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The utility of echocardiographic right ventricular parameters in predicting response to cardiac resynchronization therapy in patients with heart failure: A proof of concept

RV function and CRT response

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Abstract

Aim: Despite the guideline-based selection of patients, failure to respond to cardiac resynchronization therapy (CRT) remains common. We aimed to assess the utility of right ventricular (RV) echocardiographic parameters to predict response to CRT. Material and Method: A prospective study of 30 patients who were eligible for CRT. Echocardiographic RV parameters were assessed at baseline and 6 months post-CRT. CRT response was defined as a ≥ 15% reduction in left ventricular end-systolic volume. Results: Statistical analysis revealed that 66.7% were CRT-responders. CRT-responders had higher fractional area change (40.9 ± 6.4 vs 30.4 ± 10.1%; p = 0.002), tricuspid annular plane systolic excursion (22.1 ± 4.9 vs 15.2 ± 3.9 mm; p = 0.001), tissue Doppler–derived tricuspid lateral annular systolic velocity (S') (12.8 ± 2.3 vs 8.4 ± 1.8 mm; p < 0.0001), and RV myocardial performance index (0.41 ± 0.07 vs 0.54 ± 0.09, p < 0.0001) at baseline compared with non-responders. On multivariate analysis, pre-CRT S' was the single independent predictor of CRT response (OR: 3.21, 95% CI: 1.31 to 7.82, p = 0.01). S' >8 cm/s was 100% sensitive and 70% specific in predicting response to CRT (AUC = 0.91, p < 0.0001). Discussion: Echocardiography-derived S' >8cm/s could be considered as a highly sensitive and specific predictor of response to CRT.

Keywords

Cardiac Resynchronization Therapy; Echocardiography; Heart Failure; Device Therapy; Right Ventricle; Prediction Tools

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Introduction

Cardiac resynchronization therapy (CRT) is an established treatment for patients with systolic heart failure (HF) and ventricular electrical dyssynchrony [1,2]. Despite technological advances in device implantation and programming, nearly one-third of HF patients fail to demonstrate a satisfactory response to CRT [3]. Identification of clinical and imaging parameters that could predict patient's response to CRT could facilitate appropriate patient selection for these procedures and improve efficacy.

Prior studies have shown that right ventricular (RV) dysfunction is a poor prognostic factor in patients with moderate to severe chronic HF [4,5]. Furthermore, RV dysfunction is associated with worse outcomes in patients undergoing CRT [6]. However, assessment of RV parameters to aid selection of patients for CRT has not translated into clinical practice. This is partly due to randomized studies focusing primarily on LV indices, lack of experience with echocardiographic assessment tools to appropriately assess the RV, and the paucity of studies providing normal reference values of RV size and function [7].- In the current proof-of-concept prospective study, we sought to evaluate the feasibility of various echocardiographic RV function parameters to predict the response of HF patients to CRT.

Material and Method

We conducted a prospective, open-labeled, single-center study that enrolled a cohort of 30 consecutive patients who presented to our tertiary medical center between January and December 2016 with a diagnosis of chronic systolic HF and met guideline-based indications for CRT implantation. In accordance with the current guidelines [8], inclusion criteria included symptomatic HF despite optimal pharmacological therapy for at least 3 months prior to inclusion, with New York Heart Association (NYHA) functional class II-IV, ejection fraction (EF) ≤ 35% and QRS duration ≥ 120 ms (in presence of LBBB) or ≥ 150 ms (in absence of LBBB). Exclusion criteria were patients with: life expectancy less than 1 year such as advanced malignancy or dementia, acute HF requiring inotropic support, permanent atrial fibrillation (AF), and previous pacemaker implantation. Written informed consent was obtained from every patient after meeting our inclusion criteria, and the study protocol was reviewed and approved by our local institutional human research committee as it conforms to the Declaration of Helsinki.

Data gathered at baseline (pre-CRT implantation) included following: demographic data, HF clinical status according to NYHA functional class and Minnesota living with heart failure questionnaire (MHFQ), electrocardiogram (ECG) analysis and transthoracic echocardiography (TTE). At 6-months follow up, patients were re-evaluated at a clinic visit for HF clinical status, ECG and repeat TTE for assessment of response to CRT. Physicians evaluating patients at follow-up were blinded to the pre-CRT data to avoid potential bias.

The main outcomes assessed after CRT implantation were: a) response to CRT by echocardiographic parameters, defined as ≥ 15% reduction in LV end-systolic volume, and b) clinical improvement assessed by NYHA functional class and MHFQ, at 6-month follow-up [9,10]. After determining CRT-responders, we examined the changes of RV echocardiographic parameters with CRT placement compared with non-responders.

