

## Prevalence and Prognostic Value of Ventricular Dyssynchrony in Chagas' Cardiomyopathy

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### Abstract

**Background:** Chagas' cardiomyopathy is one important cause of heart failure in Latin America. Ventricular dyssynchrony may be a factor of decompensation in the course of this disease, but there are no data on its prevalence and its main prognostic implications yet.

**Objective:** Describe prevalence and prognostic value of ventricular dyssynchrony in Chagas' cardiomyopathy.

**Methods:** 56 patients with Chagas' cardiomyopathy were consecutively selected by two positive serologies and an ejection fraction < 45% in the echocardiogram. The echocardiogram evaluated the presence of intraventricular dyssynchrony using 3 criteria and interventricular dyssynchrony using 1 criterion. Patients were followed for 21 ± 14 months and cardiac events were defined as the combination of death and hospitalization.

**Results:** The average age of the population was 56 ± 10 years, 50% males. Mean ejection fraction was 30 ± 8% and 87% presented functional class I/II (NYHA). The prevalence of interventricular dyssynchrony was 34% (95% CI: 22%-48%) and intraventricular dyssynchrony had a prevalence of 85% (95% CI: 75%-93%). The prevalence of intraventricular dyssynchrony was similar among patients with QRS duration < 0.12 s or > 0.12 s (85% and 89%, respectively,  $p=0.66$ ). Twenty events were recorded. The incidence of combined events was similar in patients with or without intraventricular dyssynchrony (35% versus 38%,  $p=0.9$ ) and those with or without interventricular dyssynchrony (39% versus 34%,  $p=0.73$ ).

**Conclusion:** Patients with Chagas' cardiomyopathy have high intraventricular and moderate interventricular prevalence of dyssynchrony. The high prevalence is independent from the QRS width. The ventricular dyssynchrony does not have any prognostic value in patients with Chagas' cardiomyopathy. (Arq Bras Cardiol 2011;96(4):300-306)

**Keywords:** Chagas' cardiomyopathy; ventricular dysfunction; prevalence; prognosis.

### Introduction

Currently, it is estimated that 10 to 18 million people are infected with Chagas' disease throughout Latin America<sup>1</sup>. Mortality due to Chagas' cardiomyopathy is closely linked to the degree of myocardial involvement<sup>2</sup>. Furthermore, the risk of death is not the same for all the patients and many authors have tried to identify clinical features that point out to patients at highest risk. Recently, Rassi et al<sup>3</sup> published a risk score with good prognostic accuracy, taking into account gender, low voltage on electrocardiogram, cardiomegaly on chest x-ray, non-sustained ventricular tachycardia, functional class and reduced ejection fraction on the echocardiogram. In addition to quantifying the degree of ventricular dysfunction, the echocardiogram has recently emerged as a tool to

determine the presence of ventricular dyssynchrony, which is related to a worse prognosis in cardiomyopathies of other etiologies<sup>4-6</sup>. The prognostic value of ventricular dyssynchrony in patients with Chagas' cardiomyopathy is not known. Recently, a controversial study named "PROSPECT trial" described the value and the high interobserver variability of the echocardiogram during dyssynchrony analysis, and it is a topic to analyze in this study with chagasic patients<sup>7</sup>. Given the need for new markers of risk in this disease that may add prognostic value to Rassi's score and the lack of data on the prevalence of ventricular dyssynchrony in this population, we evaluated dyssynchrony by echocardiogram in 56 individuals with Chagas' cardiomyopathy, which were followed for 21 ± 14 months.

### Methods

#### Study population

The study was conducted in the Cardiomyopathy Clinic of Federal University of Bahia. Chagas' cardiomyopathy was defined as two positive serologies for Chagas' disease

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(immunofluorescence and hemagglutination) and ejection fraction < 45% on echocardiogram. New patients with these characteristics were consecutively selected during the period from June 2005 to August 2008. This study was approved by the local Ethical Committee. All patients provided a written informed consent. Patients with associated heart condition (hypertensive, valvular, ischemic cardiopathies) were excluded. Those with atrial fibrillation or frequent extrasystoles were excluded because these arrhythmias impair evaluation of dyssynchrony by echocardiogram.

