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Interplay Between RV Function and CRT, Which One Affects the Other?

Hesham Boushra Mahmoud, Yasser Ahmed Abdelhady, Ahmed Mohammed Eldamaty, Mohammed Shafiq Awad, Ahmed Shaaban Ali

Cardiovascular medicine department,Beni-suef university,Egypt

Corresponding Author: Ahmed Shaaban Ali
emara782@yahoo.com

ABSTRACT

Background: Cardiac resynchronization therapy (CRT) is an established treatment of heart failure with reduced EF (HFrEF) and wide QRS complex. Nearly 30% of candidates are non-responders. One of the suggested mechanisms of inadequate response is the reduced baseline RV function; also the effect of CRT on right ventricular systolic function has not been well studied. We examined the effect of CRT on right ventricular (RV) dimensions and overall systolic function and whether RV function prior to CRT could have an impact on CRT response. **Methods:** 30 patients with a mean age of 51.9 ± 9.2 years including 9 (30%) females, with advanced HF (EF < 35%, LBBB > 120 ms, or non-LBBB > 150 ms, with NYHA class III or ambulatory class IV) were enrolled and underwent CRT implantation. Standard two dimensional (2D) echocardiography, tissue Doppler imaging, for assessment of Left ventricular (LV) end-diastolic (LVEDV), and end-systolic volumes (LVESV), ejection fraction, RV maximum basal (RVD1 basal), maximum mid (RVD2 mid) transverse, maximum longitudinal (RVD3 long) diameters, TAPSE, fractional area change (FAC), right ventricle index of myocardial performance(RIMP) and tricuspid lateral annular systolic velocity (S'), were done before CRT implantation and at the end of the follow up period (6 months). Patients presenting with reduction of LVESV of >15% were considered responders. **Results:** 20 (67%) cases were responders. Both groups were similar regarding demographic, clinical, ECG, and echocardiographic criteria at baseline however, the RA volume and RV transverse diameters were smaller and systolic function parameters were significantly better in the responders group prior to CRT compared to non-responders (NR) group. At the end of the follow up, only the responders group had further significant reduction in RV basal, mid and longitudinal diameters together with significant improvement in RV systolic function, in contrast to non-responders group who showed more RV dilatation and more decline of RV systolic function, compared to baseline readings(with P value <0.0001 for all parameters), Correlation between RV parameters before CRT implantation and CRT response was performed and ROC curves were plotted to define cutoff values for each parameter with FAC of >40 % has 85% sensitivity and 90 % specificity (P value= 0.004). TAPSE of >20 mm has 85% sensitivity and 80 % specificity (P value=0.002), S' of >10 cm/s % has 85% sensitivity and 70 % specificity (P value=0.001) and RIMP of <0.52 has 85% sensitivity and 70 % specificity (P value=0.003) in predicting CRT response. **Conclusions:** CRT induces RV reverse remodeling and improves RV systolic function particularly in cardiac volumetric responders. RV systolic dysfunction before CRT implantation could identify patients that might not benefit from CRT thus helping proper patient selection and optimizing CRT response.

Keywords: CRT, right ventricle,echocardiography, heart failure

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1. INTRODUCTION

Heart failure (HF) is a global public health problem affecting millions worldwide. Approximately 1–2% of the adult population in developed countries has HF, with the prevalence rising to ≥10% among persons 70 years of age or older(1).

Heart failure pharmacotherapy including beta-blockers (BB), angiotensin converting enzyme inhibitors/Angiotensin II Receptor Blockers (ACEI/ARB), and aldosterone antagonists have resulted in dramatic improvements in the morbidity and mortality of patients with heart failure (HF) with a reduced ejection fraction. However, in many patients, medical management alone is insufficient to achieve adequate symptom control and HF associated morbidity and mortality remains high. In a subgroup of these patients with prolonged QRS duration, particularly with left bundle branch block (LBBB) morphology, cardiac resynchronization therapy (CRT) has demonstrated additional benefit(1).

