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Impact Of RV Lead Positioning On Global Longitudinal Strain As A Surrogate Of Clinical Response In Patients With Non-Ischemic Cardiomyopathy Treated By Cardiac Resynchronization Therapy

Mostafa Abdelmonaem*, Amira Nour, Ahmed Kadry, Ahmed Reda
Department of Cardiology, Faculty of Medicine, Ain Shams University, Cairo, Egypt
***Corresponding author:** Mostafa Abdelmonaem, **Mobile:** (+20) 01020139399, **E-Mail:** mostafaabdelmonaem@yahoo.com

ABSTRACT

Background: Cardiac resynchronization therapy (CRT) provides an excellent therapeutic option for patients with heart failure and reduced systolic functions, optimizing the CRT implantation procedure is mandatory to improve clinical response. The site of right ventricle (RV) pacing remains a puzzling issue that needs to be solved to assess the impact of non-apical RV pacing on CRT clinical and echocardiographic response.

Objective: To compare the impact of RV apical pacing versus RV septal pacing in patients with non-ischemic cardiomyopathy treated by CRT in terms of global longitudinal stain, 6 minutes walk test, and QRS complex width.

Patients and Methods: An observational prospective trial study was conducted on 100 patients with dilated cardiomyopathy who were candidates for CRT implantation. Fifty consecutive patients had RV pacing lead in the apical position and the other 50 consecutive patients had the pacing lead in mid septal position.

Results: The GLS significantly increased post-procedure within the whole patients (11.9 ±2 vs. 11 ±2.1), the apical group (12.1 ±1.9 vs. 11.1 ±2.1), and the septal group (11.8 ±2.1 vs. 10.9 ±2.1) ($P < 0.001$ for each). No significant difference was detected between both groups of patients regarding QRS width, 6 min walking test, and GLS. A positive correlation was found between delta GLS and % of 6 minutes walk test among the group of patients with mid-septal RV lead position.

Conclusion: This study concluded that septal RV pacing is not superior to standard RV apical pacing in patients with non-ischemic cardiomyopathy candidate for CRT, in terms of clinical and echocardiographic response.

Keywords: Cardiac resynchronization therapy, Heart failure, Global longitudinal strain, septal pacing.

INTRODUCTION

Heart failure is an expanding public health crisis and is by far the most common cause of hospitalization, especially in elderly subjects beyond 70 years of age [(1)]. It is believed that 1-2% of the general population is suffering from heart failure and this percentage increases to 10% at least of the elderly population, it is well believed that these values are underestimated as many patients are undiagnosed or not seeking medical advice. Heart failure constitutes approximately 8% of hospital admissions and those successfully discharged to home after compensation still have significant mortality risk, especially in 1st year [(1-4)].

Cardiac resynchronization therapy (CRT) is a globally accepted therapeutic tool for patients with symptomatic heart failure. It is a widely accepted option for patients with depressed left ventricular systolic function and conduction delay, particularly those with left bundle branch block morphology. The idea beyond this helpful tool is to restore biventricular synchrony through right and left ventricular simultaneous or sequential pacing with atrial tracking provided that patients are in sinus rhythm. [(5-7)] Left ventricular pacing is achieved by placing a pacing lead in coronary sinus tributaries preferably posterolateral and lateral branches, besides the conventional placement of right ventricular and right atrial pacing leads. Adjunctive sites of right ventricular pacing other than apical pacing were proposed as RVOT or mid-septal pacing [(8,9)].

CRT showed evidence-based success in reducing patient mortality and morbidity besides improving quality of life and reducing hospitalizations. Despite great success in optimal lead placement, CRT response is only valuable in nearly 70% of candidates. Many factors were proven to influence clinical response to CRT implantation as the percentage of biventricular pacing, programming adequacy, coronary sinus lead position, gender, and etiology of cardiomyopathy. Response to CRT can be judged through different parameters; as a clinical response in terms of 6 minute walking test and improvement of New York Heart Association (NYHA) functional class, electrocardiographic response manifested as a reduction in QRS duration and electric vectors in lead I and V1, echocardiographic response evidenced in the improvement of left ventricular systolic functions and improvement of valvular incompetence [(10-12)].

It is previously accepted that isolated RV apical pacing is a predictor of worsening left ventricle (LV) dysfunction. A positive correlation was noticed between the percentage of conventional RV apical pacing and the magnitude of the decline in LV systolic functions. So, alternative sites of RV pacing were proposed as a trial to minimize this negative impact on myocardial performance [(13-15)].