### Study protocol

A commercially available ultrasound system (*Vingmed system FiVi/Seven, General Electric- Vingmed, Milwaukee, WI, USA*) was used. Images were obtained by using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal and apical views. Tissue Doppler parameters were measured from color images of three consecutive heart beats by offline analysis. The observer was not aware of the clinical condition of the patient. Intraventricular dyssynchrony was defined by the following criteria: 1) Standard deviation (SD) of the delay between the onset of R wave on electrocardiogram and the peak of S wave velocity measured on the 12 segments of left ventricle > 33 ms<sup>8-10</sup>; 2) The maximum interval (MI) measured between any 2 segments > 100 ms<sup>11</sup>; 3) Delay between septal-basal and basal-lateral segments (SLD) > 60 ms<sup>12</sup>. For interventricular dyssynchrony, pulsed Doppler was used. It was determined as the difference in the time intervals of Q wave to the onset of flow in the pulmonary artery compared with the time intervals of Q to the onset of aortic flow, respectively. A value > 40 ms is considered to be abnormal<sup>13</sup>. Ejection fraction was calculated by the modified Simpson's method. In addition, a 24-h Holter recording was performed in all patients. Rassi's score was calculated as previously validated<sup>3</sup>. Briefly, this score takes into account gender, low voltage on electrocardiogram, cardiomegaly on chest x-ray, non-sustained ventricular tachycardia, functional class III/IV and reduced ejection fraction on the echocardiogram.

The patients were monitored regularly, every 3 months, through ambulatory appointments and phone calls. Clinical events such as total death, cardiovascular death, hospitalization for heart failure or arrhythmias were recorded.

### Statistical analysis

Relative frequency of interventricular and intraventricular dyssynchrony was described with 95% confidence interval. In order to identify predictors in the univariate analysis, clinical, electrocardiographic and echocardiographic data, including criteria of dyssynchrony, were compared between patients with and without events. Categorical variables were compared by Pearson's chi-square test and numeric variables by Student's t test or Mann-Whitney's test; those variables associated with events ( $p \leq 0.10$ ) entered the logistic regression analysis to assess independent predictors. Rassi's score was chosen instead of individual predictors. Based on a pilot study involving 28 individuals, where there was a 70% prevalence of dyssynchrony, 56 subjects were considered sufficient, given a precision error of  $\pm 12\%$  and 95% confidence interval. In

relation to the prognostic value, based on the study of Rassi et al, to define independent prognostic factors in Chagas' disease and in the case of combined events, an absolute risk of 40% was estimated. Therefore, 56 patients were also considered sufficient, of which 39 had dyssynchrony and 17 did not. For the group with dyssynchrony this risk reaches 60%, and for the group without dyssynchrony this risk would be 20%. The study was given a power of 80% and an alpha equal to 5%. In the analysis of intraobserver and interobserver variability, the coefficient of variability (CV) was calculated between the measures in relation to the criteria of intraventricular and interventricular dyssynchrony. For this analysis, about 10% of the sample was used, a total of 6 patients, with two observers during the last six patients of the study. A  $p < 0.05$  was considered significant. The software SPSS 14.0 for Windows (SPSS inc, Chicago, IL) was used.

There are no financial or personal relationships among the authors and other people or organizations that could inappropriately influence (bias) his or her actions.

