Ventricular Synchrony in Patients with Dilated Cardiomyopathy and Normal Individuals: Assessment by Radionuclide Ventriculography

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Summary

Objectives: To establish the parameters of intra- and interventricular synchrony in normal individuals and to compare them with patients with dilated cardiomyopathy with and without conduction disorders shown in the electrocardiogram (ECG) examination.

Methods: Three groups of patients were included in this study: 18 individuals (G1) with no cardiomyopathy and with a normal ECG (52±12 years, 29% male); 50 patients with dilated cardiomyopathy and severe left ventricular dysfunction, with 20 patients (G2) presenting QRS <120ms (51±10 years, 75% male) and 30 patients (G3) with QRS >120ms (57±12 years, 60% male). All patients underwent RNV. Evaluation of left intraventricular dyssynchrony was carried out with the measurement of the phase histogram width and interventricular dyssynchrony was evaluated by the difference of the mean phase angle between the right and left ventricles (RLDif).

Results: Left ventricle ejection fractions (LVEF)s were: 62 ± 6% (G1), 27 ± 6% (G2) and 22 ± 7% (G3) and right ventricle ejection fractions(RVEF) were: 46 ± 4% (G1), 38 ± 9%(G2) and 37 ± 9% (G3). Evaluation of the phase histogram width was: 89 ± 18 ms (G1), 203 ± 54 ms (G2) and 312 ± 130 ms (G3), p<0.0001. The measurement of RLDif was: 14 ± 11 ms (G1), 39 ± 40 ms (G2) and 87 ± 49 ms (G3); comparing G1 *vs* G2 and G1 *vs* G3, p<0.0001 and G2 *vs* G3, p=0.0007.

Conclusion: The parameters analyzed discriminate the three groups of patients according to the ventricular synchrony degree. Patients with dilated cardiomyopathy and with no branch block in ECG (QRS <120 ms) may present dyssynchrony, but at a lower degree than patients with widened QRS.

Key word: Radionuclide ventriculography, phase image, ventricular synchrony.

Introduction

With emergence of Cardiac Resynchronization Therapy (CRT) in the beginning of the 1980's, the study of ventricular contraction synchrony became very important[1]. CRT, by means of atrial-biventricular stimulation, improves quality of life and tolerance to exercise; and reduces the number of hospitalizations[2,3], mortality due to progression of heart failure (HF) and total mortality[4,5]. According to the heart failure treatment guidelines of the American College of Cardiology and American Society of Cardiology, this therapy is indicated for patients with HF refractory to optimized clinical treatment, QRS duration longer than 120 ms in the electrocardiogram (ECG), especially in the presence of left bundle branch block (LBBB) and left ventricle ejection fraction (LVEF) lower than 35%[6]. Moreover, it is known that the isolated presence of LBBB does not specifically translate dyssynchrony and that about 27% of patients with HF and QRS <120 ms have ventricular dyssynchrony[7].

In view of the technical complexity, CRT costs and specially the benefits that it can offer to patients with HF, it is important to identify the individuals who are potentially responsive to the therapy in the population of individuals with dilated cardiomyopathy, in whom the evidence of ventricular dyssynchrony is essential. QRS duration has been the main parameter used in the identification of ventricular dyssynchrony[1]. However, increasing evidence has shown a poor correlation between the clinical and functional response to CRT and the duration of QRS interval[8,9]. On the other hand, direct measurements of electromechanical dyssynchrony based on simple and non-invasive imaging methods may improve the selection criteria and better predict the response to CRT[9,10]. Some studies have used radionuclide ventriculography (RNV) to assess synchrony of ventricular movements, by means of phase and amplitude parametric images[11-20]. Thus, quantitative parameters that objectively evaluate the degree of interventricular and left intraventricular synchrony can help in the better selection and follow-up of those patients before and after CRT, adding information to the measurement of QRS interval in the ECG.

The purpose of this study was to establish the values of interventricular and intraventricular synchrony in individuals without cardiomyopathy and with a normal ECG, by means of phase images derived from Fourier transformation of

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RNV and to compare them with patients with dilated cardiomyopathy and QRS duration in the ECG longer and shorter than 120 ms.

Methods

A prospective, cross-section study evaluating the data of 68 radionuclide ventriculographies performed at the Department of Nuclear Medicine of the *Instituto do Coração*, in São Paulo, Brazil, between March 2005 and May 2006. The Institution Ethics Committee approved the project.

