel portable recording system (*Dynamis*, *Cardios*, São Paulo, Brazil). Patients were stimulated to do their normal activities during the recording period. Recordings were analyzed using the Burdick/DMI Hospital Holter System (Spacelabs Burdick Deerfield, WI, USA) through a semi-automatic technique and by an experienced cardiologist from *Serviço de Cardiologia e Cirurgia Cardiovascular* (Cardiology and Cardiovascular Surgery Service) of *Hospital das Clínicas/ UFMG*, where ectopic beats were coded and artifacts were excluded producing a consolidated report.

Echocardiographic Study

The echocardiographic study was conducted using Vivid Q and S6 systems (GE Vingmed Ultrasound AS system) and a commercially available software (EchoPAC; GE Healthcare, Milwaukee, WI). The LVEF was assessed using the Simpson's biplane method [28].

Global longitudinal strain through standard views, apical four-chamber, two-chamber and long-axis views were obtained by speckle-tracking echocardiography. Three cardiac cycles from each view were recorded for offline analysis with a frame rate > 50 frames/s. Peak negative strain was assessed in 16 LV segments, defined as the peak negative value throughout the cardiac cycle, including postsystolic shortening and the mean was defined as GLS. The time interval from the electrocardiographic onset of the Q/R wave to peak negative strain was assessed in each of the 16 LV segments. Mechanical dispersion was defined as the standard deviation of time to peak negative strain in the same 16 LV segments. Bull Eye's plots were constructed. Mitral inflow E velocity was recorded using pulsed Doppler. The e' velocity (tissue Doppler) was the mean of the septal and lateral mitral annuli and the E/e' ratio was measured. The echocardiographic studies were conducted by three echocardiographers.

Statistical Analysis

The database and the statistical analysis were carried out using the SPSS software version 20.0 (*Statistical Package for Social Sciences*). Parametric data were shown as means and standard deviation and compared to *Student's t test and chi-square test*. Non-normal distribution data were studied by the median and variance and compared to the Mann-Whitney U test. Increased MD was defined as the primary outcome and the frequency and complexity of ventricular extrasystoles were defined as secondary outcomes. *Spearman's* correlation between MD and parameters of dynamic electrocardiography and echocardiography was evaluated.

Finally, in the univariate analysis, significant markers of MD and the density and complexity of ventricular extrasystoles were analyzed in a multivariate logistic regression model, together with gender and age of

participants. Significance level was set at 5% and analyses were performed using the *Statistical Package for the Social Sciences* (SPSS) 20.0 software.

Results

Population Study

Seventy-seven outpatients who were clinically compensated (functional class according to NYHA classification I/II) were evaluated. General characteristics of patients were shown in Table 1. Mean age was 56 years and 46 patients were males (60%). Most of the patients (55.8%) were in NYHA functional class II and 34 patients were class I at the time of inclusion in the study. Sixty-five were on beta-blockers (84.4%), 45 (58.4%) angiotensin-converting enzyme inhibitors, 20 (26%) angiotensin receptor blockers therapy, 36 (46,8%) diuretics, 2 (2,6%) digitalis and 17 (22,1%) anticoagulants.

Holter recordings

The median VES (ou PVCs – premature ventricular contractions) from Holter recordings was 1423 (range 636 - 4272), 223 (4-101) paired VSV, 14 (1-229) bigeminismo VSV and NSVT 1 (0-3).

Echocardiographic Parameter

The analysis of variables obtained by the echocardiography are shown in Table 1. The mean dimensions of left chambers (LVDd = 60 mm and LVSd = 46mm) were slightly increased and E/e' ratio was normal in all patients. Mean LVEF was 43% (35%-46%) in all patients and GLS was 14 ±3%. Mean mechanical dispersion was increased in these patients reaching 60 ms (50 ms-80 ms).

Correlation between mechanical dispersion, global longitudinal strain and ventricular extrasystoles on 24h Holter.