Over the last two decades CRT has become a key component of the staged treatment of drug-refractory heart failure and left ventricular (LV) mechanical dyssynchrony(1). Approximately 30% of CRT candidates are inadequate responders(2). Thus, the mechanisms for such a high proportion of non-responders are being actively investigated.

It is well established that CRT reverses left ventricular (LV) remodeling, reduces pathological neurohormonal activation and improves functional status. However, the effect of CRT on right ventricular systolic function has not been well studied, owing to difficulty in measuring this parameter. Furthermore, there has been some debate whether patients with right-sided heart failure benefit from CRT, but this has not been adequately addressed(2).

The right ventricle (RV) plays an important role in the morbidity and mortality of patients presenting with signs and symptoms of heart failure and pulmonary diseases. However, the systematic assessment of right heart function has not been routinely carried out prior to CRT. This is due partly to more attention given to the evaluation of the left heart, a lack of familiarity with ultrasound techniques that can be used in imaging the right heart due to its crescent shape and complex geometry(3).

2. METHODS

Study population

30 consecutive patients representing a sample from the pool of patients presenting to the outpatient HF clinic at our hospital, during the period from May 2015 to October 2016, and meeting inclusion criteria (symptomatic heart failure despite optimal medical therapy, NYHA class III or ambulatory class IV, ejection fraction ≤ 35%, sinus rhythm, LBBB(left bundle branch block) with QRS ≥ 120 ms, or non LBBB with QRS ≥ 150 ms) were enrolled in the current study. Patients with decompensated NYHA class IV, rheumatic or congenital heart diseases, and sustained atrial arrhythmias, were excluded.

Methodology

Detailed history (symptoms duration and analysis, NYHA class, hospital admissions, previous revascularization, latest medical therapy, Minnesota living with heart failure questionnaire: (MLHFQ), clinical examination, 12 lead ECG (QRS morphology and duration), Were done in all cases. MLHFQ was translated into Arabic and included 21 questions. Scoring of the questionnaire was done by summating 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(6).

Echocardiography

Baseline echocardiographic examination was performed using a standard commercial ultrasound machine with a 2.5 MHz transducer and repeated after 6 months. Examinations were made by the same operator to minimize inter-observer variability.

LV assessment

Standard M-mode, 2D echocardiographic views, and Doppler examination were used to assess LV end-diastolic diameter (EDD), end-systolic diameter (ESD), 2D ejection fraction (EF) by modified biplane Simpson’s method, end-diastolic volume (LVEDV), end-systolic volume (LVESV), mitral E and A velocities (diastolic function). Patients presenting with reductions of LVESV >15% at the end of the follow up period were termed responders for further statistical analysis.

Right side assessment

RA volume was measured using single plane area length method, maximum basal transverse diameter, maximum mid-level transverse diameter (2 cm from

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the tricuspid valve), and maximum longitudinal dimension were measured at the end-diastole in RV focused apical 4 chamber view. Values >42, 35, 83 mm respectively indicated RV dilatation$^{(4)}$. In apical 4 chamber view, RV systolic function was assessed by measuring the distance of systolic excursion of the RV annular segment along its longitudinal plane (TAPSE) and RV fractional area change (FAC) which is calculated as (end-diastolic area – end-systolic area)/end-diastolic area X 100). TAPSE < 17 mm and FAC < 35% indicated RV dysfunction. In addition, tricuspid lateral annular systolic velocity (S') and Right ventricle Index of Myocardial Performance (RIMP) which is calculated as (isovolumic relaxation time + isovolumic contraction time)/ejection time. were obtained by Doppler tissue imaging where measurements of S'< 9.5 cm/s and RIMP> 0.54 indicated RV dysfunction. Finally, RV systolic pressure (RVSP) was calculated using the simplified Bernoulli equation$^{(4)}$.