Patients - The analysis of phase images of RNV was performed in selected examinations of patients who were referred to a non-invasive evaluation of the ventricular function. All patients were appropriately informed about the purpose of this study and signed the informed consent form.

Patients were separated into three groups. The first group (G1) included 18 individuals without cardiomyopathy and normal ECG (mean age 52±12 years, 29% male); the second group (G2) included 20 patients with dilated cardiomyopathy, LVEF <35% in the echocardiogram, Functional Class (FC) of Heart Failure by New York Heart Association (NYHA) from I to III and QRS interval in the ECG <120 ms (mean age 51±10 years, 75% male); and the third group (G3) comprised 30 candidates to CRT, with dilated cardiomyopathy, NYHA FC III or IV with optimized drug treatment, LVEF <35% in the echocardiogram and QRS interval in the ECG ≥120 ms (mean age 57±12 years, 60% male). The population characteristics are summarized in Table 1.

Table 1 - Characteristics of the population studied

	G1	G2	G3
Sample (n)	18	20	30
Mean Age (±sd)	52 ± 12*	51 ± 10*	57 ± 12**
Men	33%***	75%	60%
Etiology (n) • Idiopathic • Ischemic • Chagas		11 (55%) 6 (30%) 3 (15%)	19 (63%) 6 (20%) 5 (17%)
CF NYHA (n) • I • II • III • IV		4 (20%) 8 (40%) 8 (40%) 0	0 1 (3%) 22 (74%) 7 (23%)

** p > 0.05 between G1 and G2 and between G1 and G3. **p = 0.03 between G2 and G3. ***p = 0.02: G1 different from G2 and G3.*

ECG-gated radionuclide ventriculography - Red blood cells labeling was performed by *in vivo* technique. Patients were administered intravenous stannous hydrochloride (2 mg); after 20 minutes, patients received a dose of 740 MBq pertechnetate ($99mTcO_4^-$). Images were obtained in a gamma camera (LEM-Siemens) equipped with a high sensitivity, low energy and general purpose collimator and processed in a computer using ERNA software. ECG peak of R wave was used to define the beginning of image acquisition. The images were initially obtained in the left anterior oblique view with better ventricular separation (best septal view) and then in left anterior oblique at 30°. A total of 32 images were obtained in each cardiac cycle with about 300000 to 400000 counts in per frame, using a 64 x 64 matrix. For the analysis of ventricular function, the LVEF and the EF of the right ventricule (RVEF) were calculated with the following equation:

$$EF = 1 - \frac{\text{ventricular systolic counts (L or R)}}{\text{ventricular diastolic counts (L or R)}}$$

Analysis of phase images - The sequence of movements of ventricular walls was quantitatively evaluated through parametric phase images obtained with the first Fourier harmonic for the time *versus* activity curve of each pixel of the images obtained[20]. The cardiac cycle is a periodical phenomenon and it can be represented by the view of a circular movement with the same duration as R-R. Thus, it is possible to obtain a correspondence between the moments, or times, of R-R cycle and the respective circumference angles, the so-called phase angles. The counts of each pixel vary according to the phase of the ventricular movement. Each pixel positioned in the phase image was codified in a color scale. Pixels with the same phase angle, i.e., with simultaneous reduction of counts or same movement phase will show the same color. Phase histograms of both ventricles and of each ventricle separately were built based on this data. The histogram absciss contains the phase angles of ventricular movement and the histogram ordinate contains the number of pixels in each phase angle. The phase image shows the relative delay of ventricular movements in relation to the R wave peak in the ECG for each image pixel (electromechanical delay). Interventricular synchrony (DVV) was evaluated through the difference between the mean phase angle of right ventricle (RV) and left ventricle (LV) movements. Left intraventricular synchrony (DVE) was evaluated through the width of LV phase histogram, and the regions with a number of pixels lower than 10% of the mean value of all pixels in the interest region of LV were excluded. Therefore, it was possible to standardize the measurements for all patients in the study. The values obtained were transformed into milliseconds for statistical analysis (Figures 1 and 2).

Statistical analysis - The numerical variables were described through the mean ± standard deviation (SD). Parametric tests were used. Comparison of RNV data among the 3 groups of patients was carried out through the ANOVA test followed by Bonferroni test to locate the differences. Chi-square test was used to evaluate the difference in the distribution of men and women among the groups. A *p*-value lower than 0.05 was considered statistically significant.