According to the results shown in Table 1, a significant correlation was seen between MD and global longitudinal strain (R = - 0.696; $p < 0.001$) (Chart 1), whereas no significant correlation was seen between MD and LVEF (R = - 0.247; $p < 0.032$). Mechanical dispersion was still correlated LVDd (R = 0.266; $p < 0.021$) and LVSd (R = 0.250; $p < 0.266$). No correlation was seen regarding E/e' (R = 0.128; $p < 0.184$).

Regarding ventricular extrasystoles, MD showed a positive correlation (R = 0.317; p = 0.005) (Figure 1) as well as the paired extrasystoles (R = 0.349; p = 0.002), with a moderate correlation with the presence of NSVT (R = 0.411; p = 0.001).

In the logistic regression, MD was the only variable associated with the presence of paired VES (OR 1.05; CI 95%: 1.003 – 1.099, p = 0.038) and bigeminy (OR 1.03; CI 95%: 1.001 – 1.058 p = 0.044). Regarding the presence of NSVT, MD and GLS were statistically significant in univariate analysis ($p < 0.01$), MD being the only independently associated with NSVT (OR 1.04; CI 95%: 1.004 – 1.201, p = 0.031) (Figure 1) (Table 3).

Table 1: Characteristics of the sample evaluated (n=77).

Variables		Values
Age (years)		55.8±10.4
Males, n (%)		46 (59.7)
NYHA Functional class, n (%)	I	34 (44.2)
	II	43 (55.8)
Medications, n (%)		
Diuretic		36 (46.8)
ACE inhibitor		45 (58.4)
AT2-receptor inhibitor		20 (26)
Digitalis		2 (2.6)
Amiodarone		37 (48.1)
Anticoagulant		17 (22.1)
Beta-blocker		65 (84.4)
ASA		12 (15.6)
ECG Parameters		
VES (n)		1423 (636 – 4272)
Paired VES (n)		23 (4 – 101)
Bigeminy (n)		14 (1 – 229)
NSVT (n)		1 (0 – 3)
Echocardiographic Parameters		
LVDd (mm)	60 (57 – 65)	
LVSd (mm)	46 (43 – 52)	
E/e' ratio	9 (8 – 13)	
LVEF (%)	43 (35 – 46)	
GLS (%)**	14±3	
MD (ms)	60 (50 – 80)	

NYHA, New York Heart Association; ACE angiotensin-converting-enzyme inhibitor; ASA, acetylsalicylic acid.
VES, ventricular extrasystole; NSVT, nonsustained ventricular tachycardia; LVDd, left ventricular diastolic diameter; LVSd, left ventricular systolic diameter; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; MD, mechanical dispersion.
Data are expressed as mean ± SD or as a number (percentage).
Data are expressed as median (25%-75%) since they are not normal.
** Only variable that is normal and therefore is presented as mean ± SD

Table 2: Correlation between MD and electro- and echocardiographic parameters in the sample evaluated.

Variable	p-value	Correlation Coefficient (rho)
Total VES	**0.005****	0.317
Paired VES	**0.002****	0.349
Bigeminy	**0.024***	0.257
NSVT	**0.001****	0.411
LVEF	**0.032***	-0.247
LVDd	**0.021***	0.266
LVSd	**0.031***	0.250
E/e' ratio	0.128	0.184
GLS	**<0.001****	-0.696

VES, ventricular extrasystoles; NSVT, nonsustained ventricular tachycardia; LVDd, left ventricular diastolic diameter; LVSd; left ventricular systolic diameter; LVEF, left ventricular ejection fraction.
**significant Spearman's correlation at the level of 1%.
*significant Spearman's correlation at the level of 5%

Table 3: Univariate and multivariate analyses to identify variables associated with the presence of NSVT

