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Improved relationship between left and right ventricular electrical activation after cardiac resynchronization therapy in heart failure patients can be quantified by body surface potential mapping

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OBJECTIVES: Few studies have evaluated cardiac electrical activation dynamics after cardiac resynchronization therapy. Although this procedure reduces morbidity and mortality in heart failure patients, many approaches attempting to identify the responders have shown that 30% of patients do not attain clinical or functional improvement. This study sought to quantify and characterize the effect of resynchronization therapy on the ventricular electrical activation of patients using body surface potential mapping, a noninvasive tool.

METHODS: This retrospective study included 91 resynchronization patients with a mean age of 61 years, left ventricle ejection fraction of 28%, mean QRS duration of 182 ms, and functional class III/IV (78%/22%); the patients underwent 87-lead body surface mapping with the resynchronization device on and off. Thirty-six patients were excluded. Body surface isochronal maps produced 87 maximal/mean global ventricular activation times with three regions identified. The regional activation times for right and left ventricles and their inter-regional right-to-left ventricle gradients were calculated from these results and analyzed. The Mann-Whitney U-test and Kruskall-Wallis test were used for comparisons, with the level of significance set at $p \leq 0.05$.

RESULTS: During intrinsic rhythms, regional ventricular activation times were significantly different (54.5 ms vs. 95.9 ms in the right and left ventricle regions, respectively). Regarding cardiac resynchronization, the maximal global value was significantly reduced (138 ms to 131 ms), and a downward variation of 19.4% in regional-left and an upward variation of 44.8% in regional-right ventricular activation times resulted in a significantly reduced inter-regional gradient (43.8 ms to 17 ms).

CONCLUSIONS: Body surface potential mapping in resynchronization patients yielded electrical ventricular activation times for two cardiac regions with significantly decreased global and regional-left values but significantly increased regional-right values, thus showing an attenuated inter-regional gradient after the cardiac resynchronization therapy.

KEYWORDS: Electrocardiography; Cardiac Resynchronization Therapy; Body Surface Potential Mapping; Heart Failure; Bundle-Branch Block; Ventricular Activation Time.

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INTRODUCTION

Heart failure (HF) has become a major health problem worldwide, and its incidence has increased over the last 60 years (1-3). This increase can be largely attributed to an aging population and longer survival rates for patients because of novel treatment strategies, which have resulted in increased hospitalizations for HF patients (1-4). Cardiac resynchronization therapy (CRT), one of the non-pharmacological approaches, has been responsible not only for

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significant improvement in patient quality of life but also for the decrease in mortality among these patients (5-10).

In spite of the favorable and clearly reproducible results of CRT, 20 to 30% of patients (i.e., the so-called non-responders) show no improvement either clinically or functionally following treatment (11-12).

Different echocardiographic variables have been studied (12-14) in an attempt to identify these non-responders, and these studies have initially yielded promising results. However, the poor sensitivity and specificity for all variables in these studies negated the prospect of using these measures of dyssynchrony to select patients for CRT (13-14). A comprehensive evaluation of the role played by electrocardiography in CRT had similarly inconclusive results (15). Furthermore, one previous electrophysiological study using electro-anatomical mapping found great variability in the electrical and hemodynamic variables (16). Other investigators have used information extracted from electrodes inserted into the ventricles (during and after CRT) in an attempt to correlate the electrical data with both hemodynamic information and the clinical evolution of patients (17-19).

In addition, studies using different approaches in individuals with either left or right bundle-branch block have elucidated the behavior of cardiac electrical phenomena (20-22). Medvegy et al. elegantly summarized the resources offered by body surface potential mapping (BSPM) and its potential application by suggesting that Selvester diagrams be used for an anatomical distribution of electrodes on the body surface (23).

Despite the results of many studies reporting data from patients with resynchronization devices, researchers worldwide continue to search for a method that could determine which patients would respond better to CRT. Such a method should be simple, quick, reproducible, easily performed, pose low risk to patients, and of high accuracy.

Our study is part of a line of investigation that began in the mid-1990s when BSPM was first employed to study patients with left bundle-branch blocks (LBBB) (20) and was later used to study the effects of CRT in those patients. The initial study conducted by Pastore et al. (24), which analyzed BSPM findings with a clinically oriented interpretation of BSPM data from a population of patients who had undergone CRT, reported gradients of regional activation. Moreover, the BSPM methodology has emerged as an alternative, noninvasive approach for studies investigating cardiac activation (24,25).

