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ORIGINAL ARTICLE

Use of GATED-SPECT for Ventricular Desynchronization Evaluation in Patients with Heart Failure Submitted to Cardiac Resynchronization Therapy

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Abstract

Background: Approximately 20 to 40% of patients with heart failure do not respond to cardiac resynchronization therapy (CRT). To improve patient selection, phase analysis by myocardial perfusion scintigraphy (GSPECT) was developed.

Objectives: To evaluate the clinical and scintigraphic response of patients with heart failure (HF) submitted to CRT using GSPECT.

Method: This was an interventional study that included consecutive patients assessed by GSPECT four weeks prior to CRT implantation and six months after it for comparison. These patients also answered the Minnesota Living with Heart Failure Questionnaire (MLHFQ). The categorical variables were compared using Fisher's exact test and chi-square test, whereas Student's t-test was used for numerical variables. The level of statistical significance was set at 5%. The scintigraphic variables analyzed were left ventricular ejection fraction, end-systolic volume, end-diastolic volume, left ventricular mass, standard deviation and bandwidth, as well as QRS duration and the Minnesota Quality of Life Questionnaire score. The presence of mechanical dyssynchrony was defined as standard deviation > 43º.

Results: Nine patients were included in the study. After the cardiac resynchronization therapy, there was a significant improvement ($p < 0.05$) in the end-systolic volume (206 ± 80 mL vs. 158 ± 108 mL), QRS (180 ± 18 ms vs. 120 ± 9 ms), left ventricular mass (248 ± 65 g vs. 193 ± 52 g) and Minnesota Quality of Life Questionnaire score (63 ± 16 vs. 34 ± 20). All patients with scintigraphic criteria of mechanical dyssynchrony showed clinical improvement. Two patients had only electrical dyssynchrony and did not achieve significant clinical improvement, although they showed QRS duration reduction.

Conclusion: GSPECT was able to differentiate patients with isolated electrical dyssynchrony from those with associated mechanical dyssynchrony, through the intraventricular dyssynchrony parameters. The cardiac resynchronization therapy is associated with the improvement of both mechanical and electrical dyssynchrony. Pre-implantation GSPECT showed that patients with associated electrical and mechanical dyssynchrony had a better response to cardiac resynchronization therapy than those with isolated electrical dyssynchrony. (International Journal of Cardiovascular Sciences. 2018;31(3)264-273)

Keywords: Heart Failure; Cardiac Resynchronization Therapy; Myocardial Perfusion Imaging / scintigraphy; Stroke Volume; Artery Coronary Disease / physiopathology; Myocardial Infarction.

Introduction

In the United States, approximately 550,000 new cases of Heart Failure (HF) are diagnosed each year, totaling 5 million Americans with the disease. Therefore, decompensated HF is responsible for more than 1 million hospitalizations per year.[1] The estimated direct and indirect costs for HF in 2011, in the United States, were US$ 215 billion, and this figure is expected to reach US$ 804 billion in 2020.[2] The Brazilian Registry of Heart

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Failure (BREATHE) has shown that 60% of the cases admitted to hospitals with HF are due to a reduction in the left ventricular systolic function.[3]

The cardiac resynchronization therapy (CRT) comprises an implantable device capable of synchronic stimulation of the left ventricle (LV) walls, improving cardiac performance and ejection fraction (EF). It has shown to be effective in restoring the synchronic contraction of the interventricular septum with the LV posterolateral wall, contributing to a reduction in neurohumoral activation and consequent reverse remodeling.[4] CRT is a well-established treatment for morbidity and mortality reduction in HF.[5]

The current criteria for CRT implantation, recommended by the European Society of Cardiology[6] with Class I and Level of Evidence A for CRT implantation, are: New York Heart Association (NYHA) functional class II and III with sinus rhythm, LVEF < 35%, QRS width > 150 ms or 120 to 150 ms with Ventricular Electrical Dyssynchrony (ED) by Left Bundle Branch Block (LBBB).