	Univariate Logistic Regression			Multivariate Logistic Regression		
	OR	CI 95%	p-value	OR	CI 95%	p-value
Presence of NSVT						
Age	1.003	0.960-1.047	0.905			
Gender	1.659	0.661-4.164	0.281			
NYHA	0.654	0.264-1.622	0.359			
LVEF	0.961	0.905-1.022	0.206			
LVDd	1.029	0.962-1.101	0.401			
LVSd	1.023	0.966-1.084	0.434			
LA	1.046	0.946-1.157	0.377			
E/e' ratio	1.074	0.965-1.195	0.193			
Diffuse hypokinesis	0.682	0.216-2.156	0.514			
GLS	0.839	0.730-0.964	**0.013**	0.976	0.815-1.076	0.788
MD	1.043	1.013-1.074	**0.005**	1.040	1.004-1.201	**0.031**

Discussion

This study demonstrated that MD correlates with arrhythmogenicity in patients with chagasic cardiomyopathy with mild to severe left ventricular systolic dysfunction. MD was significantly and independently associated with VA events, even in patients with LVEF >35%.

The presence of myocardial fibrosis has been demonstrated in several studies as an arrhythmogenic substrate [31,32]. This fibrosis causes heterogeneous ventricular activation. In Chagas cardiomyopathy, there is a change in the disposition of myocardial fibers due to collagen deposition, scar formation and remodeling, increasing myocardial heterogeneity [13, 33]. Cardiac imaging play an important role in assessing the structural substrate for arrhythmogenicity [34,35]. Previous studies have shown that fibrosis is present in patients with Chagas cardiomyopathy and that the extension of the fibrosis in myocardial magnetic resonance (MR) imaging is correlated to the risk for arrythmias [19]. Echocardiogram can also evaluate this arrhythmogenic substrate by measuring LVEF and, more recently, by speckle tracking–derived parameters (MD e SLG) [36,37,38].

Although, several studies in patients with ischemic cardiomyopathy [41], dilated idiopathic cardiomyopathy [25], hypertrophic cardiomyopathy[42], including chagasic cardiomyopathy[27], using MD, had similar results, no cross-section study in patients with chagasic cardiomyopathy has been conducted to assess association of MD with arrhythmogenicity. The MD was recently validated in a meta-analyses that concluded that can be used as a parameter to predict ventricular arrhytmias, more studies are still needed, especially in patients with LVEF> 35%, asymptomatic or with NYHA I, branch block, atrial fibrillation and with pacemaker and ICD[39]. There is only one study employing the MD technique analyzed patients with Chagas cardiomyopathy [27], despite important peculiarities of this condition, which distinguish it from other cardiomyopathies [4,7, 43]. Barros e collaborators, employing the MD technique analyzed patients with Chagas cardiomyopathy [27] showed that MD was more pronounced in patients with CCC and with ICD when compared to those without ICD. This cross-sectional study included 62 patients with Chagas disease who were separated in two groups, according to the presence and absence of ICD, aiming to evaluate whether GLS and MD are associated with malign ventricular arrhythmia. MD and GLS demonstrated a significant and independent association with malign arrhythmias. In the present study, MD was an echocardiographic variable with a significant association with the frequency and complexity of arrhythmias in Chagas cardiomyopathy.

In this article, MD was the only echocardiographic variable with a significant and independent association with the frequency and complexity of arrhythmias in Chagas cardiomyopathy. Therefore, this noninvasive method is likely to be useful to detect chagasic patients with malign arrhythmia, which makes it even more relevant due to the significant arrhythmogenicity of Chagas disease and the large number of patients with this disease that are candidates for an ICD implantation.

In our sample, LVEF did not have any association with the presence or complexity of arrhythmia, reinforcing the relative limitation of this method in the functional and prognostic evaluation of chagasic patients. Furthermore, the use of LVEF is believed not to constitute an accurate criterion to identify patients with a risk of malign arrhythmia, and may lead to inaccurate indications of ICD implantations, an expensive and invasive procedure and with a high psychological impact on patients [37, 44, 45, 46]. Thus, it is important and necessary to develop tools able to, more accurately, stratify those patients with a higher

risk of malign arrhythmias and/or sudden death, both in Chagas cardiomyopathy and in those with different etiologies.

Identifying noninvasive markers of ventricular arrhythmia may contribute to identifying subgroups of patients that deserve special medical attention, in addition to guiding medical practice aiming to prevent death. Improving arrhythmia risk predictor methodology in Chagas disease has direct clinical implications and may be transferred to medical practice.