CRT implantation

All implantations were done via percutaneous transvenous (subclavian vein) approach. The RV lead tip was placed in the apex of the right ventricle. The LV lead was placed in the posterolateral cardiac vein in most patients and in posterior or lateral veins in others. The location chosen for LV lead was that giving the highest stability, greatest spatial separation from the tip of the RV lead, suitable LV capture threshold and without diaphragmatic stimulation. The RA lead was placed in RA appendage. All patients gave a written informed consent and the study was approved by the Research and Ethics Committee of our faculty.

Data analysis

Data were collected, coded, tabulated, and then analyzed using SPSS software IBM- for MAC, version 24 (SPSS Inc, Chicago, IL, USA). Data were presented as mean (standard deviation) and frequency (%) for numerical variables and categorical variables respectively. Comparisons were performed using Paired T test and Mann-Whitney test for paired data and comparing the percentage of changes. Categorical variables were compared using Chi square test. Receiver operating characteristics (ROC) 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 (AUC) was significantly different from 0.5. A P value <0.05 was considered statistically significant.

3. **RESULTS**

The current study included 30 cases: 21 males, 9 females (30%) with a mean age of 51.9 ± 9.2 years. All patients had successful CRT implantation via transvenous left subclavian access. CRT resulted in significant improvement in NYHA class, MLHHQ, LVEDV,LVESV and EF, together with significant reduction in RA volume, RV basal and mid transverse diameters and significant improvement in TAPSE and S', compared to baseline (Table 1).

Table 1: Clinical and echocardiographic parameters in the whole study group before and after CRT

Parameter	Before CRT	6 months Post CRT	P value
NYHA	3.3±0.4	2.1±0.8	< 0.0001
MHFQ	84±8.3	47.4±14.4	< 0.0001
LVEDV(ml)	315.8±82.3	244.2±90.4	< 0.0001
LVESV(ml)	230.5±69.7	160.4±80.5	< 0.0001
EF	27.0±4.1	36.7±10.1	< 0.0001
RA volume(ml)	30.2±6.7	27.6±9.2	0.018
RVD1 basal(mm)	41.3±7.6	38.2±11.1	0.018
RVD2 mid(mm)	32.9±6.6	29.2±9.2	0.035
RV D3 long. (mm)	68.8±10.8	68.9±11.2	NS
FAC (%)	40.5±9.7	41.1±10.6	NS
TAPSE(mm)	19.9±5.9	22.4±7.4	0.002
S'(cm/s)	12.0±3.5	12.9±4.1	0.011
RIMP	0.47±0.11	0.46±0.12	NS

At the end of the follow up period, 20 (67%) cases of the study population were termed responders according to pre-specified criteria, while the remaining 10 cases were termed non-responders. Both groups were matching regarding demographic, clinical, ECG, and echocardiographic criteria apart from significantly smaller RV transverse diameters and significantly better RV systolic function parameters in the responders group prior to CRT (Table 2).

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Table 2: Clinical and echocardiographic parameters in responders and non-responders prior to CRT

Parameter	Responders	Non-responders	P value
Age(years)	53.7±8.4	48.5±10.1	**NS**
NYHA	3.25±0.44	3.5±0.52	**NS**
MHFQ	84.2±7.8	83.9±9.6	**NS**
QRS duration(ms)	151.9±8.1	141±11	**NS**
LVEDV(ml)	306.3±88.2	334.9±69.4	**NS**
LVESV(ml)	222.7±75.6	246.1±56.3	**NS**
EF	27.7±3.9	25.6±3.8	**NS**
RA volume(ml)	27.9±5.6	34.9 ± 6.6	**0.007**
RVD1 basal(mm)	37.9±4.3	48.0±8.5	**0.002**
RVD2 mid(mm)	29.5±4.5	37.0±7.3	**0.008**
RV D3 long. (mm)	64.5±8.5	77.3±10.2	**0.002**
FAC (%)	44.0 ±7	33.5±10.1	**0.003**
TAPSE(mm)	22.2±4.9	15.1±4.9	**0.001**
S'(cm/s)	13.5±3.2	9.1±2.0	**< 0.0001**
RIMP	**0.43±0.09**	**0.56±0.12**	**0.002**

At the end of the follow up period, significant differences were noted between both groups regarding NYHA class, MLHFQ, LVEF, LVEDV and LVESV (Table 3). In addition, only the responders group showed further significant decrease in RA volume and RV diameters and further improvement of RV systolic function compared to baseline data, in contrast to non-responders group who showed more RV dilatation and more decline of RV systolic function (Table 4).

