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Original Article

Assessment of right ventriclular systolic function prior to cardiac resynchronization therapy: Does it make any difference?

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) is an effective treatment for patients with advanced heart failure (HF). Nearly 30% of candidates are inadequate responders. The benefit of patients with right sided heart failure from CRT is still a matter of debate. 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: 94 patients with a mean age of 53.7 ± 14.6 years including 19 (20%) females, with advanced HF ($EF < 35\%$, $LBBB > 120$ ms, or non-$LBBB > 150$ ms, with NYHA –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 (RVD basal), maximum mid (RVD mid) transverse, maximum longitudinal (RVD long) diameters, TAPSE, fractional area change (FAC), and tricuspid lateral annular systolic velocity (S'), in addition to RV global longitudinal strain (RVGLS) measured by speckle tracking echocardiography, were done before CRT implantation and at the end of the follow up period (5.9 ± 1.2 months). Patients presenting with reductions of LVESV of >15% were termed volumetric responders for further statistical analysis.

Results: 63 (67%) cases were volumetric responders. Both groups were matched regarding demographic, clinical, ECG, and echocardiographic criteria apart from the RV significantly smaller transverse diameters and significantly better systolic function parameters 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 (33.6 ± 7.1 vs 40.7 ± 8.6, 21.4 ± 4.9 vs 27 ± 6.1, 68.3 ± 10.8 vs 81.2 ± 15, respectively), $p < 0.01$, together with significant improvement in RV systolic performance: FAC (47.7 ± 7.3 vs 40.9 ± 6.4), TAPSE (25.2 ± 4.6 vs 22.1 ± 4.9), S' (15.3 ± 2.3 vs 12.8 ± 2.3), and GLS (26.1 ± 2.1 vs 18.5 ± 1.6), $P < 0.01$, compared to baseline readings. S' and GLS were the only independent predictors of CRT response by multivariate analysis. $S' > 9$ cm/s, and GLS >12.45% had 100% sensitivity and 70%, 99.7% specificity, respectively for prediction of response to CRT.

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.

1. Introduction

Heart failure (HF) prevalence is rising throughout the world. 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]

Cardiac resynchronization therapy (CRT) is an established treatment of drug-refractory heart failure and left ventricular (LV) mechanical dys-synchrony. In addition to the clinical benefits, improvement of LV systolic function and associated LV reverse remodeling had been reported, however nearly 30% of potential CRT candidates are inadequate responders.[2,3]

The right ventricle (RV) plays an important role in the morbidity and mortality of patients presenting with signs and symptoms of heart failure. The benefit of patients with right sided heart failure from CRT is a matter of debate. However, the systematic assessment of right heart function prior to CRT is not uniformly carried out, partly due to the attention given to the evaluation of the left heart, non-familiar ultrasound techniques used in imaging

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the right heart, and rarity of ultrasound studies providing reference values of right heart size and function.[3,4] RV global longitudinal strain (RVGLS) measured by 2D speckle tracking echocardiography being less angle and load dependent than traditional RV function indices, could offer additional value for RV function assessment.[4]

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.

2. Methods

2.1. Study population

94 consecutive patients representing a convenient sample from the pool of patients presenting to the heart failure clinic at Ain Shams University hospitals, during the period from march 2015 to march 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 with QRS ≥ 120 ms, or non LBBB with QRS ≥ 150 ms) were enrolled in the current study. Poorly echogenic patients, and those with decompensated NYHA class IV, rheumatic or congenital heart diseases, and sustained atrial arrhythmias, were excluded.

2.2. Methodology

Detailed history (illness duration, 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), and six minute walk test[5] (the distance in meters an individual was able to walk on a hard, flat surface with self-pacing and rest as needed), 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]

2.3. 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.

2.4. 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 Simpson's method, end-diastolic volume (EDV), end-systolic volume (ESV), mitral E and A velocities (diastolic function).

Patients presenting with reductions of LVESV >15% at the end of the follow up period were termed volumetric responders for further statistical analysis.

