Left atrium in cardiac resynchronization therapy: Active participant or innocent bystander

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Background: Cardiac resynchronization therapy (CRT) is an established treatment for patients with advanced heart failure that results in improvement of left ventricle (LV) systolic function and LV reverse remodeling. This may have a positive effect on the size and the function of the left atrium (LA). We assessed the LA function, dimensions, and volumes before and after CRT implantation.

Methods: A total of 37 patients with mean age of 55.3 ± 9.64 years including 11 (29.7%) females, having symptomatic heart failure [ejection fraction (EF) <35%, left bundle branch block >120 ms, with New York Heart Association III or ambulatory class IV] were enrolled, and underwent CRT implantation. M-mode, two-dimensional (2D) echocardiography, tissue Doppler imaging, and 2D strain (e) imaging were done assessing LV volumes, ejection fraction, and diastolic function, LA diameter, area, maximal and minimal volumes, LA EF, and longitudinal strain (e). Patients were reassessed after 3 months. A reduction in LV end-systolic volume of ≥10% was defined as volumetric responders to CRT. Patients with decompensated New York Heart Association class IV, sustained atrial arrhythmias, rheumatic or congenital heart diseases, nonleft bundle branch block, and those who were poorly echogenic, were excluded.

Results: Twenty-four (64.8%) patients were volumetric responders (group A). Both groups were matched regarding demographic, clinical, electrocardiographic, and echocardiographic criteria apart from the LA dimension and volumes which were significantly lower in the responders group prior to CRT. At the end of the follow-up, only the responders group had further significant reduction in LA diameter (41.6 ± 1.67 vs. 43.88 ± 1.82 mm, p < 0.01), maximal volume (62.2 ± 18.3 vs. 73.04 ± 21.78 ml, p < 0.01), minimal volume (32.6 ± 12.3 vs. 41.8 ± 13.97, p < 0.01), together with a significant increase in LA EF (48.3 ± 11.3 vs. 41.99 ± 13.9, p < 0.01), positive longitudinal strain (16.59% ± 5.89 vs. 12.45% ± 6.12, p < 0.01), and negative longitudinal strain (−3.3 ± 1.9 vs. −1.62 ± 1.2, p < 0.01) compared to baseline readings, a finding that was not present in the nonresponders group. In addition, atrial fibrillation was significantly higher in the nonresponders group. Baseline LA diameter and volumes were found to be independent predictors of response to CRT by multivariate analysis.

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Conclusions: CRT induces LA anatomic, electrical, and structural reverse remodeling that could be assessed by conventional 2D echocardiography and 2D (e) strain imaging. LA dimension and volumes were independent predictors of response to CRT and can help in selection of candidates for it.

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Keywords: Cardiac resynchronization therapy, Left atrium, Reverse remodeling

Introduction

The left atrium (LA) is not a simple passive transport chamber. In fact, the atrial function is relatively complex. Apart from active blood pump function during atrial systole, atrial compliance is an important determinant of atrial reservoir and conduit functions [1].

As a continuum of the left ventricle (LV), especially during diastole, LA size and function are influenced by the compliance of the LV [2]. LA enlargement is a marker of both the severity and chronicity of diastolic dysfunction and magnitude of LA pressure elevation. In addition, relationships exist between increased LA size and the incidence of atrial fibrillation and stroke, risk of overall mortality after myocardial infarction, and risk of death and hospitalization in patients with dilated cardiomyopathy [3–6].

Cardiac resynchronization therapy (CRT) is now an established treatment for patients with advanced heart failure. In addition to the clinical benefits, improvement of LV systolic function and associated LV reverse remodeling had been reported [7].

With the improvement of LV function and reduction of mitral regurgitation, LA size could be reduced. Furthermore, the pressure unloading effect in the atrium may result in the improvement of atrial function [1].

Assessment of atrial regional function is now possible with the advancement of echocardiographic technology particularly strain imaging. We examined whether LA function and dimensions affect the response to CRT and if CRT improves atrial function and induces atrial reverse remodeling.

Methods

Study population

Thirty-seven consecutive patients presented to the heart failure clinic at Ain Shams University with symptomatic heart failure despite optimal medical therapy, including angiotensin converting enzyme inhibitor or angiotensin receptor blocker, β-blocker, and aldosterone antagonist [7], who were potential candidates for CRT [New York Heart Association (NYHA) functional class III or ambulatory class IV, ejection fraction ≤35%, sinus rhythm, left bundle branch block with QRS duration ≥120 ms] were enrolled in the current study. Poorly echogenic patients, and those with decompenated NYHA class IV, sustained atrial arrhythmias, rheumatic or congenital heart diseases, or nonleft bundle branch block were excluded.