Despite the benefit observed with the use of CRT, there is still a high rate of nonresponders (between 20 and 40%).[7-11] Patients with coronary artery disease and patients with acute myocardial infarction (AMI) are less likely to show a good response to the resynchronizer implantation and a lower chance of undergoing reverse remodeling.[12] Therefore, it becomes necessary to improve patient selection for CRT, considering not only the ED criteria, which would be QRS enlargement (> 150 ms) and LBBB, but also the presence of mechanical desynchronization (MD), according to scintigraphic criteria.

The aim of our study was to assess the clinical and scintigraphic responses of patients with HF submitted to CRT using the phase analysis based on the gated-Single Photon Emission Computed Tomography (GSPECT).

Methods

We performed a prospective intervention study that included consecutive patients (age > 18 years) according to the following inclusion criteria: NYHA functional class II to IV, despite receiving optimal medical treatment according to the guidelines,[6] in sinus rhythm, LVEF < 35%, QRS width > 150 ms or 120 to 150 ms with ventricular dyssynchrony (presence of LBBB). Patients with CRT indication, who signed the Free and Informed Consent Form, were invited to participate in the study.

The patients were referred from the Cardiology Outpatient Clinic of Hospital Universitário Antônio Pedro and the Electrophysiology Outpatient Clinic of Instituto Estadual de Cardiologia Aloysio de Castro. All patients were submitted to GSPECT within 4 weeks prior to CRT implantation and 6 ± 1 month after implantation for comparison. These patients also answered the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and underwent a speckle-tracking echocardiography before and 6 months after implantation, to obtain the EF and end-systolic volume (ESV) variables, with all these evaluations being carried out in a single day, at Hospital Universitário Antônio Pedro.

This study is part of a multinational research project, funded by the International Atomic Energy Agency, which evaluates the use of GSPECT in finding the best left ventricular segment for resynchronizer electrode implantation. This study is being carried out in several countries, aiming at following patients with CRT indication.[12]

Exclusion criteria were: death before completing the follow-up period; severe illness with risk of death in the following 6 months; acute coronary syndromes; CABG surgery or percutaneous coronary intervention in the 3 months before enrollment and within 6 months after CRT implantation.

Patients were submitted to GSPECT at rest in the supine position after intravenous administration of the 99mTc-sestamibi radiotracer (RPH, Brazil). The administered activity was 10 to 20 mCi (adjusted by weight 0.2 mCi/kg). The waiting time between the injection and image acquisition was 40 to 60 minutes. Patients received fatty foods after the injection to minimize liver uptake.

The Millenium MPR gamma-camera (GE, Milwaukee, USA) was used, and the images were processed through the Xeleris 3.0 workstation. Ventricular function analysis was performed using the Emory Cardial Toolbox™, version 3.0 2012 (Syntermed, USA), which generated values of LVEF, ventricular volume and LV mass. Quantitative analyses and image processing were performed using the SyncTool™ software, which was developed for the evaluation of LV MD by GSPECT.[13] The phase analysis technique can transform the four-dimension images (three spatial planes and time) into two-dimensional paired images. The computer program generates an analysis of the cardiac contraction sequence (phase). Each pixel of the cardiac images has its own cycle of contraction and relaxation, having a characteristic temporal association (phase) in relation to the R wave. Based on the phase histogram, the software calculates five quantitative indices: PP (Peak Phase), SD (Standard Deviation), HBW

(Histogram Bandwidth), S (Skewness) and K (Kurtosis). Potential benefits of the phase analysis technique include its wide availability, automation and reproducibility.[14]

All patients in the study were considered as having ED according to the inclusion criteria (QRS width > 150 ms or 120 to 150 ms with ventricular dyssynchrony). MD was defined by the GSPECT phase analysis using the cut-off value SD > 43° and HBW > 135°.