Limitations

The study had an adequate sample size but is limited due to the fact that participants are outpatients and, most of them, are clinically compensated (functional class according to the NYHA classification I/II) and, also because all patients were seen at the same reference center. Multicenter studies are necessary to confirm the findings. Moreover, prospective studies with patients with Chagas cardiomyopathy should be conducted to compare echocardiographic parameters with clinical outcomes.

Most patients were using beta blockers and amiodarone, which may interfere with arrhythmogenicity and with ventricular contractility. For ethical reasons, these medications were not discontinued.

Conclusion

The present study has shown that MD measurement was the only echocardiographic variable studied that was associated with density and complexity of ventricular extrasystoles in patients with chronic Chagas cardiomyopathy. This study gains perspectives on the evaluation of this technique of the risk stratification of these patients from longitudinal studies.

Declarations

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Conflict of interest There is no potential conflict of interest relevant to this article exist.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The research project was evaluated and approved by the Research Ethics Committee of *Universidade Federal de Minas Gerais* (CAAE: 48354315.8.3001.5091).

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Figures

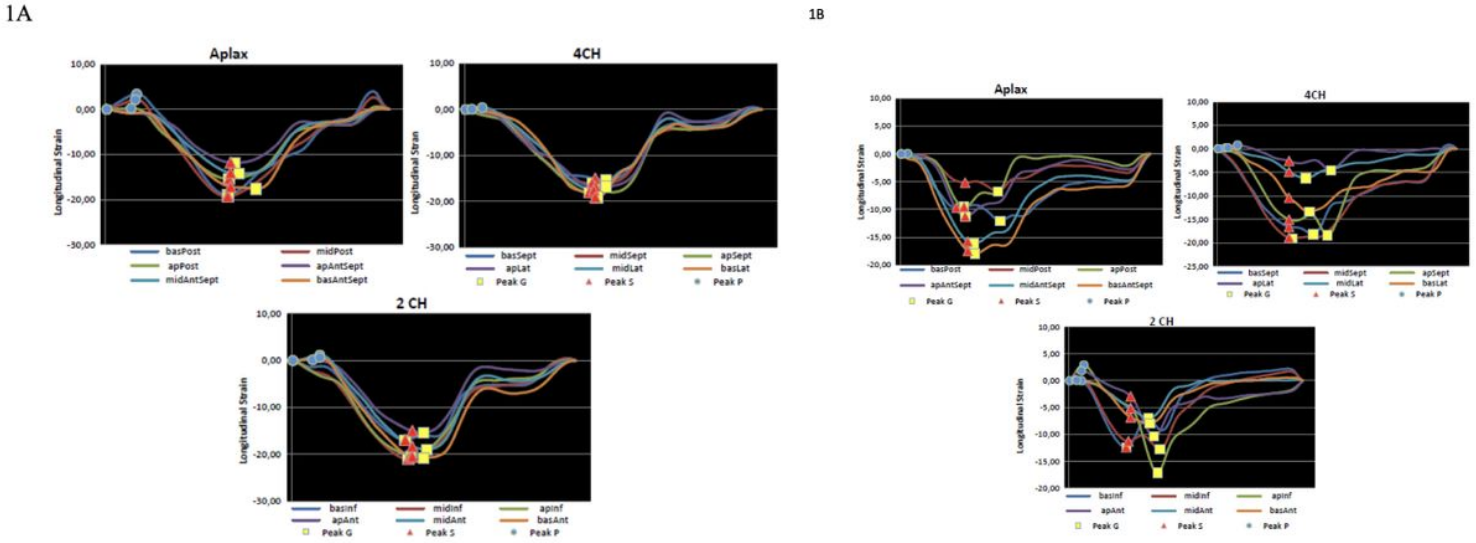

Figure 1

Strain curves from chagasic patients with (A) and without (B) ventricular taquycardia. Mechanical dispersion shows values of 40 and 85 ms respectively.