We aimed to compare the impact of the right ventricle (RV) apical pacing versus RV septal pacing in patients with non-ischemic cardiomyopathy treated by CRT in terms of global longitudinal stain, 6 minutes walk test, and QRS complex width.

PATIENTS AND METHODS

This study is an observational prospective trial conducted on 100 consecutive patients who were

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candidates for CRT device implantation. Patients were classified into two groups, the first group included 50 patients having the RV lead positioned in the RV apex, and the second group included 50 patients with the RV lead positioned in the RV septum, the outcomes regarding QRS complex duration, global longitudinal strain and clinical response will be compared between the two groups, 3 months post CRT implantation.

Inclusion Criteria:

1. Non-ischemic cardiomyopathy patients, eligible for CRT implantation as a treatment for heart failure with reduced left ventricular functions, based on European society guidelines of heart failure [(1)].
   - Left ventricular systolic functions ≤ 35%.
   - Heart failure symptoms while receiving the best medical care.
   - Sinus rhythm with QRS width ≥130 ms in Left bundle branch block (LBBB) morphology patients and ≥150 ms in non-LBBB morphology patients.
2. Willing and capable to provide informed consent.
3. Success in achieving biventricular pacing exceeding 95% 3 months post-implantation.

Exclusion Criteria:

1. Limiting co-morbid conditions that may hinder CRT clinical response as a chronic obstructive pulmonary disease (COPD), multi-organ dysfunction.
2. Patients with a pre-existing indication of pacing for heart block of sinoatrial (SA) nodal disease.
3. Patients with atrial fibrillation either persistent or permanent.
4. Ischemic etiology of heart failure.

All patients recruited in this study were subjected to:

1. Detailed history taking regarding age, gender, risk factors, etiology of heart failure, co-morbid conditions, current and past medical therapy, and NYHA functional class.
2. Precise clinical examination to assess vital data and hemodynamics and any limitations for device implantation.
3. CRT implantation was done following the universal consensus of implantation, in which coronary sinus lead was placed in the lateral or postero-lateral tributary. RV pacing lead was placed in RV apex in 50 consecutive subjects and its position was confirmed in RAO and lateral fluoroscopic projections. RV pacing lead was placed in mid-septum in the other group of patients, this position was achieved by proper pre-shaping of the lead stylet, using a small primary bend followed by a wide secondary bend. After crossing the tricuspid valve gentle counter-clockwise rotation was done to park in the septal region. The septal position was confirmed in the right anterior oblique (RAO) and left anterior oblique (LAO) projections. The right atrial lead was placed in the right atrial appendage provided good sensing capabilities [(16)].
4. Resting 12 leads ECG was done pre-implantation to assess the type of conduction delay, rhythm, and QRS width. Post-implantation and post-interrogation ECGs were serially done to assess the criteria of electrocardiographic response in terms of QRS width, R wave in lead V1, and lead I and AVR vectors [(17)].
5. CRT interrogation was done serially post-implantation and 3 months later and at any time when indicated. Emphasis was done on; lead impedance, pacing thresholds, sensing parameters, AV delay, VV delay, and BIV pacing percentage.
6. Echocardiography will be done for each patient 3 months post-implantation and compared to pre-implantation Echocardiography regarding LV systolic functions, LV dimensions, valvular incompetence, and global longitudinal strain (GLS) [(18)].

Protocol of 2-Dimensional speckle tracking echocardiography: ECG gated Cine Loops from apical 4 chambers, apical 2 chamber, and apical long axis views were stored at a frame rate of 40–80 frames/second. Offline analysis was performed with workstation software Echo PAC Dimension (113 GE medical systems GmbH, Germany). The program then creates segmental and overall longitudinal strain by segmenting the LV myocardium into six sections. The longitudinal strain will be shown below the baseline because the myocardium often shortens longitudinally during systole. Each segment's peak systolic longitudinal strain will be calculated from these graphs. To get the overall longitudinal strain, the strain values for all the segments are saved and averaged (GLS). The regional and global longitudinal strains of each of the 17 investigated segments are then automatically shown topographically (Bull's eye configuration) [(19)].

Follow-up was done for all patients after 3 months, to assess electrocardiographic changes and clinical response in terms of 6 minutes walk test and GLS. A comparison was held between the group with RV apical lead position and the group with the septal position.

Ethical consent:

An approval of the study was obtained from Ain Shams University Academic and Ethical Committee.. After explaining our research objectives, written informed consent was obtained from all study participants. This study was conducted in compliance with the code of ethics of the world medical association (Declaration of Helsinki) for human subjects.