Table 3: Clinical and LV echocardiographic parameters in both groups after CRT

Parameter	Responders	Non-responders	P value
NYHA	1.75±0.63	3.0±0.66	**<0.0001**
MHFQ	41.5±10.8	59.4±13.6	**0.006**
LVEDV(ml)	195.3±54.9	342.4±62.9	**<0.0001**
LVESV(ml)	113.2±39.4	255.0±52.1	**<0.0001**
EF	**42.7±6.0**	**24.7±3.2**	**<0.0001**

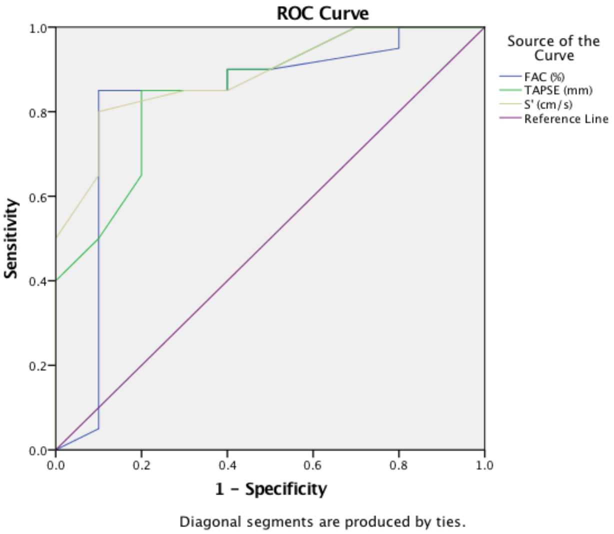
Table 4: The difference in right side echocardiographic parameters before and after CRT in responders and non-responders.

Parameter	Responders	Non-responders	P value
Δ RA volume(ml)	-5.8 ± 3.1	3.8 ± 1.1	**<0.0001**
Δ RVD1 basal(mm)	-6.1 ± 5.9	3.2 ± 2.4	**<0.0001**
Δ RVD2 mid(mm)	-5.7 ± 6.3	2.9 ± 2.6	**<0.0001**
Δ RVD3 long. (mm)	-1.8 ± 3.8	3.9 ± 3.0	**<0.0001**
Δ FAC (%)	3.3 ± 5.8	-4.6 ± 3.2	**<0.0001**
Δ TAPSE(mm)	4.4 ± 3.4	-1.1 ± 2.1	**<0.0001**
Δ S'(cm/s)	1.7 ± 1.0	-0.9 ± 0.7	**<0.0001**
Δ RIMP	**-0.04 ± 0.07**	**0.03 ± 0.01**	**<0.0001**

Correlation between RV parameters before CRT implantation and CRT response was performed and ROC curves were plotted to define cutoff values for each parameter (Table 5, Fig. 1).

Table 5: Cut-off values of RV systolic parameters as predictors of CRT response

	Cut-off	AUC	Sensitivity	specificity
FAC	>40 %	0.83	85%	**90%**
TAPSE	>20 mm	0.85	85%	**80%**
S'	>10 cm/s	0.88	85%	**70%**
RIMP	**<0.52**	**0.84**	**85%**	**70%**