## Results

### Baseline characteristics

A total of 56 patients with Chagas' cardiomyopathy were studied,  $56 \pm 10$  years (36 to 79 years), 50% male, 82% African-Brazilians. They were effectively treated regarding their blood pressure, heart rate, renal function and electrolytes. In general, the patients were undergoing appropriate medical treatment with inhibitors of angiotensin converting enzyme, beta-blockers and aldosterone blockers, with 93% on regular use of medications and 87% functional class I/II. This good functional class can be explained by the specific clinic they attended (Cardiomyopathy Clinic), with different health professionals and the regular use of medications. A significant number used pacemakers (25%), 23% had right bundle branch block and 14% had left bundle branch block. The degree of left ventricular dysfunction was severe, as measured by a mean ejection fraction of  $30 \pm 8\%$ . Cavities were dilated, with left ventricular diastolic diameter average of  $66 \pm 8$  mm. Segmental disorders of the ventricular contractility were very common in this population (73%), and the most commonly affected segment was the posterior one (56%). These characteristic are shown in Table 1.

### Prevalence of dyssynchrony

When any of the 3 criteria was considered, a significant 85% (95% CI: 75% - 93%) prevalence of intraventricular dyssynchrony was observed. Based on the standard deviation of 12 segments alone, there was a 75% prevalence (95% CI: 62% - 86%), the maximum interval criterion was present in 79% (95% CI: 65% - 88%), and the septal-lateral delay in a smaller proportion, 48% (95% CI: 35% - 62%). The prevalence of interventricular dyssynchrony was 34% (95% CI: 22% - 48%) - Table 2. Intraventricular dyssynchrony remained high independent from QRS width. It was present in 89% (95% CI: 74% - 97%) of patients with QRS > 0.12 sec and in 84% (95% CI: 62% - 96%) of patients with QRS < 0.12 sec ( $p = 0.66$ ) - Table 3. When the three criteria were separately analyzed, no

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**Table 1 - Demographic and clinical characteristics of sample population**

Characteristics	
Sample size	56
Clinical	
Age (years)	56 ± 10
Male	50%
Non-white race	82%
Functional class I / II	87%
Systolic blood pressure (mmHg)	110 ± 15
Diastolic blood pressure (mmHg)	73 ± 8.0
Heart rate (bpm)	64 ± 9.0
Pacemaker	25%
Right bundle branch block	23%
Left bundle branch block	14%
Echocardiographic	
Ejection fraction (%)	30 ± 8.0
LV diastolic diameter (mm)	66 ± 8.0
Segmental contractility dysfunction	73%
Laboratorial	
Hemoglobin (g/dl)	13 ± 2.0
Sodium (g/dl)	140 ± 5.0
Potassium (g/dl)	4.0 ± 1.0
Creatinine (mg/dl)	1.0 ± 0.60
Current medical therapy	
Beta-blockers	82%
ACE inhibitors	70%
AR inhibitors	29%
Spironolactone	63%
Diuretic	84%
Regular use	93%

LV - left ventricle, ACE - angiotensin-converting enzyme, AR - angiotensin receptors. Regular use - more than 90% use during the follow-up period.

**Table 3 - Prevalence of dyssynchrony according to qrs duration**

Dyssynchrony	QRS > 0.12 s (n=36)	95% CI	QRS < 0.12 s (n=20)	95% CI	p 1	p 2
Intraventricular						
Standard deviation	49 ± 15 ms	81 % (64-92 %)	40 ± 14 ms	70 % (46-88%)	0.03	0.31
Maximum interval	144 ± 48 ms	81 % (64-92 %)	121 ± 34 ms	75 % (51-91%)	0.06	0.85
Septal-lateral delay	63 ± 45 ms	47 % (30-64 %)	70 ± 40 ms	50 % (27-72%)	0.64	0.78
Total		89 % (74-97%)		85 % (62-97%)	0.66	
Interventricular						
LV-RV difference	38 ± 30 ms	44 (28-62%)	22 ± 15 ms	15 (3-38%)	0.052	0.30

Standard deviation of the measure of 12 segments of the left ventricle; Maximum interval between the 12 segments of left ventricle, Difference between the septum-basal and latero-basal segments of left ventricle; LV-RV difference-the time difference between the output of left and right ventricles. Percent (%) refers to the percentage of affected individuals, accompanied by the 95% confidence interval. p 1 refers to p value when comparing medium values and p 2 refers to p values when comparing percentages of affected individuals.