Echocardiographic imaging

TTE examination with machine-integrated ECG recording was performed, preferably with the patients lying in the left lateral decubitus position, using a Vivid 5, S5 or 7 machines (General Electric Vingmed Ultrasound, Horten, Norway) with an M4S matrix sector array probe (frequency of 2.5 MHz). Standard images were obtained in the parasternal (long- and short-axis) and apical (2- and 4-chamber) views. RV parameters evaluated included following: RV longitudinal and transverse diameters, tricuspid annular plane systolic excursion (TAPSE), tissue Doppler-derived tricuspid lateral annular systolic velocity (S'), Percentage RV fractional area of change (FAC), RV myocardial performance index (MPI), RV systolic pressure (RVSP), and tricuspid regurgitation (TR) severity. LV parameters evaluated included LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LVEF and mitral regurgitation (MR) severity. We followed the current guidelines in echocardiographic assessment of right and left heart in adults [7,11,12]. All echocardiographic analysis was conducted by two independent and experienced cardiologists. The detailed description of the definitions and echocardiographic assessment methods are reported in the supplemental appendix (1).

CRT-P pacemakers were successfully implanted in all patients under fluoroscopic guidance. Pacing leads were implanted via the left axillary/subclavian vein approach. The right atrial lead was positioned in the right atrial appendage and the RV lead tip was placed at the apex of the right ventricle. The LV lead tip was positioned in the posterolateral cardiac vein (n= 27), posterior vein (n= 2) and lateral vein (n= 1). All implanted devices were QUADRA ALLURE MP™ RF CRT-P (St. Jude Medical, Minnesota, USA).

Statistical analysis

Categorical variables were presented as number and percentages and compared by using the Chi-square test. Continuous variables were presented as the mean and standard deviation and compared using Independent t-test when the data were parametric and Mann-Whitney test when the data were non-parametric. Receiver operating characteristic curve (ROC) was used to assess the cutoff point with the highest sensitivity and specificity. Logistic regression analysis was used to identify the predictors of CRT response. Predictors associated with a P value <0.1 on univariate analysis were entered a stepwise multivariate logistic regression model to identify independent predictors of reverse remodeling. The p-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 16 for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

Baseline clinical and echocardiographic characteristics:

The mean age of the study population was 52.8 ± 15.4 years, 80% men. Sixty percent of patients had non-ischemic etiology for HF. Patients with LBBB represented 76.6% of the study cohort with a mean QRS duration of 148.1 ± 10.1 msec. The majority of patients (80%) had NYHA class III symptoms. Mean indexed LVEDV was 223.9 ± 73.1 ml/m^2, mean indexed LVESV was 166.1 ± 60.7 ml/m^2 and mean EF was 25.9 ± 5.9%. The mean basal transverse RV diameter was 43.8 ± 9.5 mm, mid

RV diameter was 28.9 ± 6.4 mm, and longitudinal diameter was 82.7 ± 13.6 mm. RV systolic parameters showed a mean S' of 11.3 ± 3 cm/s, FAC of 37.4 ± 9.1%, TAPSE of 14.8 ± 5.6 mm, and MPI of 0.46 ± 0.1. Forty percent of patients had at least moderate of tricuspid regurgitation. Details of baseline clinical and echocardiographic characteristics of the study population are shown in Table 1.

Clinical and echocardiographic outcomes

At 6-months follow-up, CRT was associated with a significant improvement in MHFQ (70.8 ± 15.1 vs 43.8 ± 22.9; p < 0.0001), and mean NYHA class (3.2 ± 0.4 vs 2.1 ± 0.7; p < 0.0001) in the entire cohort. There was significant reduction in post-CRT QRS duration (148.1 ± 10.4 vs 128.3 ± 8.2 msec, p < 0.001). Echocardiographic LV parameters post CRT showed significant reduction in LVESV (138.3 ± 56.4 ml vs 166.1 ± 60.7 ml; p = 0.002), and significant increase in LVEF (25.9 ± 5.9% vs 33.8 ± 10.7%; p < 0.0001) compared with pre-CRT parameters. Successful response to CRT (defined by a reduction of ≥ 15% in LVESV) was achieved in 20 patients (66.7%).

Regarding echocardiographic RV parameters, there was a significant reduction in RV basal (43.8 ± 9.5 vs 39.7 ± 11.8 mm; p < 0.0001), and longitudinal dimensions (82.7 ± 13.6 vs 75.6 ± 15.4 mm; p < 0.001) with CRT compared to baseline. CRT implantation was also associated with significant improvement in RV systolic function parameters including S' (11.3 ± 3 vs 12.8 ± 4.2 cm/s; p < 0.0001), TAPSE (14.8 ± 5.6 vs 21.5 ± 6.9 mm; p = 0.002), and FAC (37.4 ± 9.1% vs 41.0 ± 12.8%; p = 0.01). No significant difference was observed in post-CRT RV systolic pressure (39.3 ± 10.5 vs 38.8 ± 9.7 mmHg; p= 0.16), MPI (0.46 ± 0.1 vs 0.44 ± 0.12, p= 0.15) and degree of TR (1.53 ± 0.7 vs 1.56 ± 0.7; p= 0.88) compared with pre-CRT parameters. Comparison of clinical and echocardiographic parameters before and after CRT for the study population is reported in Table 2.