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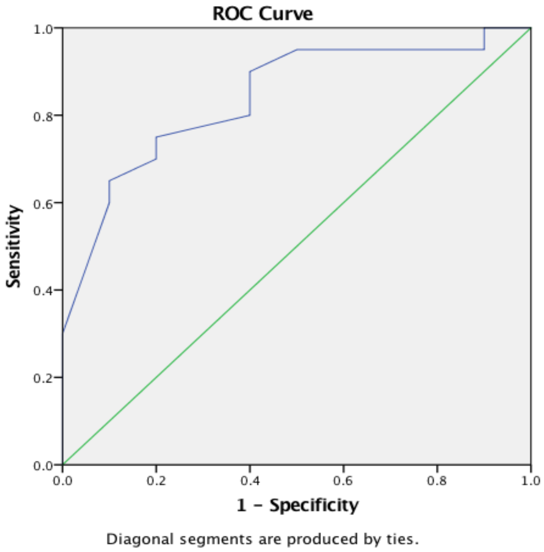

Fig. 1. Receiver of operating characteristics (ROC) curve for pre CRT FAC, TAPSE and S' (upper panel), and RIMP (lower panel) and relation to CRT response

4. DISCUSSION

In the current study, using American society of echocardiography (ASE) and European association of cardiovascular imaging (EACVI) recommendations for chamber quantifications methods and cutoff values(3) we examined the effect of CRT on RV dimensions and overall systolic function and whether RV function prior to CRT could have an impact on CRT response and hence influence patient selection for this kind of treatment.

Our study enrolled 21 males and 9 females with a mean age of 51.9±9.2 years. all females were responders which is consistent with Arshad A et al. (data from MADIT CRT trial) and Yin et al. meta-analysis who stated that , Women seem to obtain greater benefits from CRT both in clinical and echocardiographic outcomes compared with men(8,9).

In our study there was no significant difference between responders and non-responders as regard QRS duration which correlates with M.J.H. Khidir et al. large study which concluded that, QRS morphology but not duration was independently associated with long-term survival(10). On the other hand Steffel J et al. (Echo-CRT trial) concluded that no benefit of CRT was evident in patients with QRS duration of 120-130 ms(11).

The effect of HF symptoms on daily activities in our study was assessed by MLHFQ which improved significantly after 6 months follow up. These results are consistent with S. Chen et al. meta-analysis which concluded that CRT was associated with a substantial improvement in quality of life parameters measured by MLHFQ(12).

RV Reverse Remodeling

Regarding RV diameters, the basal RV, mid RV transverse diameters showed a significant decrease after CRT. The change in RV longitudinal diameter was statistically non-significant, as regard RV systolic function TAPSE improved significantly after also. RV systolic function assessed by tissue Doppler imaging S' also showed a significant improvement after CRT, FAC increased from but this increase was statistically non-significant. The improvement in RIMP before and after CRT was also statistically non-significant.

These results match with many studies among which Sharma et al. meta-analysis for 13 studies assessed RV dimensions and function concluded that CRT improves right ventricular long axis and short axis diameters and RV size also,CRT led to improvements in RV function as measured by TAPSE, RV FAC and RV basal strain(13).

There was a significant right side reverse remodeling in the responders group at follow up with the difference in changes in right side dimensions between both responders and non-responders groups was highly significant with P value < 0.0001 for RA volume, RVD1 basal,RVD2 mid,RV D3 longitudinal .In addition There was also a significant improvement in RV systolic function in the responders group at follow up with the difference in changes in right side systolic function parameters between both responders and non-responders groups was highly significant with P value < 0.0001 for FAC ,TAPSE,S' and RIMP .

These results match D'Andrea et al who studied RA dimensions and function indices and mentioned that right atrial volume index increased and RA myocardial deformation was impaired in patients with DCM who were non-responders to CRT.(14), Also Sharma et al. and Aksoy et al. concluded that RV diameters and systolic indices after CRT improved only in the responders group. Improvement in RV systolic performance after CRT is correlated with the reduction of LVESV(13,15).