2.5. RV assessment

Maximum transverse diameter at the RV base and mid-level (2 cm below the tricuspid valve), and maximum longitudinal dimension were measured at the end-diastole in RV focused apical 4 chamber view. Values >42, 35, 86 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 <16 mm and FAC <35% indicated RV dysfunction. In addition, tricuspid lateral annular systolic velocity (S′), was obtained by tissue Doppler imaging where measurements <10 cm/s indicated RV dysfunction. Finally, RV systolic pressure (RVSP) was calculated using the simplified Bernoulli equation.[4]

RV 2D global longitudinal strain (RVGLS): RV endocardial border was manually traced by a point and click approach in 4 chamber view. An epicardial surface tracing was automatically generated by the system creating a region of interest. The software divided the RV endocardium into 7 segments (basal RV free wall, mid RV free wall, apical RV free wall, apex, apical septum, mid septum, and basal septum) and calculated average for 7 RV segments. The images taken for 2D strain were digitized and analyzed offline using EchoPAC-PC version BT12, application SW 112 (GE Healthcare, Milwaukee, WI).

2.6. CRT implantation

All implantations were done via percutaneous transvenous (subclavian) approach. The LV pacing lead was inserted targeting the lateral or postero-lateral cardiac vein, achieving a stable LV lead position in mid LV segment with suitable threshold and absence of diaphragmatic stimulation.

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.

2.7. Statistics

Data were collected, coded, tabulated, and then analyzed using SPSS version 19 for Windows (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. Multivariate stepwise logistic regression analysis was used to identify predictors of CRT response (reverse remodeling). 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 94 cases: 75 males, 19 females (20%) with a mean age of 53.7 ± 14.6 years. All patients had successful CRT implantation via transvenous left subclavian access targeting postero-lateral vein in 66 (70.2%) cases, lateral vein in 18 (19%) cases, and posterior vein in the remaining 10 cases. The RV lead tip was placed in the apex and the RA lead in RA appendage.

CRT resulted in significant improvement in NYHA class, QRS duration, MLHHQ, LVESV and EF, together with significant reduction in RV basal and longitudinal diameters and significant improvement in RV systolic function, compared to baseline irrespective of HF etiology whether dilated 59 (62.7%), or ischemic (Table 1).

At the end of the follow up period, 63 (67%) cases of the study population were termed volumetric responders according to pre-specified criteria, while the remaining 31 cases were termed non-responders (NR) for further statistical analysis. Both groups were matched regarding demographic, clinical, ECG, and

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

	Pre CRT	Post CRT	P
NYHA class3	73 (77.6%)	15 (15.9%)	<0.01
NYHA class 4	21 (23.4%)	3 (3.1%)	
NYHA class (mean)	3.2 ± 0.4	2.1 ± 0.7	
MLHFQ	71.8 ± 14.1	43.4 ± 21.9	<0.01
QRS duration	149.1 ± 10.8	131.2 ± 10.5	<0.01
Echocardiograpy			
LV parameters			
LVEDV	223.9 ± 73.1	205.4 ± 63.8	NS
LVESV	166.1 ± 60.7	138.3 ± 56.4	<0.01
LVEF	25.9 ± 5.9	33.8 ± 10.7	<0.01
RV parameters			
RVD basal	43.8 ± 6.4	39.7 ± 11.8	<0.01
RVD mid	28.9 ± 13.6	26.8 ± 9.9	NS
RVD long	82.7 ± 9.1	75.6 ± 15.4	<0.01
FAC	37.4 ± 5.6	41.0 ± 12.8	0.01
TAPSE	19.8 ± 3.1	21.5 ± 6.9	<0.05
S′	11.3 ± 3	12.8 ± 4.2	<0.01
RVSP	29.3 ± 10.5	28.8 ± 9.7	NS
GLS	15.3 ± 4.8	20.3 ± 8.4	<0.01

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).

However, at the end of the follow up period, significant differences were noted between both groups regarding NYHA class, MLHFQ, six minute walk test, LVEF, LVEDV and ESV (Table 3). Interestingly, only the responders group showed further significant decrease in RV diameters and further improvement of RV systolic function compared to baseline data, in contrast to NR group who showed trend towards more RV dilatation and decline of RV systolic function (Table 4).