Results

Groups of patients - The mean duration of QRS in each group is shown in Table 2. As to the overall systolic ventricular function analyzed with RV, the mean LVEF in G1 was 62 ± 6%, in G2, 27 ± 6%, and, in G3, 22 ± 7%; the difference among groups was statistically different (p<0.0001). The mean

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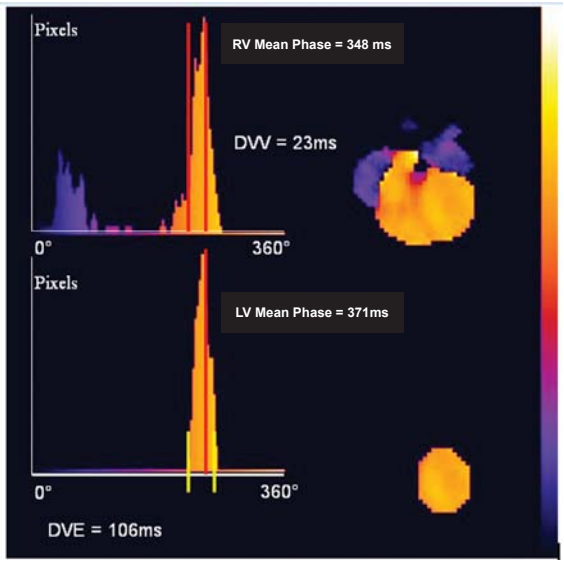


Fig. 1 - *Above, on the right, a phase image of atria and ventricles; on the left, the respective phase histogram of a patient from group 1, with no cardiomyopathy and with a normal ECG. Below, on the right, LV phase image; on the left, its phase histogram. The degree of interventricular synchrony (DVV) was 23 ms and the degree of left intraventricular synchrony (DVE) was 106 ms.*

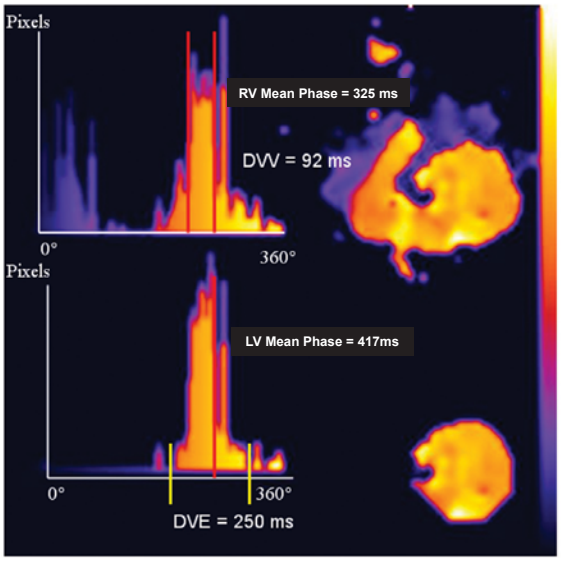


Fig. 2 - *Above, on the right, a phase image of atria and ventricles; on the left, the respective phase histogram of a patient from group 3 with dilated cardiomyopathy and QRS> 120 ms. Below, on the right, LV phase image; on the left, its phase histogram. The degree of interventricular dyssynchrony (DVV) was 92 ms and left intraventricular dyssynchrony (DVE) was 250 ms.*

RVEF was 46 ± 4%, 38 ± 9% and 37 ± 9% in G1, G2 and G3 groups, respectively. The difference was statistically significant between G1 and G2 (p= 0.002), and between G1 and G3 (p= 0.0006), but not between G2 and G3 (p= 0.7) (Table 2).

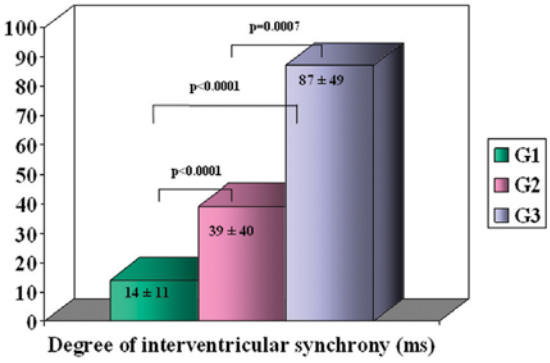
Evaluation of interventricular synchrony (DVV) - The time difference of mean motility between the two ventricles (RVLFdif) was 14 ± 11 ms in G1, 39 ± 40 ms in G2 and 87 ± 49 ms in G3, p< 0.0001. The delay was significantly greater in G2 as compared to G1 (p< 0.0001), and in G3, as compared to G1 and G2, p< 0.0001 (Graphic 1).