Patients who responded to the therapy were defined as having three of the following four criteria: improvement of one functional class; increase of at least 5% of LVEF; reduction of at least 15% of the ESV; and a 5-point increase in the MLHFQ score.

This project was submitted to the Research Ethics Committee of Hospital Universitário Antônio Pedro through the Brazil platform, being approved under number 884,844, on November 25, 2014.

Statistical analysis

Statistical analysis was performed using the Excel program (2010, Microsoft Corporation) and the software Statistical Package for Social Sciences (SPSS), version 21.0 (2012, IBM Corporation), with data shown as means and standard deviations. The One-Sample Kolmogorov-Smirnov test was performed to confirm data normality. The categorical variables were compared using Fisher's exact test and chi-square test and, as for the numerical variables, the Student's t-test was used. The linear correlation between the continuous variables was used for the calculation of Pearson's linear correlation coefficient. The phase analysis histogram was generated by the Syntool ECT software and correlated with the QRS duration, using Pearson's linear correlation coefficient calculation. The level of statistical significance was set at 5%.

Results

Fifteen patients were recruited from July 2014 to October 2016. Of these, nine were included in the study, as they were able to complete the exams 6 months after the resynchronizer implantation. The reasons for non-inclusion were: death (two patients died in the fifth month after implantation, one due to heart disease decompensation and another due to severe pneumonia); technical problems (one patient was unable to undergo CRT because of an intraventricular thrombus and another showed no adherence to treatment); loss of follow-up (one patient lost contact with the team); and protocol withdrawal (one patient refused to repeat the scintigraphy 6 months after the implantation).

The patients were followed for up a mean time of 193 ± 16 days. All patients underwent anamnesis, MLHFQ, 6-minute Walk Test (6MWT), speckle-tracking echocardiography, and myocardial perfusion scintigraphy before and after implantation, according to the protocol.

The basal general characteristics of the patients included in the study are shown in table 1.

The patients had pre-implantation electrocardiograms with controlled heart rate (beta-blocked) and enlarged QRS, with a mean of 214 ± 17 ms – all with LBBB morphology. In the 6MWT, the average distance traveled was 341 ± 77 m. High values of the Minnesota score (63 ± 16) were observed, showing a higher frequency of symptoms in patients.

Table 2 shows the scintigraphic parameters of systolic function and basal left ventricular mass of the patients included in the study.

Table 3 shows the basal scintigraphic parameters of the phase analysis related to the ventricular synchrony. Two patients did not have MD, according to the scintigraphic criterion (SD > 43°), but only ED.

Table 4 shows patients' clinical response after the cardiac resynchronizer implantation. It was observed that NYHA functional class decreased for all patients with FC > III, with two patients with NYHA IV showing a decrease to NYHA III, and only one FC III patient did not show FC improvement, with statistical significance by Fisher's exact test. There was a statistically significant reduction in the MLHFQ scores, which, despite being subjective, showed a marked improvement in patients' symptoms, with quality of life improvement. Regarding the 6-minute Walk Test, there was an increase in the distance covered, a decrease in the Borg index (subjective dyspnea score) and in the dyspnea assessed by the examiner, although not statistically significant.

In table 5, the findings of imaging methods in relation to desynchronization were compared. The scintigraphic values of ventricular function (LVEF, EDV, ESV and LV mass) and the values that evaluated dyssynchrony (PP, HBW, SD, S and K) were analyzed. There was a statistically significant reduction in mean systolic volume and LV mass after CRT, due to probable post-resynchronization reverse remodeling.