Methodology

A detailed history including NYHA class, previous revascularization, medical therapy, Minnesota Living with Heart Failure Questionnaire (MLHFQ), clinical examination, 12-lead electrocardiogram, and 6-minute walk test [8] (the distance in meters an individual was able to walk on a hard, flat surface with self-pacing and rest as needed), were obtained in all patients.

MLHFQ was translated into Arabic and included 21 questions. Scoring of the questionnaire was done by summing the responses to all 21 questions where each question was scaled from 0 [no effect on quality of life (QOL)], to 5 (highest impact on QOL) where higher scores reflected poorer QOL [9].

CRT implantation

The LV pacing lead was inserted by a transvenous (subclavian) approach targeting the lateral...
or posterolateral cardiac vein, achieving a stable LV lead position in mid LV segment with suitable threshold and absence of diaphragmatic stimulation.

**Echocardiography**

Two-dimensional grayscale and tissue Doppler imaging (TDI) were performed at baseline and 3 months after CRT. Images were acquired in the standard parasternal and apical (apical 4-chamber, apical 2-chamber, and apical long-axis) views, using standard commercial ultrasound machine with a 2.5 MHz transducer. Examinations were made by the same operator to minimize interobserver variability.

**LV assessment**

LV volumes and ejection fraction were calculated using the biplane Simpson’s equation in standard apical views. LV volumes were indexed to body surface area. Patients presenting with reductions of LV end-systolic volume (ESV) of >10% at the end of the follow up period were termed volumetric responders for further statistical analysis.

Standard pulse wave Doppler was used to calculate early diastolic mitral inflow velocity (E), late diastolic mitral inflow velocity (A) velocity, and E/A ratio. Early diastolic mitral annular velocity (E') was recorded by TDI and E/E' ratio was also calculated.

Dyssynchrony index (standard deviation of all 16 segment durations from the onset of QRS to peak systolic velocity) was calculated with a cutoff value of ≥33 ms signifying mechanical dyssynchrony [10,11].

**LA assessment**

LA diameter was measured in the parasternal long-axis view. Maximal and minimal LA area and volume were measured at ventricular end-systole (just before mitral valve opening) maximum volume (Vmax), and at end-diastole (at closure of mitral valve) minimum volume (Vmin), respectively. LA volume was calculated using the biplane area–length formula (0.85 A1 × A2/L) where A1 and A2 represent the maximal planime-
tered LA area acquired from the apical four- and two-chamber views, respectively, and L is length from the middle of the plane of the mitral annulus to the superior aspect of the LA in four- and two-chamber view where the shorter length was used. LA volumes were indexed to body surface area as LA volume index.

LA emptying (ejection) fraction (EF) was calculated as the difference between LA Vmax and Vmin/Vmax.

LA two-dimensional (2D) longitudinal strain ($e$). LA endocardial border was manually traced by a point and click approach in four and two-chamber views. An epicardial surface tracing was automatically generated by the system creating a region of interest. The software divided the LA endocardium into six segments and calculated average $e$ for six LA segments for each apical view. The images taken for 2D strain were digitized and analyzed offline using EchoPAC-PC version BT12, application SW 112 (GE Healthcare, Milwaukee, WI, USA). Segmental longitudinal strain curves were generated. The dashed curve represents the average strain. Peak positive and negative atrial longitudinal strain were calculated by averaging values observed in all LA segments [12–14].

The echocardiography was done by the same operator to avoid interobserver variability, and regarding the intraobserver variability it was assessed in 12 randomly selected patients. Randomly selected images were analyzed by the same operator at different time. The operator was blind to the study results and previous measurements. The intraobserver variability was 7.1% and 8.2% for peak positive and negative strains respectively. This was calculated as standard deviation divided by the mean of the intraobserver differences.

All patients gave a written informed consent and the study was approved by the Research and Ethics Committee of the cardiology department, faculty of medicine, Ain Shams University.