The present study was designed to quantify and obtain detailed characterization of the effect of CRT on ventricular electrical activation in patients with congestive heart failure using the noninvasive BSPM methodology.

MATERIAL AND METHODS

Study population

We conducted a retrospective study of noninvasive BSPM performed in 91 non-consecutive patients who had undergone CRT. BSPMs were performed in two settings: 1) after CRT implantation and 2) with the device turned off in native sinus rhythm + LBBB. The two BSPM examinations were performed within a maximum interval of 300 days (median time, 98 days). The final population included 55 patients, after 36 patients were excluded (exclusion criteria below).

Inclusion criteria – Patients adhering to the Artificial Pacing Unit of the Heart Institute (InCor) after undergoing CRT with the classic indications for therapy (i.e., sinus rhythm, LBBB, depressed left ventricle ejection fraction [LVEF], New York Heart Association functional class III/IV, and routine use of medications for HF) were included.

Exclusion criteria – Patients with atrial fibrillation (n = 20), and/or those dependent on a permanent pacemaker prior to CRT (n = 9), and/or with right bundle-branch block (RBBB, n = 3), and/or a diagnosis of hypertrophic (n = 3) and/or congenital cardiopathy (n = 1) were excluded.

This study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of the Heart Institute (InCor-HC-FMUSP).

Body surface potential mapping (BSPM)

The 87 unipolar electrodes of the Fukuda Denshi model 7100 BSPM equipment (Fukuda Denshi Co., Ltd., Tokyo, Japan) were attached to adhesive strips, distributed over the anterior chest (59 leads) and back (28 leads), and recorded simultaneously. Electrical potentials were digitized, processed, and visualized at the BSPM matrix as PQRST complexes distributed according to the lead system orientation. The potentials were also indexed using letters and numbers, with each strip corresponding to a letter (A through I on the chest and J through M on the back) and numbers one to seven corresponding to the lines) (Figure 1).

This system was used to assess traditional electrovectorcardiographic variables (i.e., the rhythm, PR interval, axes, QRS complex width, and orientation and direction of loops in the horizontal and frontal planes). Additionally, this software enables the acquisition of other cardiac electrical data, such as a map of the isochronal lines and ventricular activation times, as described below.

The isochronal lines of activation provided by the body surface potential mapping are based on the QRS complex duration values. During the process of electrocardiographic data acquisition, one of the QRS complexes is selected to guide the acquisition of the QRS complex durations in all 87 leads. By positioning the two cursors available on the display, one at the onset and the other at the end of the chosen QRS complex in each lead, these measurements are semi-automatically performed. Then, it is possible to quantify the QRS complex width for all 87 leads. With these point-by-point measurements, the entire electrical process of the QRS complex can be studied. If we assume that the QRS complex duration is obtained, it is then possible to interpret the meaning of such values as the quantification of the ventricular electrical activation. Thus, the analysis of the 87 QRS complex duration values enables the temporal visualization of the path that an electrical stimulus has travelled through the ventricles, and it is also possible to identify the leads in which the QRS complex was generated the fastest and slowest.

Based on the values obtained from our patients, and using the data defined by the Selvester diagrams reported by Medvegy et al. (23), we identified three distinct areas by comparing the activation time values from the 87 leads. First, we noticed that the first four electrode strips (A to D) displayed a similar pattern, the second set of four strips (E to H) showed another pattern, and the third set of four strips (I to L) showed a third pattern, thereby demonstrating separation into three different areas with distinct mean activation times. By comparing the results from the QRS

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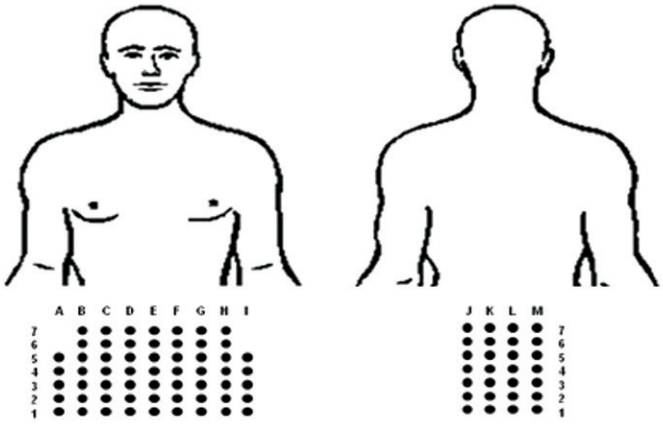