Several correlations of the dyssynchrony scintigraphic parameters with electrocardiographic findings were performed aiming to demonstrate the

Table 1 - Basal general characteristics

Characteristics	n = 9
Age, years	62.4 ± 8
Body mass index, kg/m²	27.3 ± 5.5
Female gender	6
Diabetes Mellitus	5
Hypertension	7
Dyslipidemia	6
Smoking	0
Previous coronary disease	6
Previous infarction	5
CABG surgery	2
Percutaneous Coronary Intervention	1
NYHA functional class	
II	2
III	5
IV	2
Beta-blocker	9
Angiotensin-converting enzyme inhibitor	3
Angiotensin-receptor blocker	5
Acetylsalicylic acid	2
Diuretics	9
Statins	3
Mineralocorticoid-receptor antagonist	6
Digoxin	4

Results expressed as number or mean ± standard deviation. NYHA: New York Heart Association.

Table 2 - Scintigraphic parameters of basal ventricular function of patients included in the study

Patients	LVEF (%)	EDV (mL)	ESV (mL)	Mass (g)
1	38	287	178	233.5
2	23.5	161	123	175
3	28	143.5	102.5	169
4	35	225.5	146.5	213.5
5	26	210	154	200
6	26.5	325	238	274.5
7	31.5	483.5	333.5	378.5
8	30.5	375.5	260	294
9	26	432	320.5	302.5
Mean ± SD	29.4 ± 4.5	293 ± 112.9	206 ± 80.2	248.9 ± 65

LVEF: left ventricular ejection fraction; EDV: end-diastolic volume; ESV: end-systolic volume; SD: standard deviation.

association between QRS duration and the presence of dyssynchrony. Figure 1 analyzes QRS duration with the SD values of the phase histogram. It was known that the higher the SD (SD > 43°), the higher the intraventricular dyssynchrony. Likewise, a QRS > 130 ms was associated with a higher probability of dyssynchrony. The association of both parameters was directly proportional. When analyzed with HBW, it was also observed that the longer the QRS duration, the greater its value. This demonstrates that HBW and SD were also directly associated, as both increased with QRS enlargement and the presence of dyssynchrony.

SD and HBW values were higher for responders than for non-responders, and the difference between HBW in both groups was statistically significant (Figure 2).

Discussion

The present study evaluated dyssynchrony at pre and post-implantation of CRT through GSPECT. CRT had a positive impacted on functional capacity, MD and ED of patients with advanced HF and LBBB and demonstrated the use of GSPECT to identify patients with a higher probability of responding to CRT.

GSPECT is a useful tool for assessing systolic function in patients submitted to perfusion studies by adding diagnostic and prognostic information without additional exposure to radiation.[15] Technological evolution has allowed phase analysis to be employed in GSPECT studies, providing significant data regarding ventricular synchrony.[13] Trimble et al.[16] used the technique of phase analysis in myocardial perfusion scintigraphy, comparing patients with left ventricular dysfunction with patients with LBBB or right bundle branch block, patients with pacemakers and controls for the evaluation of MD. The parameters of phase analysis were able to identify the subgroups according to the degree of ED.[16] Our findings confirm, as those by Trimble et al.,[16] the feasibility of using myocardial perfusion scintigraphy

Table 3 - Scintigraphic parameters of the pre-implantation synchronization of the resynchronizer

Patient	PP	SD	HBW	S	K
1	110	61.08	171	2.96	9.34
2	118	74.04	160	4.09	5.15
3	105.5	22.41	58.5	3.15	10.37
4	153	46.77	146	2.36	5.54
5	191.5	57.74	203	2.31	6.00
6	109	49.26	129	2.99	11.83
7	44.5	15.91	35.5	3.32	10.27
8	131.5	85.71	257	2.09	5.13
9	81	69.93	134.5	1.72	2.82
Mean ± SD	116 ± 39	53 ± 21	144 ± 64	2.7 ± 0.7	7.4 ± 3

PP: peak phase; SD: standard deviation; HBW: histogram bandwidth; S: skewness; K: Kurtosis; SD: standard deviation.