Statistical methods

Using SPSS version 28, data management and statistical analysis were conducted (IBM, Armonk, New York, United States). Utilizing both the Kolmogorov-Smirnov test and direct data visualization techniques,

quantitative data were examined for normalcy. Quantitative data were summarised using means and standard deviations or medians and ranges following normality. Numbers and percentages were used to represent a categorical set of data. Independent t-tests or Mann-Whitney U tests, for normally and non-normally distributed quantitative data, respectively, were used to compare quantitative data between the groups under study. We compared categorical data using the Chi-square test. Using a paired t-test, GLS was compared in all patients, the apical group, and the septal group before and after the surgery. Spearman's correlation was used to conduct correlation analysis. All statistical tests were two-sided. P-values less than 0.05 were considered significant.

RESULTS

The mean age of the studied population was 60 years ranging from 40 to 70 years of age, males comprised 82 % of the studied cohort of patients. Regarding demographic data; 81% of patients were hypertensives, 70% were diabetic on treatment and 62% were active smokers. All patients had non-ischemic cardiomyopathy which was objectively confirmed by coronary angiogram or non-invasive stress testing. At the time of presentation, NYHA functional class was assessed revealing that 63% were in NYHA class III, 30% in NYHA class II, and 7% in NYHA class IV. Baseline ECG criteria were recorded as follows; QRS complex duration ranged between 140 -240 ms. with a mean value of 166 ms. Complete LBBB was the recognized conduction delay pattern in 83% of patients.

Regarding baseline echocardiographic parameters; LV systolic functions ranged between 19 and 34% with a mean of 28%±4, left ventricular end-diastolic diameter ranged between 58 and 79 mm with a mean of 66±7 mm, left ventricular end-systolic dimensions ranged between 43 and 62 mm with mean of 53±4 mm and 8 patients had severe mitral incompetence while 50 patients had a moderate degree of incompetence.

Regarding the procedure of CRT implantation; all patients had RA lead placed in the right atrial appendage, 50 patients had RV lead placed in RV apex and 50 patients had the lead placed in the mid septum, LV pacing lead was placed in the postero-lateral tributary in 82% of subjects, 16% had the lead in lateral tributary and only 2 patients had pacing lead in a lateral tributary of the anterior vein.

Post-implantation follow-up was done for all patients 3 months post-procedural. Regarding clinical data. The mean percentage of 6 minutes walk test was 84±3 % of the expected, there was a highly significant improvement in NYHA functional class post CRT implantation with a P-value of 0.001, in which 55 patients were in NYHA class I and 23 patients were in NYHA class II. Also, there was a highly significant reduction in QRS width post-implantation with a P-value of 0.001, with mean QRS width of 110 ms±24 ms. Regarding Echocardiographic parameters, significant improvement of left ventricular systolic functions were noticed (mean pre-implantation EF value was 28 ± 4 % vs. 37.3 ± 5.62 in post-implantation, P-value < 0.001), highly significant reduction in left ventricular end-diastolic (LVED) diameter (mean pre-implantation LVED value was 66 ± 7 mm vs. 58 ± 6.3 mm, P-value < 0.001), highly significant reduction in left ventricular end-systolic (LVES) diameter (mean pre-implantation LVES diameter value was 53 ± 4mm vs. 42 ± 8.5 mm post-implantation, p-value <0.001), and a highly significant reduction in the degree of mitral regurgitation (P-value <0.001). The GLS significantly increased post-procedure within the whole patients (11.9 ±2 vs. 11 ±2.1), the apical group (12.1 ±1.9 vs. 11.1 ±2.1), and the septal group (11.8 ±2.1 vs. 10.9 ±2.1) (P < 0.001 for each).

A comparison was held between 2 groups of patients, the 1st group included 50 patients with RV apical lead position, and the 2nd group of 50 patients with RV septal lead position. As shown in **Table 1,** no significant differences were observed between the studied groups regarding age (P = 0.07), sex (P = 0.603), diabetes (P = 0.509), and hypertension (P = 0.799).