**Table 2 - Overall prevalence of dyssynchrony**

Dyssynchrony	Mean ± SD	Percent	95% CI
Intraventricular			
Standard deviation	46 ± 15 ms	75 %	(62-86 %)
Maximum interval	136 ± 44 ms	79 %	(65-88 %)
Septal-lateral delay	65 ± 43 ms	48 %	(35-62 %)
Total		85 %	(75-93 %)
Interventricular			
LV-RV difference	32 ± 26 ms	34 %	(22-48 %)

Standard deviation of the measurement of 12 segments of the left ventricle; Maximum interval between the 12 segments of left ventricle; Difference between the septum-basal and latero-basal segments of left ventricle; LV-RV difference-the time difference between the output of left and right ventricles. Percent (%) refers to the percentage of affected individuals.

significant difference was observed in relation to the percentage of QRS width in the two groups - standard deviation- 81% vs 70% (p = 0.31), maximum interval - 81% vs 75% (p = 0.85) and septo-lateral delay - 47% vs 50% (p = 0.78). Interventricular dyssynchrony was similar between the subgroups with QRS < or > 0.12 s (15% vs 44%, p = 0.30). Table 3 includes the medium value of the 4 criteria and p values. When the percentages were compared, there was no difference. But when the medium values were compared, it was significant for the standard deviation criterion (p = 0.03) and quite significant for the LV-RV difference criterion (p = 0.052).

At the moment of dyssynchrony assessment, all paced patients were under ventricular stimulation, with the ventricular electrode in the apex of the right ventricle. In relation to patients with a pacemaker, the intraventricular dyssynchrony showed no difference when the percentage and medium values were compared (p = 0.09). However, in relation to the interventricular dyssynchrony there were differences when percentage (57% vs 24%, p = 0.04), and medium values (26 ± 22 ms vs 48 ± 33 ms, p = 0.007) were compared. When patients without a pacemaker (42) were analyzed, the prevalence of intraventricular dyssynchrony was 90% and of interventricular dyssynchrony was 24%, which can explain these results.

Another observation is that segmental disorders of the ventricular contractility were significantly more prevalent in patients with intraventricular dyssynchrony, when compared with the group without dyssynchrony (81% versus 57%,  $p = 0.01$ ). The segmental disorders of the ventricular contractility were a predictor of intraventricular dyssynchrony (multivariate analysis,  $p = 0.01$ ).

### Prognostic value of dyssynchrony

During a follow-up of  $21 \pm 14$  months, 20 events were recorded (11 deaths and 9 hospitalizations). An incidence of combined events in patients with and without intraventricular dyssynchrony was similar (35% vs 38%,  $p = 0.9$ ). When considering only deaths, the incidence was 19% and 25%, respectively ( $p = 0.68$ ). Regarding the analysis of present or absent interventricular dyssynchrony, the incidence of events was 39% and 34%, respectively ( $p = 0.73$ ). When considering only deaths, the incidence was 28% compared with 16% in patients without dyssynchrony ( $p = 0.29$ ).

In the univariate analysis, the following variables were prevalent in individuals with events compared with those free of events: functional class III / IV (30% vs 6%,  $p = 0.02$ ), cardiothoracic index  $> 50\%$  (70% vs 36%,  $p = 0.02$ ). The medium Rassi's score was higher in patients with events (8), when compared with the remaining patients (6,  $p = 0.01$ ) and the ejection fraction was lower in patients with events ( $27\% \pm 7\%$  vs  $32\% \pm 8\%$ ,  $p = 0.02$ ). When examining the four criteria for dyssynchrony, the septal-lateral delay and the RV-LV difference showed  $p = 0.10$  - Table 4.