### Statistics

Data were collected, coded, tabulated, and then analyzed using SPSS version 16 for Windows.

| Table 1. Baseline demographic, clinical, electrocardiographic, and echocardiographic data in both study groups. |
|---|---|---|---|
| | Responders | Nonresponders | p |
| Age | 56 ± 9.8 | 53 ± 9.5 | NS |
| Male sex | 17 (70.8%) | 9 (69.2%) | NS |
| HF etiology | | | |
| Dilated cardiomyopathy | 19 (79%) | 10 (76.9%) | NS |
| Ischemic cardiomyopathy | 5 (20.8%) | 3 (23%) | NS |
| New York Heart Association class | | | |
| III | 16 (66.6%) | 7 (53.8%) | NS |
| IV | 8 (33.3%) | 6 (46%) | NS |
| MLHFQ | 61.8 ± 12.34 | 65.63 ± 20.49 | NS |
| ACEI/ARB | 23 (95.8%) | 13 (100%) | NS |
| β-blockers | 22 (91.6%) | 12 (92.3%) | NS |
| Spironolactone/eplerenone | 23 (95.8%) | 13 (100%) | NS |
| 2D echo and TDI | | | |
| LV EDV | 255.5 ± 74.76 | 251.13 ± 66.96 | NS |
| LV ESV | 192 ± 67 | 194.13 ± 58.18 | NS |
| LV EF % | 25.44 ± 7.4 | 23.63 ± 6.48 | NS |
| E wave | 0.63 ± 0.18 | 0.69 ± 0.13 | NS |
| A wave | 0.67 ± 0.24 | 0.4 ± 0.17 | 0.01 |
| E/A | 1.14 ± 0.66 | 2.11 ± 1.07 | NS |
| E/E' | 10.59 ± 2.89 | 10.69 ± 3.33 | NS |
| TDI SD | 44.72 ± 5.98 | 43 ± 19.39 | NS |
| LA diameter | 43.88 ± 1.82 | 50.3 ± 5.8 | <0.001 |
| LA Vmax | 73.04 ± 21.78 | 104.89 ± 30.93 | <0.001 |
| LA Vmin | 41.8 ± 13.97 | 71.75 ± 28.67 | <0.001 |
| LA Vmax index | 37.1 ± 10.72 | 52.08 ± 12.36 | <0.05 |
| LAEF | 41.99 ± 13.9 | 31.3 ± 16.29 | NS |
| Global LA + ve strain | 12.45 ± 6.12 | 8.35 ± 6.87 | NS |
| Global LA – ve strain | −1.62 ± 1.2 | −1.34 ± 0.74 | NS |

QRS width in ms; LV ESV, EDV in mL, E, E', and A in m/s; LA diameter in mm, Vmax and Vmin in mL.

A = late diastolic mitral inflow velocity; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; E = early diastolic mitral inflow velocity; E' = early diastolic mitral annular velocity; EDV = end-diastolic volume; EF = ejection fraction; ESV = left ventricular end-systolic volume; LA = left atrium; LV = left ventricle; TDI = tissue Doppler imaging; Vmax = maximal volume; Vmin = minimal volume.
(SPSS Inc, Chicago, IL, USA). Data were presented as mean (standard deviation) and frequency (%) for numerical variables and categorical variables respectively. Categorical variables were compared using Chi-square test or fisher exact test according to sample size. Comparisons were performed using paired t test and Mann–Whitney test for paired data and comparing the percentage of changes. Multivariate stepwise logistic regression analysis was used to identify predictors of CRT response. Receiver operating characteristics curve analysis was done to find the impact of different echocardiographic parameters on response to CRT. Cutoff values were selected if area under the curve was significantly different from 0.5. A p value <0.05 was considered statistically significant.

Results

The current study included 37 patients [26 men and 11 (29.7%) women], with a mean age of 55.3 ± 9.6 years. All patients had successful CRT implantation via transvenous left subclavian access targeting posterolateral vein in 27 (72.9%) patients, and lateral vein in the rest of the patients. CRT implantation resulted in significant reduction in LV ESV in 24 patients who were termed responders (group A), while the remaining patients were termed nonresponders (group B) (see Fig. 1).

At baseline, the two groups were similar regarding demographic, clinical, electrocardiographic, and echocardiographic criteria (Table 1).

The LA dimensions and volumes were significantly lower in the responders group prior to CRT. At the end of the follow-up period significant differences were noted between both groups regarding NYHA class, MLHFQ, LV EF and ESV, in addition to diastolic function and TDI derived DI (Table 2).

Regarding atrial dimensions and function, group A patients showed trend towards improved LA EF, together with significant reduction in LA diameter and LA volumes in addition to significant improvement of positive and negative longitudinal strain compared to baseline parameters, a finding that was not seen in group B patients (Table 3, Fig. 2). In addition, atrial fibrillation occurred in 6 (46%) patients of group B compared to a single case (4%) in group A, p < 0.05 (see Fig. 3, Table 4).
Figure 2. Reduction in left atrium diameter after cardiac resynchronization therapy in the same patient (right panel) compared to baseline (left panel).