Table (1): General characteristics of the studied groups

	Apical (n = 50)	Septal (n = 50)	P-value
Age (years)	61 ±7	59 ±7	0.07
Sex			
Males	40 (80)	42 (84)	0.603
Females	10 (20)	8 (16.0)	
Diabetes	37 (74)	34 (68)	0.509
Hypertension	40 (80.0)	41 (82)	0.799

Data are presented as mean ±SD or number (percentage)

Primary endpoints

No significant differences were observed between the studied groups regarding % achieved of the 6-min walk test (P = 0.06), delta QRS (P = 0.429), GLS pre (P = 0.559), GLS post (P = 0.410), and delta GLS (P = 0.621) (**Table 2, Figures 1, 2).** The GLS significantly increased post-procedure within the whole patients (11.9 ±2 vs. 11 ±2.1), the apical group (12.1 ±1.9 vs. 11.1 ±2.1), and the septal group (11.8 ±2.1 vs. 10.9 ±2.1) (P < 0.001 for each).

Table (2): Primary endpoints in the studied groups

	Apical (n = 50)	Septal (n = 50)	P-value
% achieved of 6 min walk test	85 ±3	84 ±3	0.06
Delta QRS	60 (30 - 100)	60 (20 - 120)	0.429
GLS pre (%)	11.1 ±2.1	10.9 ±2.1	0.559
GLS post (%)	12.1 ±1.9	11.8 ±2.1	0.41
Delta GLS %	0.9 (0.1 - 2.6)	0.9 (0.3 - 1.8)	0.621

Data are presented as mean ±SD or median (min-max)

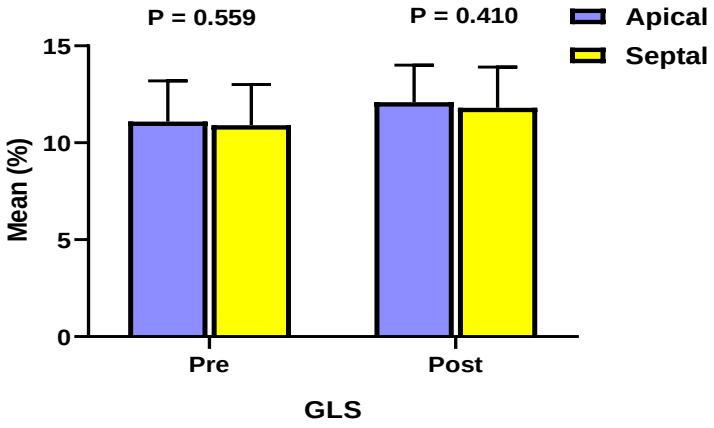

Figure (1): Pre- and post-GLS in the studied groups.

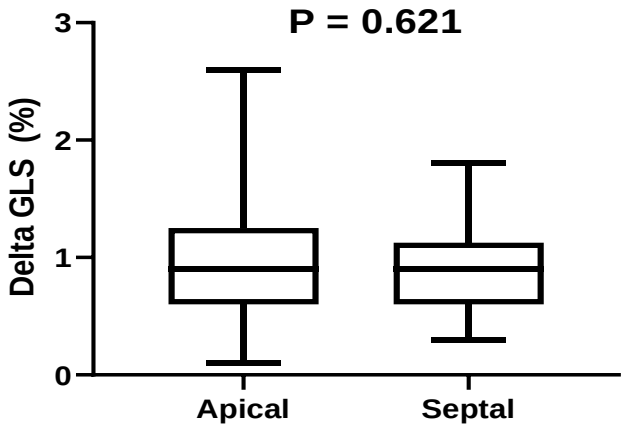

Figure (2): Delta GLS in the studied groups.

Correlation of delta GLS with delta QRS and % achieved of the 6-min walk test

In the septal group, a significant positive correlation was observed between delta GLS and % achieved of 6 min walk test (r = 0.299, P = 0.035). No other significant correlations were observed (**Table 3**).

Table (3): Correlation of delta GLS with delta QRS and % achieved of 6-min walk test

	Delta GLS (%)	
	r	**P-value**
All patients		
Delta QRS	0.02	0.841
% achieved of 6 min walk test	0.132	0.191
Apical		
Delta QRS	0.17	0.237
% achieved of 6 min walk test	-0.017	0.907
Septal		
Delta QRS	-0.151	0.295
% achieved of 6 min walk test	0.299	0.035*