The multivariate analysis by logistic regression showed that Rassi's score was the only predictor of combined events (odds ratio-OR - 1.19; 95% CI: 1.02 to 1.40,  $p = 0.01$ ). The variables of dyssynchrony- septal-lateral delay (intraventricular) and RV-LV difference (interventricular) were not significant- septal-lateral delay-OR 0.98 (95% CI: 0.97-1.00) and LV-RV difference - 1.01 (95% CI: 0.98-1.04) - Table 5.

### Interobserver and intraobserver variability

There was a low intraobserver variability for the variable standard deviation and the maximum interval (9 and 10%, respectively) and a moderate interobserver variability (23 and 18%, respectively). Concerning the variable septal-lateral delay and the LV-RV difference, both intraobserver and interobserver variability were moderate to high (23 to 64%). Intraobserver variability (9 to 27%) was much lower when compared to the interobserver variability (18 to 64%) in any one of the four variables.

## Discussion

This is the first study that evaluated the prevalence of ventricular dyssynchrony and its clinical implications among individuals with Chagas' cardiomyopathy. Firstly, we observed that dyssynchrony is a highly prevalent condition; secondly, the presence of dyssynchrony may not affect prognosis of individuals with Chagas' cardiomyopathy.

The prevalence of 85% of intraventricular dyssynchrony should be considered substantially high, especially when

Table 4 - Combined events (univariate analysis)

Variable	Event (n=20)	No event (n=36)	p value
Age (years)	57 ± 12	56 ± 9	0.64
Male	11(55%)	17 (48%)	0.45
Functional class III/IV	6 (30%)	2 (6%)	0.02
Systolic blood pressure (mmHg)	106 ± 17	113 ± 15	0.18
Heart rate (bpm)	63 ± 10	64 ± 9	0.83
Cardiothoracic index > 50%	14 (70%)	13 (36%)	0.02
Rassi's score	8	6	0.01
Ejection fraction (%)	27 ± 7	32 ± 8	0.02
Segmental contractility dysfunction	16(80%)	25(70%)	0.23
LV diastolic diameter (mm)	68 ± 9	65 ± 8	0.20
Standard deviation	45 ± 16	46 ± 15	0.92
Maximum interval	143 ± 49	131 ± 42	0.35
Septal-lateral delay	51 ± 39	72 ± 44	0.10
LV-RV difference	39 ± 32	27 ± 21	0.10
Intraventricular dyssynchrony *	17 (85%)	31 (86%)	0.84
Interventricular dyssynchrony †	7 (35%)	10 (28%)	0.63
Pacemaker	5 (25%)	9 (25%)	0.96
NS ventricular tachycardia	7(35%)	9 (25%)	0.75
QRS > 0.12 seg	13 (65%)	22(61%)	0.88

LV - left ventricle; Standard deviation of the measure of 12 segments of the left ventricle; Maximum interval between the 12 segments of left ventricle; Difference between the septum-basal and latero-basal segments of left ventricle; LV-RV - difference-the time difference between the output of left and right ventricles; NS - non-sustained ventricular tachycardia; events-death and/or hospitalizations; (\*) intraventricular dyssynchrony using any of the 3 criteria; (†) interventricular dyssynchrony using the LV-RV difference criterion.

Table 5 - Predictors of combined events (multivariate analysis)

Variable	p value	Odds ratio (95% CI)
Rassi's score	0.02	1.19 (1.02-1.40)
LV-RV difference	0.29	1.01 (0.98-1.04)
Septal-lateral delay	0.21	0.98 (0.97-1.00)

Difference between the septum-basal and latero-basal segments of left ventricle; LV-RV difference-the time difference between the output of left and right ventricles; 95% CI - 95% confidence interval.

compared with other etiologies such as ischemic and dilated cardiomyopathy, with the prevalence reported to be 58% in patients with left bundle branch block, and 42% in those with right bundle branch block associated with divisional block<sup>14</sup>. Possible explanations for this higher prevalence in chagasic patients would be the segmental alterations secondary to areas of fibrosis associated with the chronic, diffuse inflammatory process, which is persistent and inherent to this disease<sup>15,16</sup>.