An important issue of our study was the importance of echocardiographic evaluation of right ventricular function before CRT implantation as a predictor of response. Regarding right sided parameters; baseline RA volume was smaller in responders (P= 0.007) also, baseline longitudinal and basal and mid transverse

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diameters were smaller in responders (P= 0.002, 0.008 and 0.0002 respectively).

Baseline FAC, TAPSE, S', and MPI were better in responders (P= 0.003, 0.001, <0.0001, and 0.002 respectively). In predicting response to CRT from baseline RV parameters, ROC curve analysis showed that FAC of >40 % has 85% sensitivity and 90 % specificity (AUC= 0.83, P value= 0.004). TAPSE of >20 mm has 85% sensitivity and 80 % specificity (AUC= 0.85, P value=0.002) Also S' of >10 cm/s % has 85% sensitivity and 70 % specificity (AUC= 0.88, P value=0.001) and finally RIMP<0.52 has 85% sensitivity and 70 % specificity to CRT response (AUC= 0.84,P value=0.003) in predicting CRT response.

These results match Damy et al.CARE-HF (Cardiac Resynchronization-Heart Failure) trial which found that,Right ventricular dysfunction is a powerful determinant of prognosis among candidates for CRT, and also concluded that patients with lower TAPSE at baseline had a higher mortality, regardless of assigned treatment (P = 0.001).16 it also matches Cappelli et al. who had shown relatively similar results their study. They found after a follow up of 6 months that TAPSE, at 17 mm is an optimal cut-off, yielded 64% sensitivity and 60% specificity in predicting CRT response(17).

Also Schmeisser et al. used baseline RV-PA coupling (RV function related to pulmonary vascular afterload) and PA compliance and found it an independent predictors of left ventricular reverse remodeling after CRT(18). Also Scuteri et al. used the same method, the same follow-up period and the same end-point and found that baseline RV function and dimensions were significantly more impaired in non-responders than responders to CRT: (TAPSE 15 ± 4 mm vs. 20 ± 5 mm, P = 0.001), and RV fractional area change (30 ± 12% vs. 48 ± 8%, P < 0.001).Also defined Severe RV dysfunction as TAPSE ≤14 mm and the population was stratified into two groups based on baseline TAPSE ≤ or > 14 mm. As compared to those with high TAPSE (n = 30), patients with low TAPSE (n = 14) were less likely to show LV reverse remodeling after CRT (76% vs. 14%, P < 0.001)(19). And finally concluded that RV function significantly affects response to CRT. Poor LV reverse remodeling occurs after CRT in patients with HF having severe RV dysfunction at baseline(19). Field et al. assessed effect of baseline RIMP on adverse outcome in patients undergoing CRT. This study showed that RV dysfunction measured by the Doppler-derived RIMP was a predictor of the composite end-point of all-cause mortality, transplantation and the implantation of left ventricular assist devices(20).

Some studies assessed RV function by methods not used in our study like Alpendurada et al. who used RVEF assessment by cardiovascular magnetic resonance to predict response to and major adverse clinical events in HF patients undergoing CRT and found that Right ventricular function is an important predictor of both response to CRT and long-term clinical outcome. Patients with marked RV dysfunction (RVEF < 30%) had a particularly low response rate (18.2%) to CRT(21).

Also Burri et al.study using the RV radionuclide aniography evaluated response to CRT according to a reduced baseline RVEF of ≤ 35% and found that patients with a reduced baseline RVEF were less likely to improve in NYHA class (P = 0.016), and also tended to improve less in 6MWD and LVEF (P = 0.06) when compared with patients with preserved RVEF(22).

Limitations This study is a single center study with relatively small number of patients; also the echocardiography study was non-blinded.

5. CONCLUSIONS

In conclusion we believe that the RV is an active participant in CRT patients rather than a passive chamber as it not only benefits from CRT improvement of LV volumes or systolic function, but also is a major predictor of LV response to CRT and even long-term outcome in responders and that the need for routine evaluation of right ventricular volume and function especially by echocardiography before CRT implantation should be fully investigated to optimize CRT response.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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