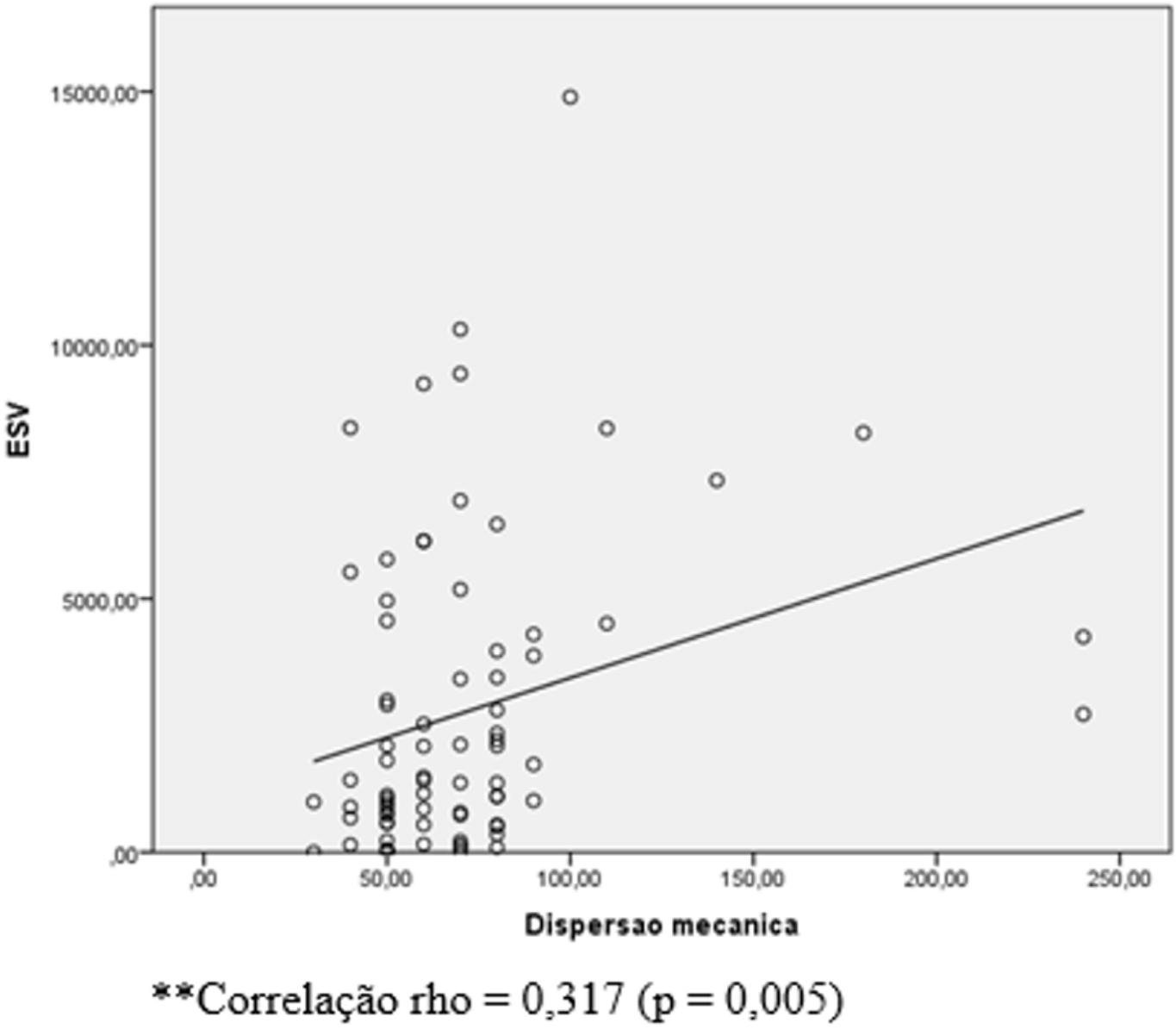

Figure 2

Correlation between MD and VES. Correlation between MD (X-axis) and VES (Y-axis). MD, mechanical dispersion; VES, total number of ventricular extrasystoles.