* Significant; r: Correlation coefficient

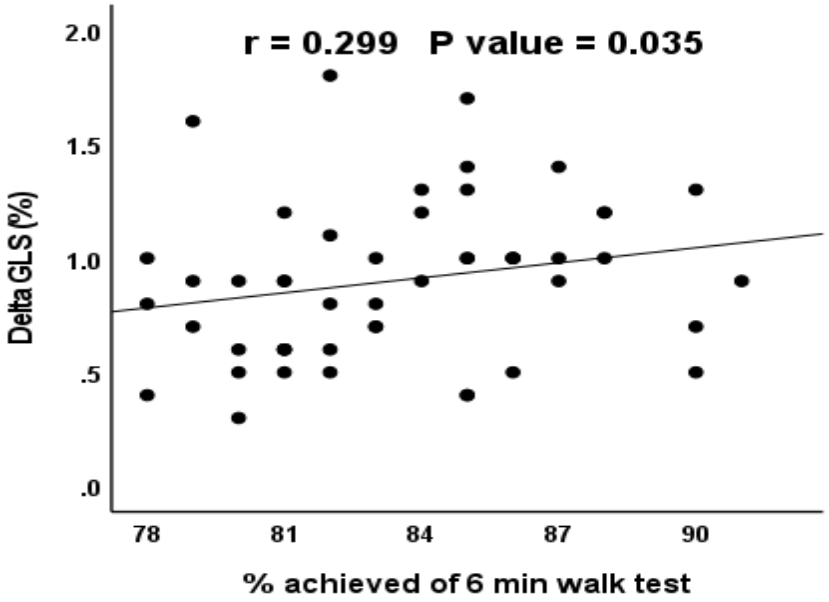

Figure (3): Correlation between delta GLS and % achieved of 6-min walk test in the septal group.

DISCUSSION

Through the treatment of ventricular dyssynchrony, which affects up to one-third of patients with severe systolic heart failure symptoms, CRT aims to provide the failing heart with a mechanical advantage that can significantly reduce symptoms and death. Although such implantation is technically successful in 90% of patients, only 2/3 of patients have clinical improvement or left ventricular reversal remodeling [20-22].

It's debatable whether or not moving the RV pacing lead will improve the CRT response. The apical position is the traditional position, especially for patients who are candidates for CRT-defibrillators (CRT-D). However, long-term RV apical pacing may negatively impact cardiac performance in intracardiac cardioverter defibrillator (ICD) patients. Recent proposals for alternative RV pacing sites in CRT patients, primarily the RV septum. Initiating the wave of depolarization in the RV septal wall, across the base of the mitral septal papillary muscle, where the initial activation vector often starts, is the physiological basis for pacing the septum rather than the apex [23,24].

We have studied 100 patients with dilated non-ischemic cardiomyopathy who were candidates for CRT device implantation. Patients were classified into two groups, the first group included 50 patients having the RV lead positioned in the RV apex and the second group included 50 patients with the RV lead positioned in the RV septum, the outcomes regarding QRS complex duration, global longitudinal strain and clinical response were compared between the two groups, 3 months post CRT implantation. Regarding clinical data; the mean percentage of 6 minutes walk test change was 84±3% of the expected, there was a highly significant improvement of NYHA functional class post CRT implantation with a P-value of 0.001, in which 55 patients were in NYHA class I and 23 patients were in NYHA class II. Also, there was a highly significant reduction in QRS width post-implantation with a P-value of 0.001, with mean QRS width of 110 ms±24 ms. Regarding Echocardiographic parameters, significant improvement of left ventricular systolic functions were noticed (mean pre-implantation EF value was 28 ± 4 % vs. 37.3 ± 5.62 in post-implantation, P- value < 0.001), highly significant reduction in LVED diameter (mean pre-implantation LVED value was 66 ± 7 mm vs. 58 ± 6.3 mm, P value < 0.001), highly significant reduction in LVES diameter (mean pre-implantation LVES diameter value was 53 ± 4mm vs. 42 ± 8.5 mm post-implantation, p-value <0.001), and a highly significant reduction in the degree of mitral regurgitation (P value <0.001). In our study 70% of the patients were echocardiographic responders, 81 % of the patients were clinically responded, and 85 % of the patients were electrocardiogram (ECG) responders. Our results elucidated that 70 patients (70%) were both echocardiographic and clinically responders while 11 patients (11%) were clinically responders without showing echocardiographic criteria of LV reverse remodeling in which their clinical improvement might be due to placebo effect.

Regarding the improvement of clinical response, the findings of our investigation corroborate those of the Multisite Stimulation in Cardiomyopathy (MUSTIC) experiment. Exercise tolerance and quality of life were compared by the MUSTIC investigators between right ventricle-only backup pacing and effective biventricular pacing for three months. The experiment revealed better peak oxygen consumption, quality of life, and 6-minute walk distance—all of which were statistically significant improvements [25].