	A	B	C	D	E	F	G	H	I	J	K	L	M
7		33	36	35	34	34	34	36		64	63	25	21
6		36	37	38	34	36	37	56		61	57	22	30
5	28	31	39	37	38	37	59	61	61	58	63	25	25
4	12	41	38	38	37	60	59	59	58	60	65	23	23
3	52	47	44	42	41	59	60	57	57	56	64	12	23
2	51	53	45	46	49	59	59	55	56	58	55	11	12
1	50	50	48	47	48	55	56	56	58	55	55	50	49
	A	B	C	D	E	F	G	H	I	J	K	L	M

RV | Intermediate | LV

RV – right ventricle
LV – left ventricle

Figure 1 - Distribution of the 87 electrodes on the anterior chest and back, which were indexed by letters (strips or columns) and numbers (lines), and their regional distribution. Three distinct areas (denominated right ventricle region, an intermediate region, and left ventricle region) could be identified based on the three different mean activation patterns shown by each set of four strips of electrodes (i.e., A to D, E to H, and I to L, see details in the Methods section).

duration obtained from the 87 leads in our study with the knowledge of a typical LBBB activation pattern, we could associate these three distinct areas with the right ventricle (RV) region, an intermediate region, and the left ventricle (LV) region (Figure 1).

Therefore, the moments in which the different regions within the myocardium were activated could be characterized, which meant that we were able to observe and regionalize the ventricular electrical activation process.

Because the intermediate region identified may comprise areas that relate to the right ventricle and other areas that relate to the left ventricle, we decided to measure and analyze only two regions: those with electrical characteristics that are typical of the right ventricle or the left ventricle.

Global and regional ventricular activation time (VAT) values and inter-regional gradients were calculated according to the BSPM maps, first during biventricular pacing with CRT on and then in the intrinsic rhythm (sinus rhythm + LBBB) with the resynchronization device off.

The maximal global VAT was collected based on the maximal values obtained in the 87 leads, and mean global VAT was obtained by calculating the arithmetical average of all 87 values.

Second, we measured the regional ventricular activation times, which were calculated based on the VAT values in the regions described above. The VAT mean values for the right ventricle (RV) and left ventricle (LV) regions were obtained by arithmetically averaging the VAT values from the 26 leads apportioned to the RV region and the VAT values from the 26 leads apportioned to the LV region (Figure 1).

The inter-regional gradients were calculated based on the difference between the regional mean RV and LV values described above.

These three sets of variables allowed us to better characterize the global, regional, and inter-regional behavior of the ventricular electrical activation sequence during both the intrinsic rhythm (sinus rhythm + LBBB) and atrio-biventricular (BIV) pacing.

After obtaining these measures, we were able to analyze the impact of CRT on ventricular electrical activation by calculating the percentage of variation in the VAT values. This measurement revealed the changes promoted by CRT and was calculated as follows:

variation = {[VAT in BIV pacing]-[VAT in sinus rhythm+LBBB]} × [100]/[VAT in sinus rhythm+LBBB].

This calculation was performed for the global and regional values and the inter-regional gradients.

Statistical analysis

Because some of the data showed a non-Gaussian or skewed distribution, we chose to express the continuous variables as medians with the respective maximum and minimum values. Categorical variables were expressed as percentages. Global, regional, and inter-regional VATs were compared using the nonparametric Mann-Whitney U-test and the Kruskal-Wallis test. The level of significance was established at $p \leq 0.05$.

RESULTS

The following clinical characteristics were observed for the 55 patients included in this study: mean age, 61 ± 10 years; 60% (n = 33) male; etiology of HF as predominantly idiopathic (51%, n = 28), ischemic (20%, n = 11), chagasic (14.5%, n = 8), or hypertensive (14.5%, n = 8); mean left ventricle ejection fraction, 0.28 ± 0.09; mean QRS duration, 182 ± 24 ms; and New York Heart Association functional class III (78%, n = 43) and IV (22%, n = 12).