Table 4 - Clinical response before and after cardiac resynchronizer implantation

Variables	Pre-resynchronization	Post-resynchronization	p value
NYHA Functional Class			
II	2	7	
III-IV	7	2	0.015*
MLHFQ	63.6 ± 17.5	34.1 ± 20.5	0.006†
6-minute Walk Test			
Distance covered, m	342.7 ± 82.2	376.6 ± 84.0	0.314**
Borg index	3.1 ± 1.8	1.2 ± 1.3	0.023†
Dyspnea	2.4 ± 2.0	0.89 ± 0.93	0.049†

Fisher's exact test; † paired t-test. MLHFQ: Minnesota Living with Heart Failure Questionnaire.

with phase analysis, as well as the fact that it can be used in patients with HF and CRT indication.

The pathophysiological basis for the resynchronizer implantation is the correction of a mechanical disorder secondary to an altered LV activation due to LBBB. The presence of LBBB is a sign of electrical abnormality and has been the main criterion for the selection of patients to undergo CRT.[17] However, the current criteria used to indicate CRT are still imperfect, as a group of 20 to 40% of patients does not respond to treatment.[18,19] Bleeker et al.[20] compared the echocardiogram with QRS duration for MD evaluation, and found that 30 to 40% of the patients with QRS duration > 120 ms did not have mechanical desynchronization, suggesting that there is an association between the findings of non-response to CRT and absence of MD.[20] MD was not necessarily associated with ED, as evidenced by the absence of MD in patients with QRS duration > 120 ms.[20] This finding was also demonstrated in the present study, in which 22% of patients with clinical indication for CRT (and QRS duration > 150 ms) did not show electrocardiographic criteria for MD. These patients did not show clinical improvement after CRT implantation.

The use of imaging methods to identify desynchronization has been validated;[16] however, its routine use as a support tool for the selection of patients for CRT remains a topic to be studied, such as the study of Henneman et al.,[21] who evaluated patients with CRT indication through GSPECT and observed a 29% rate of nonresponders after 6 months of therapy – comparable to the 22% observed in the present study. In the study by Henneman et al.,[21] the responders had significantly higher dyssynchrony parameters compared to non-responders (HBW of 175° vs. 117°; and SD of 56° vs. 37°, respectively). These values are close to those found in our results (HBW of 177° vs. 76° and SD of 62° vs. 36°, respectively), confirming that the presence of MD identified at GSPECT is a strong predictor for CRT response.[21] Henneman et al.[21] derived, from the sample of 42 patients, cut-off values of the scintigraphic parameters to indicate the presence of MD and to predict good response to CRT in patients with HF: HBW > 135° and SD > 43°.[21]

Table 5 - Statistical analysis of the pre and post-implantation resynchronizer findings between scintigraphy and echocardiography parameters, using Student's t-test, considering p values < 0.05 as statistically significant

Scintigraphy	Pre-implantation	Post-implantation	p value
Ejection fraction, %	29.4	33.89	0.32
End-diastolic volume, mL	293.7	231.1	0.08
End-systolic volume, mL	206.2	158	0.05
Mass, g	249	193.9	0.02
PP	116	114	0.94
SD	53.66	45.8	0.53
HBW	143.8	130.3	0.68
S	2.78	3.28	0.27
K	7.38	15. 35	0.17

PP: peak phase; SD: standard deviation; HBW: histogram bandwidth.

Medical therapy decision-making should always focus on treatments that lead to changes in clinical outcomes, rather than just changes in imaging or laboratory tests. Thus, more than ventricular function improvement, the aim of this study was to select an ideal patient, who shows a reduction in morbidity and mortality after CRT. Recent studies have demonstrated that the phase analysis parameters are markers of adverse prognosis, as observed by Al Jaroudi et al.,[22] who evaluated 144 patients with chronic renal failure and had higher mortality at 2 years in those with HBW ≥ 62° – a value well below that of the study by