Correlation between RV parameters prior to CRT implantation and cardiac CRT response was performed and ROC curves were plotted to define cutoff values for each parameter (Table 5,Fig. 1). Multivariate stepwise logistic regression analysis with each of pre-CRT RV systolic function parameters showed that pre-CRT S' (p = 0.01, odds = 3.21, 95% CI = 1.32 to 7.82), and RVGLS (p = 0.01, odds = 0.45, 95% CI = 0.4–0.8) were the only significant independent predictors of response to CRT.

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

	Responders n = 63	Nonresponders n = 31	P
Age	54.9 ± 14.6	52.5 ± 14.4	NS
Male sex	52 (82.5%)	23 (74.1)	NS
HF etiology			
Dilated CM	41 (65%)	18 (58%)	NS
Ischemic CM	22 (34.9%)	13 (41.9%)	NS
NYHA class 3	50 (79.3%)	23 (74.1%)	NS
MLHFQ	70.4 ± 15.2	73.2 ± 13	NS
QRS duration	150.9 ± 8.9	147.4 ± 12.7	NS
Echocardiography			
LV parameters			
LVEDV	229.8 ± 76.7	212.1 ± 67.4	NS
LVESV	166.9 ± 62.3	164.5 ± 60.5	NS
LVEF	26.8 ± 5.1	24.9 ± 7.3	NS
RV parameters			
RVD basal	40.7 ± 8.6	50.1 ± 8.4	<0.01
RVD mid	27 ± 6.1	32.6 ± 5.9	<0.01
RVD long	81.2 ± 15	85.9 ± 10.1	NS
FAC	40.9 ± 6.4	30.4 ± 10.1	<0.01
TAPSE	22.1 ± 4.9	15.2 ± 3.9	<0.01
S′	12.8 ± 2.3	8.4 ± 1.8	<0.01
GLS	18.5 ± 1.6	8.88 ± 1.3	<0.01

Table 3
Clinical and echocardiographic parameters in both groups after CRT.

	Responders n = 63	Non-responders n = 31	P
NYHA class	1.75 ± 0.44	3 ± 0.47	<0.01
MLHFQ	31.2 ± 12.3	50.3 ± 4.8	<0.01
6 min walk test	310 ± 50	103 ± 27	<0.01
LVEDV	188.6 ± 55.4	239 ± 55.2	<0.01
LVESV	115.9 ± 44	183.1 ± 53.1	<0.01
LVEF	39.1 ± 7.9	23.2 ± 6.9	<0.01

Table 4
RV parameters before and after CRT in both study groups.

	Resp pre	Resp post	P	NR pre	NR post	P
RVD basal	40.7 ± 8.6	33.6 ± 7.1	<0.01	50.1 ± 8.4	52 ± 9.8	NS
RVD mid	27 ± 6.1	21.4 ± 4.9	<0.01	32.6 ± 5.9	37.6 ± 8.4	<0.01
RVD long	81.2 ± 15	68.3 ± 10.8	<0.01	85.9 ± 10.1	90.4 ± 12.5	NS
FAC	40.9 ± 6.4	47.7 ± 7.3	<0.01	30.4 ± 10.1	27.5 ± 10.7	NS
TAPSE	22.1 ± 4.9	25.2 ± 4.6	<0.01	15.2 ± 3.9	14 ± 4	NS
S′	12.8 ± 2.3	15.3 ± 2.3	<0.01	8.4 ± 1.8	7.9 ± 2.3	NS
RVSP	29.7 ± 12.1	28.6 ± 10.5	NS	28.5 ± 6.8	29.2 ± 8.4	NS
GLS	18.5 ± 1.6	26.1 ± 2.1	<0.01	8.88 ± 1.33	8.7 ± 1.34	NS

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

	Cutoff value	AUC	Sensitivity	specificity
FAC	>32%	0.83	100%	80%
TAPSE	>18 mm	0.87	90%	80%
S′	>9 cm/s	0.91	100%	70%
GLS	>12.45%	0.99	100%	99.7%

4. Discussion

Many studies have proven the clinical and echocardiographic benefits of CRT in management of patients with heart failure. However despite proper patient selection, nearly one third of the candidates are inadequate responders and remain an unsolved problem.[2,3]

The majority of the clinical trials have focused on the LV parameters which are the basis of patient selection. Also in case of inadequate response all the maneuvers were directed towards the LV namely LV lead position optimization, echo guided optimization, and the concept of multipoint LV pacing, unfortunately not completely solving the problem.[7,8]

The presence of RV dysfunction is a strong and independent predictor of mortality and morbidity in patients with chronic LV heart failure. RV failure is poorly understood and its therapeutic management is largely empirical.[3,9–11] In the current study, 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.