Evaluation of left intraventricular synchrony (LVDif.) DVE - The time difference of movement of ventricular regions was statistically different in the 3 groups (p< 0.0001) and it was much greater in G3 (312 ± 130 ms) when compared with G2 (203 ± 54 ms) and G1 (89 ± 18 ms) (Graphic 2).

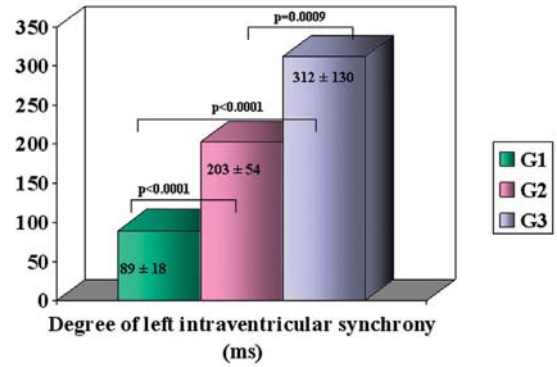
Table 2 - Measurements of QRS duration in the ECG and right and left ventricular function evaluated through RV

Data (mean ± SD)	G1	G2	G3
QRS (ms)	85 ± 9	99 ± 11	160 ± 24
RVEF (%)	46 ± 4	38 ± 9*	37 ± 9*
LVEF (%)	62 ± 6	27 ± 6	22 ± 7

*The difference of QRS mean duration and LVEF among the groups was statistically significant. RVEF difference was statistically significant between G1 and G2, and G1 and G3 but not between G2 and G3. *p= 0.7*



Graphic 1 - *Bar histogram showing the mean values of interventricular synchrony (difference of mean phase angles between RV and LV) in the 3 groups of patients.*



Graphic 2 - *Bar histogram showing the values of left intraventricular synchrony (width of phase histogram of LV) in the 3 groups of study patients.*

Discussion

In the heart, the electrical conduction system controls from atrial systole to coordination of ventricular wall contraction. Patients with dilated cardiomyopathy present increased ventricular volumes due to functional and structural changes which interfere with the cardiac dynamics, thus causing delays and impairing atrial contraction and the coordination of ventricular contraction (delayed interventricular and intraventricular conduction). This contraction dyssynchronization worses cardiac performance and heart failure symptoms[21-24]. For example, in cases of LBBB, there is an earlier activation of the septal region associated with an stress of lateral region, resulting in delayed contraction of this wall and a great stress of the already activated septum, impairing myocardial contraction[25]. CRT leads to improved electrical activation with consequent improvement of ventricular synchrony and pump function efficiency, as well as reduction of mitral regurgitation[1-6].

Approximately 30% of patients receiving a pacemaker for resynchronization do not present the expected benefits. On the other hand, a significant proportion of patients with HF, marked left ventricular dysfunction and QRS <120 ms may benefit with this therapy. However, according to the current selection criteria, patients with QRS <120 ms are not candidates to CRT[1,8,26]. Several studies have suggested that the measurement of ventricular dyssynchrony degree by means of diagnostic methods, such as nuclear magnetic resonance, echocardiogram with tissue Doppler and radionuclide ventriculography could better predict the response to CRT[8-12,14-17,26].

In the current study it was possible to verify which quantitative parameters of ventricular synchronism obtained in the phase analysis allow us to establish the differences among the 3 groups of patients according to the functional performance of ventricular myocardium and QRS width. It was noted that in patients who are candidates to CRT, the electromechanical delay of ventricular movement is much greater when compared to the one in patients without cardiomyopathy and normal ECG. Furthermore, patients with dilated cardiomyopathy and with severe LV systolic dysfunction and QRS <120 ms may present ventricular dyssynchrony although at lower levels when compared with patients with widened QRS.