Table 1 displays the ventricular electrical activation development (in ms) for the two settings with and without CRT action (medians and max-min values). The effect of CRT is shown in terms of variation in the study variables and the respective significance level.

The maximal global VAT in sinus rhythm+LBBB was prolonged (138 ms) in comparison to the CRT-on situation (131 ms). However, the mean global VAT showed the opposite trend, with a nearly 10% increase during biventricular pacing (64.8 ms vs. 70.5 ms).

An analysis of the regional ventricular electrical activation revealed significant differences between the two areas during the intrinsic rhythm. There was also a considerable delay between the activations of the LV and RV regions (95.9 ms vs. 54.5 ms, $p<0.001$). During CRT, these differences were less pronounced, with an increased RV (78.9 ms) and decreased LV regional value (77.3 ms) (Figure 2). In addition, note that we observed almost simultaneous activation of the RV and LV regions during CRT.

Inter-regional relationships during intrinsic rhythm+LBBB showed significant delay between the LV-RV regions (43.8 ms) ($p<0.001$), which were attenuated by CRT. The analysis of inter-regional gradients characterized this phenomenon by showing significantly reduced LV-RV delay (17.0 ms) (Figure 3).

Finally, the results of the percentage variation highlighted the impact of CRT on ventricular electrical activation, as we found that the maximal global VAT was reduced by 5.1%, but the mean global VAT was increased by 8.8% with CRT.

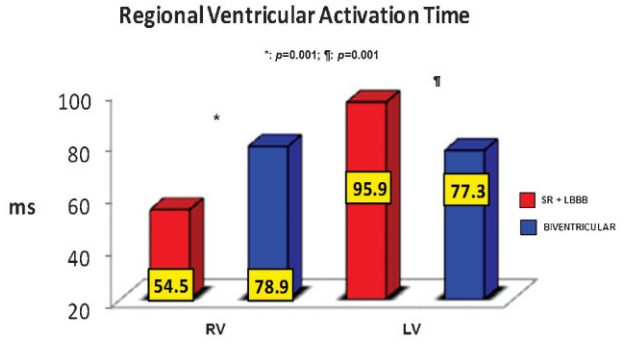

Figure 2 - Comparison of regional RV and regional LV activation times during sinus rhythm and biventricular pacing.

Furthermore, the regional analysis showed that the CRT effect increased the VAT value of the RV region by 44.8%, while the VAT of the LV region was decreased by 19.4% (Figure 4). Consequently, we observed a significant reduction (61.2%) in the inter-regional LV-RV gradient (Figure 5).

DISCUSSION

Many studies have been conducted to better understand the cardiac electromechanical phenomenon in patients indicated for CRT, with the goal of reducing the number of non-responders.

In the present study, we quantitatively characterized the ventricular electrical activation in a patient population implanted with CRT. Therefore, we analyzed the global and regional ventricular activation times as well as the inter-regional gradients. In addition, we obtained the measurements for the percentage variation in the VAT values, which enabled us to better understand how CRT works from an electrical perspective.

During intrinsic rhythm+LBBB, we were able to quantify the significantly increased (80%) regional-LV VAT value. Thus, we observed a prolonged inter-regional LV-RV gradient.

Therefore, BSPM could assess the typical electrocardiographic presentation of an LBBB conduction disorder, which, according to our findings, demonstrated a maximal global ventricular activation time >120 ms, a mean global VAT >60 ms, and a greater regional-LV VAT value compared to the regional-RV VAT value.

Two studies investigating the electrical activation of individuals with LBBB used electro anatomical mapping for such characterizations (21,22). Using a different methodology may explain why these studies were unable to provide a clear discrimination or quantification of the time when activation occurs in the right ventricle, intermediate, and left ventricle regions. The relationships between those

Table 1 - Ventricular electrical activation development (in milliseconds).

	Sinus rhythm + LBBB		Biventricular Pacing		Variation	*p*-value
	Median	Min-Max	Median	Min-Max		
Maximal Global VAT	138	106-139	131	60-225	↓5.1%	0.007
Mean Global VAT	64.8	48.1-87.8	70.5	25.3-98.2	↑8.8%	**ns**
RV Regional VAT	54.5	21.7-86.9	78.9	20.0-126.5	↑44.8%	0.001
LV Regional VAT	95.9	47.3-123.4	77.3	21.9-119.2	↓19.4%	0.001
Inter-regional LV-RV gradients	43.8	0.08-96.00	17.0	0.38-46.12	↓61.2%	0.001

LBBB = left bundle-branch block; **LV** = left ventricle; **ns** = not significant; **RV** = right ventricle; **VAT** = ventricular activation time.