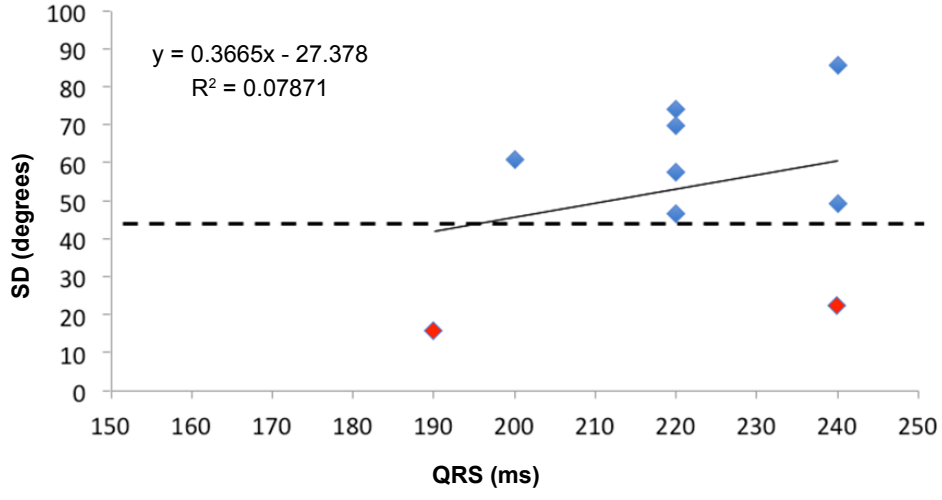

Figure 1 - Correlation between pre-implantation QRS duration and pre-implantation standard deviation (SD).

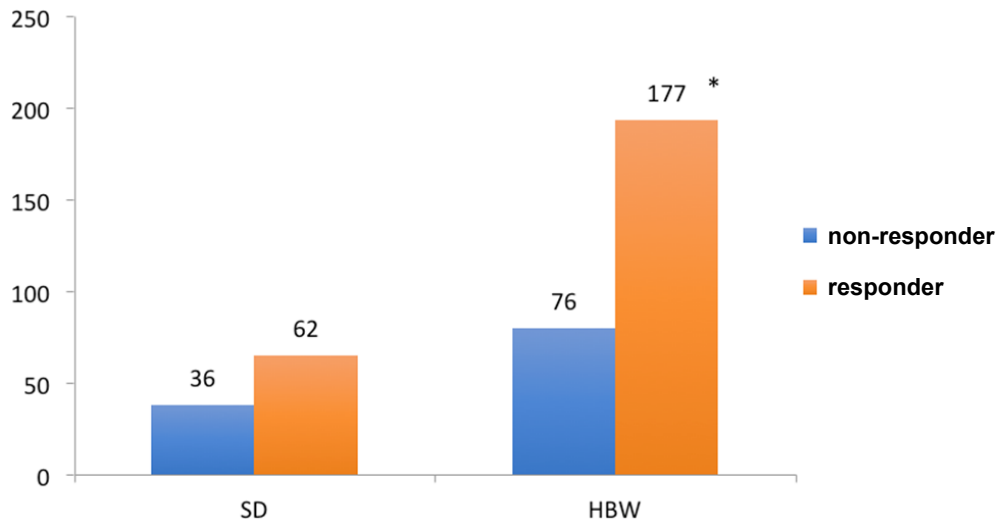

Figure 2 - Distribution of mean SD and HBW before implantation of the cardiac resynchronization therapy, according to the clinical response to implantation. *Chi-square test, with p = 0.03.

Henneman et al.,[21] but already showing some degree of desynchronization.

The subgroup of patients with end-stage renal disease was also extensively studied by Aggarwal et al.,[23] who followed 828 patients with normal EF for 5 years. It was observed that values of SD ≥ 21° or HBW ≥ 56° were associated with worse survival in 5 years. Thus, they also demonstrated that LV desynchronization through phase analysis (GSPECT) provides prognostic value in end-stage renal failure.[23]

A relatively recent study by Zafrir et al.[24] had a significant impact on desynchronization assessment and its association with cardiac mortality, by following 787 patients who underwent GSPECT in a single center for several clinical reasons.[24] These patients were followed for 18.3 ± 6.2 months for cardiac events, and it was verified that SD had the capacity to predict cardiac mortality, and that with every 10° increment, it became an independent predictor of mortality (p = 0.04). Our study did not have data on adverse clinical outcomes in the long term, but ventricular function improvement has been used in several situations, as a valuable surrogate outcome.