94 CRT candidates with a mean age of 53.7 ± 14.6 were enrolled in the current study and were followed up for a mean period of 6.2 ± 0.7 months. 67% of the study population had significant reduction of LVESV (>15%) and were termed volumetric responders. Interestingly, non responders group had significantly larger RV transverse and longitudinal diameters, in addition to significantly

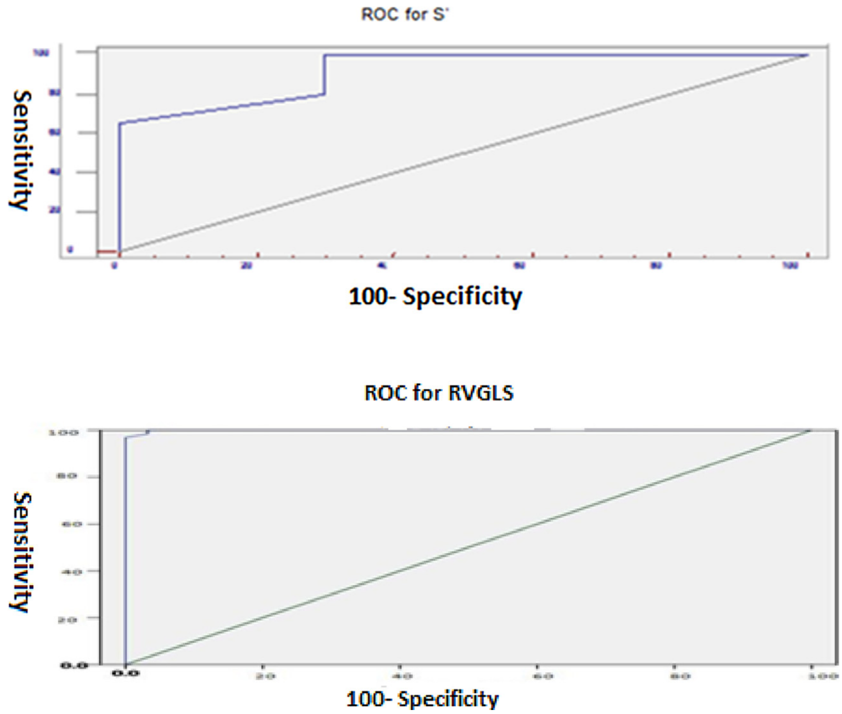

Fig. 1. Receiver of operating characteristics (ROC) curve for pre CRT S' (upper panel) (AUC = 0.91, $p < 0.0001$), and RVGLS (lower panel) (AUC = 0.99, $p < 0.0001$) and relation to CRT response.

lower RV systolic function parameters measured at baseline compared to responders group.

4.1. RV reverse remodeling

In cardiac responders only, CRT resulted in significant reduction in RV transverse and longitudinal diameters in addition to significant improvement in RV systolic function in terms of TAPSE, FAC, S' and RVGLS compared to their baseline parameters. Reduction of RV end-diastolic diameters (reverse remodeling) in responders had been reported by other investigators to be correlated with the magnitude of reduction of LVESV, however it was most outspoken in patients with the largest RV dimensions at baseline,[12,13] unlike the results of the current study where remodeling was observed in patients with significantly smaller RV diameters at baseline a finding that seems more logic reflecting an earlier stage of the disease.