Some studies showed through tissue Doppler echocardiography that the evaluation of ventricular dyssynchrony seems to be more important than QRS duration in the selection of candidates to CRT[26-28]. Fauchier et al[16] reported that the presence of left intraventricular dyssynchrony through phase images of RV was an independent predictor of a cardiac event in idiopathic dilated cardiomyopathy with no relationship with QRS width. These authors also suggested that values expressed in milliseconds, instead of degrees, are more appropriate because they take into account the duration of the cardiac cycle. In our study we also used the values expressed in milliseconds to standardize the unit with other methods that evaluate dyssynchrony.

Radionuclide ventriculography is a well established technique and it was the first one used in the evaluation of ventricular motility synchrony[13]. It is easy to use, fast, reproducible and it also allows evaluating the overall systolic function of both ventricles with little interference by the operator. Through a mathematics resource (first Fourier harmonic) it is possible to assess the degree of ventricular synchrony[29]. This method evaluates the synchrony of ventricular movement for each image pixel, which is different from the echocardiogram. In this study it was possible to find time differences in the motility of inter- and/or intraventricular walls, even in patients presenting QRS with normal duration, and the phase analysis seemed to be an extremely sensitive tool to detect dyssynchrony. This suggests that the method could be used especially in patients in whom CRT is a therapeutic option but other methods have not been able to identify dyssynchrony.

The results showed mean values of interventricular dyssynchrony through RV about three times higher in G2 and six times higher in G3; and left intraventricular dyssynchrony about twice higher in G2 and three times higher in G3, as compared with the group of normal values (G1). Values above 40 ms are used by many services in the characterization of inter- and left intraventricular dyssynchrony through echocardiogram with tissue Doppler[30]. Our study evaluated left ventricular dyssynchrony in a different way than other studies that used RV[12-16,18]. We measured the width of LV phase histogram and not the standard deviation (SD). In some patients, SD seemed to underestimate the degree of dyssynchrony, therefore we opted to use histogram width. The duration of motility in the area of interest in the LV was measured, and the results revealed higher values of left intraventricular dyssynchrony when compared to values in the literature. However, such values were very different in the three groups studied, showing that this measurement discriminates the patients according to different degrees of ventricular synchrony. The measurement of histogram width is more difficult in individuals with great dispersions of phase angles. Further studies are necessary to evaluate the reproducibility of the values found.

RV also allows calculating RVEF and it is an excellent method to evaluate right ventricular function[31]. In this study, the RVEF in groups G2 and G3 was slightly lower than in healthy volunteers. RVEF should be considered relevant because in patients with LVEF <35%, it presents as the most important prognostic factor[32]. Bleeker et al[33] have recently reported through echocardiogram that CRT induces the reverse remodeling not only in LV but also in RV. This effect was more pronounced in patients with marked RV dilation and this benefit was only reached in patients with left intraventricular dyssynchrony confirmed through an echocardiogram with tissue Doppler before the implantation of a pacemaker. Therefore, the presence of left intraventricular dyssynchrony seems to be mandatory to obtain benefits with CRT and RVEF evaluation can be used for follow-up and evaluation of the prognosis in these patients.

Limitations - We found a relatively high standard deviation in the values obtained in all groups. This fact can be explained by the low number of individuals studied. The inclusion of a higher number of female volunteers may have interfered in the values of the parameters studied.

The inclusion of patients in this study was carried out consecutively as they were sent to the nuclear medicine service for RV, which may also have influenced the results obtained.

There was a statistically significant difference in LVEF between groups 2 and 3. Therefore, the difference found in the degree of ventricular dyssynchrony, with higher values in group 3, may have been influenced by the worse contractile function seen in these patients.

Future directions - RV performed in two views can characterize abnormalities in ventricular synchrony; however, the delayed region can not be precisely located. Studies with computed tomography by single photon emission are being developed, which can improve the performance of this technique in evaluating dyssynchrony and help to determine the implantation site of the electrode in LV[34]. On the other hand, determination of normal values for specific groups, e.g. women, may refine the findings of dyssynchrony in this population. These findings suggest that this technique can be used in the selection of patients who are candidates to CRT, adding information with the purpose of decreasing the number of non-responders.

Conclusion

RV can quantitatively evaluate inter- and left intraventricular synchrony, in addition to being an excellent method to evaluate the overall function of both ventricles. The parameters analyzed discriminate the three groups of patients according to ventricular synchrony degree. Patients with dilated cardiomyopathy and without ventricular conduction disorders at the ECG (QRS< 120 ms) may present dyssynchrony but in a lower degree than that of patients with widened QRS.

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Potential Conflict of Interest

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

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