This also goes together with the (MIRACLE) trial reported in 2000[26] where CRT was linked to a significantly increased six-minute walk distance (+39 vs. +10 m, p 0.005), increased NYHA class by at least one class (68% vs. 38%, p 0.001), improved quality of

life (-18.0 vs. -9.0 points, p 0.001), increased time spent on the treadmill during exercise testing (+81 vs. +19 seconds, p 0.001), and increased ejection fraction (+4.6% [26].

Linde *et al.* [27] found no significant improvement in quality of life or exercise capacity with CRT, but this finding is not surprising in a group of patients with minimal functional impairment at baseline. As a result, the **Linde *et al.*** [27] trial's findings did not agree with ours regarding the clinical response and quality of life improvement (NYHA I and II). The trial showed that CRT, in combination with the best medical care (including the use of a defibrillator), lowers the risk of heart failure hospitalization (hazard ratio: 0.47, p = 0.03), and enhances ventricular structure and function, LV end-systolic volume index, and ventricular function in NYHA functional class II and NYHA functional class I (American College of Cardiology/American Heart Association stage C) patients (18.4 +/- 29.5 ml [27].

Similarly, our study paid an attention to LV reverse remodeling. The results of ours demonstrated statistically significant left ventricular reverse remodeling as there was a highly significant improvement in noticed (mean pre-implantation EF value was 28 ± 4 % vs. 37.3 ± 5.62 in post-implantation, P-value < 0.001), highly significant reduction in LVED diameter (mean pre-implantation LVED value was 66 ± 7 mm vs. 58 ± 6.3 mm, P value < 0.001), highly significant reduction in LVES diameter (mean pre-implantation LVES diameter value was 53 ± 4mm vs. 42 ± 8.5 mm post-implantation, p-value <0.001), and a highly significant improvement in mitral regurgitation (P-value <0.001).

Despite everything that has been said before, two-dimensional speckle tracking echocardiography allows for a thorough examination of left ventricular mechanical characteristics, such as LV dyssynchrony, strain rate, and torsion level [19]. Compared to conventional criteria, myocardial strain enables early diagnosis of decreased exercise tolerance and a worse prognosis at an earlier disease stage. Previous studies have demonstrated that the evaluation of global systolic function by speckle tracking-based global longitudinal strain (GLS) was superior to the conventional variables such as left ventricular ejection fraction (LVEF) and wall motion score index with good consistency for the prediction of outcome in patients undergoing echocardiography [28, 29].

The GLS significantly increased post-procedure within the whole patients (11.9 ±2 vs. 11 ±2.1), the apical group (12.1 ±1.9 vs. 11.1 ±2.1), and the septal group (11.8 ±2.1 vs. 10.9 ±2.1) (P < 0.001 for each).

Comparing the two groups, there were no significant differences between them regarding % achieved of the 6-min walk test (P = 0.06), delta QRS (P = 0.429), GLS pre (P = 0.559), GLS post (P = 0.410), and delta GLS (P = 0.621). In contrast to what we discovered, Riedelbauchova *et al.* discovered that after 12 months of biventricular stimulation, a septal RV lead placement was connected to a much lower LV end-diastolic diameter and higher LVEF on echocardiography than an RV apical position. The RV apical group, on the other hand, showed no signs of reverse remodeling when the RV mid-septal group was compared to them (change in LV end-diastolic diameter = +1.7 6.4 mm) [15].

When **Bulava and Lukl** [30] evaluated 117 patients with typical criteria for CRT, they discovered that the long-term outcomes of CRT were not reliant on the position of the RV lead and that both patient groups showed equivalent and significant LV reverse remodeling after 12 months of follow-up. While the RV lead was implanted at the apex (n = 82) or in the mid-septum (n = 35), the LV lead was placed on the postero-lateral or lateral LV wall. Contrary to our techniques, however, they solely used traditional echocardiographic measurements to evaluate reverse remodeling. Patients were categorized as echocardiographic responders if their LVEF increased relative to baseline by 30% or if their absolute LVEF was 45% after receiving CRT for 12 months.

CONCLUSION

This study concluded that septal RV pacing is not superior to standard RV apical pacing in patients with non-ischemic cardiomyopathy candidate for CRT, in terms of clinical and echocardiographic response. However, owing to the correlation noticed between GLS and 6 minutes walk test in the septal group, it is advisable to adopt mid septal location of the RV pacing lead.

LIMITATIONS

This study is not a limitation-free trial, it is a single-center study with, a relatively limited population size, besides the need for a longer span of follow-up, the need for more expanded design to include all forms of cardiomyopathy and utilization of other parameters to assess CRT clinical response.

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