The beneficial effect of CRT on RV systolic function has been a matter of debate taking into consideration the diversity of patient population and the method of evaluation of RV function. In agreement with the current study, many investigators have previously reported significant improvement in RV strain, strain rate in responders.[13,14] Others reported significant improvement in myocardial systolic velocity measured by tissue Doppler at RV free wall that occurred independent of improvements in LVEF.[15] Improvement in RV systolic function was reported to occur earlier before any significant change in RV dimension.[16] On the other hand, the majority of studies using radionuclide imaging have yielded negative results.[17,18]

In our opinion, CRT augments not only LV but also RV function and that a considerable part of the gains in cardiac function with CRT may be attributed to improved RV function. This augmentation is partly due to CRT induced reduction of mitral regurgitation and pulmonary vein hypertension, in addition to favorable effect on the mechanics of the inter-ventricular septum, hence influencing ventricular interdependence.[19]

4.2. RV systolic function: a predictor of response to CRT

Not only RV systolic function parameters were significantly better in responders group at baseline, but interestingly this particular cohort of patients showed further significant improvement of all RV systolic parameters at follow up.

Mean TAPSE in NR group was 15.2 ± 3.9, mean FAC was 30.4 ± 10.1, S' was 8.4 ± 1.8 cm/s, all of which indicated significant RV dysfunction according to predefined reference values. TAPSE > 18, FAC > 32% had 90, and 100% sensitivity respectively for prediction of CRT response. Relevant data of lower TAPSE and FAC in NR group has been reported by others.[20,21] Moreover, patients with low TAPSE < 14 had a two-fold risk of death and emergency heart transplantation.[21] In addition the link between low baseline RVEF(<35%) measured by echo or CMR and poor response even mortality after CRT has been also reported.[22–24]

By multivariate stepwise logistic regression, s' and RVGLS were found to be independent predictors of CRT response. Both S' > 9 cm/s, and RVGLS >12.45% had 100% sensitivity, and 70%, 99.7% specificity respectively, for prediction of response to CRT. These 2 parameters are suggested by our group as simple, highly reproducible parameters of RV dysfunction that can help in selection of CRT candidates. These parameters identify patients with mild impairment of RV systolic function reflecting a relatively early stage of the disease who could still benefit from CRT implantation. Systolic maximum velocity in the ejection phase, a tissue Doppler derived parameter of RV systolic function has been also reported to predict response to CRT.[25] Relevant data about RVGLS were stated by Klaudia Nagy et al., where a cut off value of >10.04% for RVGLS not only identified patients who could benefit from CRT implantation, but also was found to be independent predictor of short term mortality.[26]

In view of our findings and this extensive data over the past decade we can suggest that RV dysfunction may account for good percentage of non-responders despite proper patient selection and the outstanding efforts for CRT optimization, at least in terms of morbidity, symptoms and hospitalizations, if not at the level of LV volume response. Large RV volumes, diameters, and RV systolic dysfunction before implantation identify a subgroup of patients with advanced stage of disease having advanced remodeling that might not benefit from CRT. Even if the criteria of selection remained focused on LV parameters, in our opinion "this forgotten chamber" as previously called in the literature could at least serve as important prognostic marker in patients undergoing CRT. We also support the idea of early CRT implantation before severe LV and accordingly RV dysfunction is observed, an issue that was high-lightened in the MADIT-CRT and the REVERSE trials in which the beneficial effects of CRT in patients with mild heart failure were clearly observed, thus optimizing response to CRT.[27,28]

Taking into consideration the complex geometry of the RV which makes RVEF estimation sometimes a major challenge, we defined a cutoff value of $S' > 9$ cm/s, and RVGLS > 12.45%, in addition to the previously extensively studied TAPSE, as alternatives to RVEF estimation to assess RV systolic function and hence predicting CRT response.

In conclusion, we believe that the RV is an active participant in CRT patients rather than an innocent passive chamber that benefits from CRT improvement of LV volumes or systolic function, but also 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 before CRT implantation should be fully investigated to optimize CRT response.

Limitations

This study is a single centre study with relatively short follow up period, and low event rate limiting statistical analysis of outcomes. Nearly 1/3 of the study population had an ischemic etiology, which might have affected the percentage of CRT responders. RVGLS was measured using LV software due to the absence of dedicated RV software. Lastly, the absence of MRI compatible devices at our centre hindered further assessment of RV function given the known limitations of echocardiographic parameters.

Conflict of interest

The authors declare that there are no potential conflicts of interest.

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