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In relation to the interventricular dyssynchrony, our findings were similar to those reported in other etiologies<sup>17</sup>. In this population, no significant difference was observed in relation to the prevalence based on the QRS width, just in some medium values of intraventricular dyssynchrony criteria. In relation to the interventricular criterion, this difference was more evident, but it did not reach statistical significance, just in patients with pacemakers. In the literature, the prevalence of interventricular and interventricular dyssynchrony is associated with the QRS width in other etiologies<sup>17</sup>.

The degree of fibrosis in patients with Chagas' disease contradicts the benefit of resynchronization, as it has been well reported for ischemic cardiomyopathies with areas of transmural scars<sup>18,19</sup>. The septal-lateral criterion in this population was less prevalent, but there was no relation with the fibrosis area. This measurement is made at the anterior area, an area that is not normally affected by Chagas' disease. On the other hand, all the other criteria were highly prevalent and could be a factor in favor of this therapy, which has been well established in large clinical trials in other etiologies (CARE-HF and COMPANION)<sup>20-23</sup> and in small studies in the chagasic population. Silva et al<sup>24</sup> described a population of 29 patients, half of them chagasic, receiving resynchronization therapy, who evolved with clinical and ejection fraction improvement. These individuals can benefit from this therapy, but we cannot state that at this moment and a new clinical trial is necessary to define this question.

Previous data reported an association between dyssynchrony and a worse prognosis in other cardiomyopathies. Cho et al<sup>6</sup> assessed dyssynchrony in 106 patients with heart failure and found that dyssynchrony was a strong predictor of severe clinical events. Similarly, Bader et al<sup>4</sup>, describing a group of 104 patients, showed that the presence of intraventricular dyssynchrony is a determinant factor of adverse cardiac events, regardless of ejection fraction and QRS<sup>4</sup>. As opposed, in the present study, the dyssynchrony did not prove to be a marker in patients with Chagas' cardiomyopathy. Possible explanations were the high prevalence, with almost everyone presenting dyssynchrony and probably the expected variability of the method used to evaluate dyssynchrony. When analyzing the precision of dyssynchrony measurements, we can see a lower intraobserver variability, when compared with the interobserver one. These reflect, in a certain way, the high variability of these values that have been previously reported in the literature<sup>7-25</sup>. The recently published study PROSPECT showed a low predictive value of the echocardiogram in relation to dyssynchrony. This current study showed a quite similar result in relation to variability, considering the same

variable. Moreover, it can explain the negative result in relation to the prognosis. One suggestion is that the echocardiographic criteria in Chagas' cardiomyopathy could be different from the ones used in other cardiomyopathies. That can be observed when evaluating the high medium values in patients with Chagas' disease and QRS < 0.12 s.

It was decided to include patients with a pacemaker because they are very common in clinical practice and reflect an important percentage of patients with Chagas' disease. When patients without pacemakers were analyzed, the prevalence of intraventricular dyssynchrony remained high. The main limitation of the study could be the variability of the method used to evaluate dyssynchrony. The number of patients may be a question, but the number of clinical events was high. At the end of the study, it was observed that only 8 patients did not have dyssynchrony, which lead to a lower statistical power than previously calculated. Moreover, it reflects a selected group of chagasic patients with the advanced form of the disease, with strong prognostic markers, not reflecting the chagasic population as a whole. However, these results can have therapeutic implications as previously mentioned.

## Conclusion

In conclusion, chagasic cardiomyopathy patients have high intraventricular and moderate interventricular prevalence of dyssynchrony. The high prevalence is independent from the QRS width and remains high in the subgroup without pacemaker.

In this selected group of patients with Chagas' cardiomyopathy, we could not observe a prognostic value of ventricular dyssynchrony. Larger studies are required to further investigate this issue.

## Potential Conflict of Interest

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

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