Studying clinical outcomes specifically in patients with HF, Al Jaroudi et al.[22] assessed dyssynchrony in patients with an implantable cardioverter defibrillator (ICD) and showed that the higher the SD and the HBW, the higher the incidence of cardiopulmonary arrest or appropriate shock by the ICD.[23] The value of SD > 50° was a predictor of death or appropriate shock by the ICD. More recently, Zafrir et al.,[24] assessing 143 patients with HF and ICD indication, showed a higher rate of events when they also had DM evidenced by SD > 60°.[25] These authors suggest that patients referred to a defibrillator implantation should receive associated CRT when they have SD > 60°.[25]

New studies have addressed the combination of GSPECT parameters to create a MD gradation, using, in addition to HBW and SD, the K and S parameters. Aguadé-Bruix et al.[26] employed a combination of these four parameters and observed that 12% of patients with CRT indication do not have any abnormal phase parameters[26]. Perhaps the study of these combined parameters can increase the sensitivity and specificity of the technique for CRT indication.

In summary, the findings of the present study, together with the growing literature in the area, support that phase analysis by GSPECT is considered a clinically useful tool, to be used both in the assessment of patients in specific subgroups of high cardiovascular risk (end-stage chronic renal failure, hypertensive patients, patients with ICDs) and in the selection of patients with CRT indication.

Study limitations

The main study limitation was the small number of patients, which limited the statistical analysis. Despite the small sample size, statistical significance was observed in parameters that corroborate previous studies in the dyssynchrony area. Another study limitation was the absence of a control group with ventricular dysfunction without CRT. From the ethical point of view, it is not possible to maintain patients with CRT indication as controls, considering the impact of this treatment on mortality and its broad indication recommended in several guidelines.[6] The study had a short follow-up period (6 months) using secondary outcomes, such as left ventricular function, rather than clinical outcomes such as death, HF progression or hospitalization.

Conclusion

The study of phase analysis by GSPECT was able to differentiate patients with isolated electrical dyssynchrony from those with associated mechanical dyssynchrony, through the intraventricular dyssynchrony parameters. The cardiac resynchronization therapy is associated with the improvement of both the mechanical desynchronization (improvement of desynchronization parameters through the phase analysis) and electrical dyssynchrony (QRS interval reduction at the electrocardiogram). Thus, because of the pre-implantation GSPECT assessment, it was possible to verify that patients with associated electrical and mechanical dyssynchrony showed better response to cardiac resynchronization therapy than those with isolated electrical dyssynchrony.

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Author contributions

Conception and design of the research: Wiefels CC, Nascimento EA, Alves CR, Ribeiro FB, Ribeiro ML, Mesquita CT. Acquisition of data: Wiefels CC, Nascimento EA, Alves CR, Ribeiro FB, Fernandes FA, Ribeiro ML, Mesquita CT. Analysis and interpretation of the data: Wiefels CC, Nascimento EA, Alves CR, Ribeiro FB, Fernandes FA, Ribeiro ML, Mesquita CT. Statistical analysis: Wiefels CC, Nascimento EA, Alves CR, Mesquita CT. Obtaining financing: Ribeiro ML, Mesquita CT. Writing of the manuscript: Wiefels CC, Nascimento EA, Alves CR, Ribeiro FB, Fernandes FA, Ribeiro ML, Mesquita CT. Critical revision of the manuscript for intellectual content: Wiefels CC, Mesquita CT.

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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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Universitário Antônio Pedro under the protocol number 884.844. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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