Figure 3. Reduction of left atrium area in apical four-chamber view.
Positive correlation was found between A wave amplitude and LA ejection fraction before CRT and the percent of change in LV ESV after CRT, while a negative correlation was observed between, E/A ratio, LA diameter, LA Vmax, LA Vmin, and LA Vmax index before CRT, and the percent of change in LV ESV after CRT (Fig. 4).

By multivariate analysis, the following parameters: A wave, E/A, LA diameter, LA Vmax, LA Vmin, LA Vmax index, and LA EF before CRT were found to be independent predictors of response to CRT with calculated cutoff values of ≤47 mm for LA diameter, and ≤90.7 mL for LA Vmax with 100% and 93% sensitivity respectively (Table 5, Fig. 4).

**Discussion**

Atrial function is an integral part of cardiac pump function. At least one third of LV filling is dependent on active atrial pump function, espe-
cially in the elderly and in patients with chronic heart failure. In addition, atrial compliance (diastolic function) is important for atrial reservoir and conduit functions. Various studies have reported improvement of LV systolic function and associated LV reverse remodeling in CRT responders, in addition to the proven clinical value. However, few data are available regarding effect of CRT on LA structure and function. In the current study, we examined the effect of CRT on electrical (arrhythmias), structural (reverse remodeling), and functional (LA EF and longitudinal strain) aspects of the LA (see Fig. 5).

Nearly two thirds of the current study population were responders and had significantly higher EF, lower ESV, and better diastolic function and Doppler imaging, in addition to marked clinical improvement in terms of significantly better NYHA class and MLHFQ compared to the nonresponders group. It is worth noting here that this effect of reverse remodeling was pronounced despite the relative short duration of follow-up (3 months). Significant changes in LV volumes have been reported as early as 1 month and continue at slower rates till at least 6 months after CRT [15].

Table 5. Independent predictors of response to cardiac resynchronization therapy after 3 months.

| Variable                        | Odds ratio | 95% CI     | COV | Sensitivity | Specificity | p    |
|---------------------------------|------------|------------|-----|-------------|-------------|------|
| A wave                          | 0.077      | 1.05–1.37  | ≥0.465 | 87.5        | 75          | 0.0133|
| E/A                             | 0.2320     | 0.0670–0.8032 | ≤1.39 | 75          | 87.5        | 0.0211|
| LA diameter before              | 0.4605     | 0.2522–0.8410 | ≤47.5 | 100         | 75          | 0.0116|
| LA Vmax before                  | 0.9378     | 0.8923–0.9856 | ≤90.7 | 93.8        | 75          | 0.0113|
| LA Vmax index before            | 0.8979     | 0.8253–0.9768 | ≤44.6 | 81.3        | 75          | 0.0122|
| LA Vmin before                  | 0.9149     | 0.8571–0.9765 | ≤55.8 | 81          | 75          | 0.0075|
| LA EF before                    | 1.0757     | 1.0040–1.1526 | ≥36.2 | 62          | 87          | 0.0381|

A = late diastolic mitral inflow velocity; CI = confidence interval; COV = coefficient of variance; E = early diastolic mitral inflow velocity; EF = ejection fraction; LA = left atrium; Vmax = maximal volume; Vmin = minimal volume.

Figure 5. Receiver operating characteristics (ROC) curves showing sensitivity and specificity left atrium maximal volume (left panel), left atrium diameter (right panel) in predicting cardiac resynchronization therapy response.
**LA electrical function**

In the current study, atrial arrhythmias, namely atrial fibrillation, were significantly less frequent in the responders group (4% vs. 46%). In our opinion, this may point to the electrical remodeling effect of CRT, which is mainly mediated by reduction in LA volumes. This finding was highlighted by MADIT-CRT reporters who stated that only high LA volume responders >20% experienced a significant reduction in the risk of subsequent atrial tachycardia, an effect that was not seen in low LA volume responders and patients in the defibrillator-only arm [16].

**LA function (diastolic, EF)**

In CRT responders (group A), we observed significant improvement of the peak LA global positive strain as an estimate of LA compliance, LA peak global negative strain as an estimate of LA systolic function, in addition to trends towards improved LA EF compared to baseline measurements. Similar findings of improved strain and LA EF have been reported [17,18].

By multivariate analysis, LA EF before CRT (a parameter driven from volumes) was found to be an independent predictor of CRT response after 3 months (odds ratio 1.0757, 95% confidence interval, 1.0040–1.1526, p = 0.0381). LA systolic peak of strain rate has been reported recently as a novel independent predictor of CRT response (odds ratio 10.5, 95% confidence interval, 1.76–62.1, p = 0.01) [19].