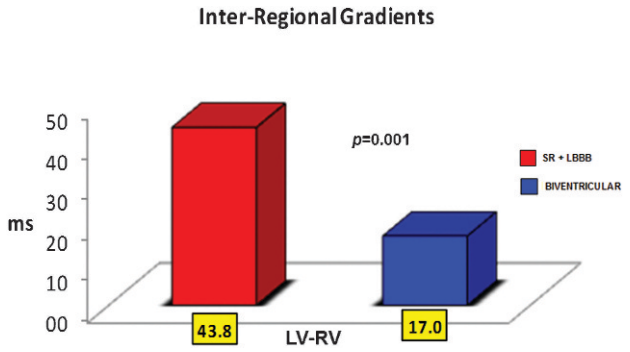

Figure 3 - Inter-regional LV-RV gradients in sinus rhythm and biventricular pacing.

regions were also unclear, as both studies showed significantly delayed activation of the LV in relation to that of the RV, ranging from 89 ms to 110 ms, which agrees with the value described and quantified in our study. In addition, the study by Fantoni et al. (22) was the only one in which a mean activation time of 75 ms could be inferred for the RV, which aligned with our results.

Regarding biventricular pacing, we were able to quantify values for the global and regional VATs and inter-regional gradients, which may facilitate understanding of the electrical phenomena that occur during CRT.

A significant reduction in the maximal global VAT to 131 ms was observed when the resynchronization device was on, albeit with a slight rise in the mean global VAT to 70.5 ms. This global VAT behavior can likely be fully explained by the changes that occur in regional VATs during biventricular pacing. In addition, under CRT, the regional-LV VAT was shortened by nearly 20%. Note that under the influence of LBBB, the maximal global VAT reflects the extremely long activation times in the left ventricle; therefore, the decrease in regional-LV VAT during CRT was associated with the concomitant decrease in maximal global VAT. However, we observed that the regional-RV VAT was nearly 45% further delayed during biventricular pacing. The increase in mean regional-RV VAT greatly surpassed the amount by which the regional-LV VAT was reduced, which indicates that the increase in mean global VAT during biventricular pacing reflects this phenomenon. Moreover, the goal of CRT (i.e., restoring the ventricular mechanics and reestablishing synchronization of the ventricles) allows better understanding of these

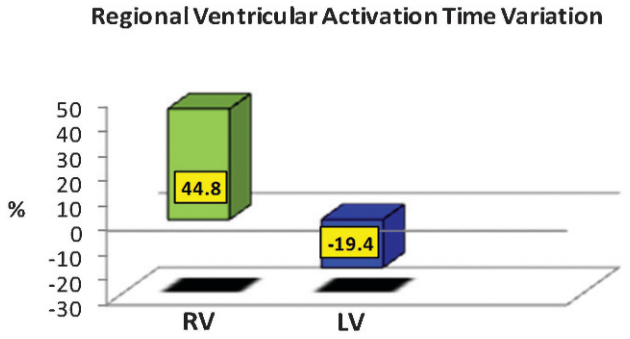

Figure 4 - Regional VAT variation for the RV (increased) and LV (decreased).

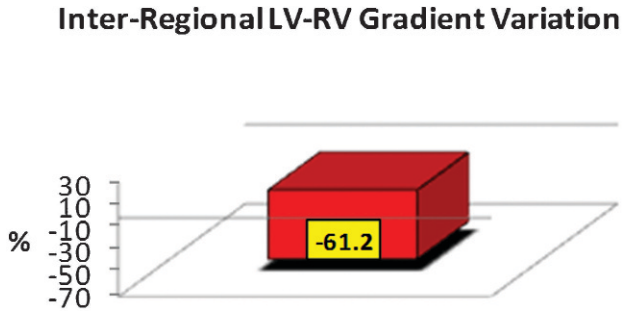

Figure 5 - The inter-regional LV-RV gradient variation showed a significant reduction.

electrical phenomena. Moreover, this synchrony (or dyssynchrony) can be better evaluated according to the temporal relationships between the ventricular regions (inter-regional gradients).