**LA reverse (structural, anatomical) remodeling**

In the current study, CRT resulted in significant reduction in LA diameter, LA Vmax and Vmin. In fact, this favorable effect of reverse LA remodeling was limited to the cardiac responders group (i.e., those with significant LV reverse remodeling). This early significant reduction in atrial volumes at 3 months was also reported by Saxon et al. [20] to occur simultaneously with LV reverse remodeling, even more early favorable changes in LA volumes were reported only 1 month after CRT implantation and keep going on till at least 6 months after implantation [15]. This finding can be simply explained by the improvement in LV systolic and diastolic functions, and filling pressures and consequently resulting in decrease in LA pressures.

In addition, we observed that LA reverse remodeling was typically seen in patients with relatively smaller LA diameter and volumes before CRT; in other words, severe LA dilatation compromises LA reverse remodeling. Mean LA diameter, Vmax, Vmin, and LA Vmax index before CRT were significantly lower in cardiac responders group. By multivariate analysis, the previously mentioned parameters were found to be independent predictors of CRT response after 3 months (Table 5).

Small LA diameter before CRT has been reported by Stefan et al. [21] as an independent predictor of super-responders to CRT in a multivariate analysis comparing baseline echocardiographic parameters before CRT in >300 patients including super-responders and two other control groups, super-responders had significantly smaller LA (42.8 ± 4.6 mm vs. 50.0 ± 6.5 mm, p < 0.001). In the current study, LA diameter cut-off value <47.5 mm was an independent predictor of cardiac CRT response (100% sensitivity, 75% specificity).

By contrast, decrease in LA maximal volume has been reported to have favorable prognostic effect in patients with dilated cardiomyopathy. To our knowledge, the current study is the first to report LA Vmax and Vmin before CRT as independent predictors of cardiac CRT response. LA Vmax cut-off value <90.7 mL, and LA Vmin <55.8 mL had 93.8% and 81.3% sensitivity, and 75% specificity respectively.

There is no doubt that the improved positive longitudinal strain is attributed to improved LV longitudinal movement which increases atrial stretch, which is definitely passive. However, we also observed significant improvement of peak negative strain, which reflects the actual contractile function of the LA rather than passive stretch by the ventricle. This improvement in LA systolic function could be partly attributed to the improvement of LV systolic function, filling pressures, mitral regurgitation, and reverse atrial remodeling. However, since the improvement in atrial strain is noted throughout the cardiac cycle (from early systole to late diastole), we propose that it may possibly reflect structural changes in the atrium leading to better atrial function. The same concept was mentioned by Yu et al. [23] who stated that LA strain is dependent on the ultrastructural components of the atrium, such as the extent of atrial myocyte hypertrophy and amount of interstitial fibrosis.

This study addresses the usual dilemma, is it the egg or the hen? Do CRT-favorable LV effects exert beneficial effect on LA, or is it much more complex: do better LA function and dimensions prior to CRT predict both LA and LV reverse remodeling? In view of our results, we can confidently say that the more the LA dimensions and
impaired function are before CRT, the less liability for LA remodeling and the less chances for being LV responders. This may be explained by the marked LA dilation and impaired function being usually due to advanced impairment of LV diastolic and systolic function, which may not respond properly to CRT.

In our opinion even if the improvement in LA parameters is exclusively due to better LV performance, the LA parameters before CRT could serve at least as a tool for proper selection of CRT candidates at an early stage of the disease before advanced LA and LV remodeling, and hence could improve the response to CRT in these patients, keeping in mind that a considerable body of data exists to support the incorporation of LA size in risk stratification schemes in patients with dilated cardiomyopathy, and that LA maximum volume, LA dimensions, and LA area were found by various reporters as predictors of mortality, hospitalization, and heart transplantation independent of LV EF, NYHA class, and atrial fibrillation [22,24,25].

Study limitations

This study is based on a single-center experience, with a small number of patients and the results should be verified by a large-scale study. Technically, there was extreme difficulty of accurately obtaining the region of interest in some patients due to markedly dilated hearts.

Conclusion

Based on the study results, we can conclude that cardiac CRT responders show remarkable LA anatomic, electrical, and structural reverse remodeling that could be assessed by conventional 2D echocardiography and 2D (e) strain imaging. LA dimension and volumes before CRT were independent predictors of response to CRT and can help in identification and selection of CRT candidates.

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