Contrary to what we found during sinus rhythm+LBBB, biventricular pacing led to a significant 61.2% reduction in the interventricular delay, which we termed the inter-regional LV-RV gradient. This reduction provides evidence that under CRT, the time of LV activation approaches that of RV activation.

Varma et al. (25) showed that CRT led to activation times of 63.0 ms and 83.5 ms for the RV and LV, respectively, which were similar to those reported in the present study. Varma et al. also reported a clear change in activation of both the RV (increasing from 37 ms to 63 ms) and LV (decreasing from 113 ms to 83.5 ms) after resynchronization, and these values were also quite similar to those observed in our study. Furthermore, both in this previous study and in our study, the RV ventricular activation time approached that of LV. Pratola et al. (16), who found a total activation time of 68.5 ms during biventricular pacing, which aligned with our mean global VAT value of 70.5 ms. In 2010, Sassone et al. (19) reported a measurement termed RVLV interlead electrical delay, which represented the time difference between intracavitary electrograms obtained from the right ventricle lead in relation to the left ventricle lead at the end of the resynchronization device implantation. Although these authors used a distinct methodology, their results were similar to our inter-regional LV-RV gradient. After a six-month follow-up period, these authors also found a significantly reduced value in the responder group (22.1 ms vs. 43.6 ms). In our study, the inter-regional LV-RV gradient of 17 ms obtained during biventricular pacing may be used to guide the placement of ventricular electrodes to adjust the interventricular pacing delay and help identify the individuals who will receive the most benefit from CRT.

We calculated the VAT variation to assess the behavior of ventricular activation times during CRT. This measurement quantifies the CRT effect upon the ventricular electrical activation process, which shortened the time difference between activation of the left and right ventricles.

The above results indicate that, from the electrical standpoint, CRT attempted to restore the coupling of the ventricles in the hearts, which did not occur under LBBB. This coupling was enabled by the simultaneous anticipation of LV activation and the delay of RV activation. We believe these findings are of the utmost importance because it was possible to quantitatively demonstrate in detail the alterations that occur with global, regional, and inter-regional

ventricular activation when the resynchronization device is operating. These data (regional-RV VAT and variation of mean global VAT) may further serve as the basis for future studies involving CRT and its clinical outcomes.

Study limitations

This was a retrospective study in which we used very strict exclusion criteria (40% of patients excluded) to obtain maximal homogeneity in the patient sample, and this resulted in a drastic reduction in the number of individuals included in the study population (only 55 patients). Other potential factors may have interfered with our results, such as the timing of the BSPM examinations, which varied from 120 to 300 days after CRT in 95% of the sample, and the lack of data concerning the localization of electrodes implanted in the left ventricle, a factor considered by some authors to be of some importance. Furthermore, new developments in drug therapy may have had implications on cardiac remodeling as well. As a retrospective study, we were unable to perform body surface mapping prior to implantation of the resynchronization device. We are also aware that we may have analyzed data from patients who had already undergone some cardiac remodeling; however, our results showed that there was a difference in activation when the devices were not operating. We can, therefore, infer that the differences we found would be even greater had we measured the cardiac electrical activation prior to implantation. Thus, this factor likely does not invalidate our findings and rather indicates that the study outcomes may be underestimated.

Analysis of the ventricular activation times obtained by body surface potential mapping enabled characterization of the ventricular electrical activation phenomenon in patients undergoing cardiac resynchronization therapy. Our results indicated that CRT led to a maximal global reduction by 5.1% and similar regional ventricular activation times in the two ventricular regions studied (78.9 ms and 77.3 ms for the RV and LV regions, respectively), which resulted in enhanced synchronization of the ventricles according to the significant 61.2% reduction in the inter-regional LV-RV gradient.

AUTHOR CONTRIBUTIONS

Samesima N managed the project, collected and analyzed the data, and wrote the manuscript. Pastore CA coordinated the project and supervised the manuscript writing. Douglas RA performed the BSPM examinations and contributed to the data processing and analysis. Martinelli Filho M supervised the data collection and contributed to its analysis. Pedrosa AA performed a critical analysis of results and discussion.

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