Predictors of CRT response

Patients were classified as CRT-responders (≥ 15% reduction in LVESV at 6-months follow-up) and non-responders. CRT-responders had a higher frequency of baseline LBBB (90% vs 50%, p = 0.03), and more prolonged QRS duration (151.9 ± 8.1 vs 141 ± 11 msec; p = 0.005) compared with non-responders. In addition, CRT-responders had lower MHFQ at baseline compared with non-responders (66.9 ± 14.7 vs 78.7 ± 13.1, p = 0.04), with no significant difference in NYHA functional class (3.2 ± 0.37 vs 3.3 ± 0.48, p = 0.37). There was no significant correlation between baseline LV echocardiographic parameters and response to CRT (Table 1). There was significant difference in degree of MR severity between the two groups (1.6 ± 0.8 vs 2.3 ± 0.7; p = 0.027).

On analysis of echocardiographic RV parameters, CRT-responders demonstrated smaller basal and transverse diameters (40.7 ± 8.6 vs 50.1 ± 8.4 mm; p = 0.009; and 27 ± 6.1 vs 32.6 ± 5.9 mm, p = 0.025, respectively), as well as higher FAC (40.9 ± 6.4 vs 30.4 ± 10.1%; p = 0.002), TAPSE (22.1 ± 4.9 vs 15.2 ± 3.9 mm; p = 0.001), S' (12.8 ± 2.3 vs 8.4 ± 1.8 mm; p < 0.0001), and MPI (0.41 ± 0.07 vs 0.54 ± 0.09; p < 0.0001) at baseline compared with non-responders. Table 1 illustrates the correlation between baseline parameters (clinical and echocardiographic) and response to CRT. The degree of change in echocardiographic RV parameters in CRT-responders and non-responders is presented in Table 3. As shown, CRT-responders had significant positive remodeling in the RV when compared to non-responders at 6-month follow-up.

Table 1. Baseline parameters in the total cohort, CRT-responders, and CRT non-responder

Variable	Total population (n=30)	CRT responder (n=20)	CRT non-responder (n=10)	p-value
Age, years	52.8 ± 15.4	53.9 ± 15.6	50.5 ± 15.4	0.57
Male, n (%)	24 (80)	16 (80)	7 (70)	0.48
Etiology				
NICM, n (%)	18 (60)	13 (65)	5 (50)	0.46
ICM, n (%)	12 (40)	7 (35)	5 (50)	
NYHA class				
III, n (%)	24 (80)	17 (85)	7 (70)	0.37
IV, n (%)	6 (20)	3 (15)	3 (30)	
MHFQ	70.8 ± 15	66.9 ± 14.7	78.7±13.1	0.04
QRS morphology				
LBBB, n (%)	23 (76.6)	18 (90)	5 (50)	0.026
Non-LBBB, n (%)	7 (23.3)	2 (10)	5 (50)	
QRS duration, msec	148.1 ± 10.4	151.9 ± 8.1	141 ± 11	0.005
Echocardiography parameters				
LV parameters				
LVEDD, mm	71.5 ± 9.1	71.8 ± 9.9	71 ± 7.6	0.89
LVESD, mm	62.6 ± 9	62.4 ± 9.9	62.9 ± 7.4	0.91
LVEDV, ml	223.9 ± 73.1	229.8 ± 76.7	212.1 ± 67.4	0.54
LVESV, ml	166.1 ± 60.5	166.9 ± 62.3	164.5 ± 60.5	0.92
EF, %	25.9 ± 5.9	26.8 ± 5.1	24 ± 7.3	0.22
MR grade	1.83 ± 0.8	1.6 ± 0.8	2.3 ± 0.7	0.03
RV parameters				
RV basal diameter, mm	43.8 ± 9.5	40.7 ± 8.6	50.1 ± 8.4	0.01
RV mid diameter, mm	28.9 ± 6.4	27 ± 6.1	32.6 ± 5.9	0.03
RV longitudinal diameter, mm	82.7 ± 13.6	81.2 ± 15	85.9 ± 10.1	0.38
FAC, %	37.4 ± 9.1	40.9 ± 6.4	30.4 ± 10.1	0.002
TAPSE, mm	14.8 ± 5.6	22.1 ± 4.9	15.2 ± 3.9	0.001
S', cm/s	11.3 ± 3	12.8 ± 2.3	8.4 ± 1.8	0.0001
MPI	0.46 ± 0.1	0.41 ± 0.07	0.54 ± 0.09	0.0001
RVSP, mmHg	39.3 ± 10.5	39.7 ± 12.1	38.5 ± 6.8	0.77
TR grade	1.5 ± 0.7	1.4 ± 0.6	1.6 ± 0.8	0.16

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

NICM= non-ischemic cardiomyopathy, ICM= ischemic cardiomyopathy, NYHA= New York heart association, HF= heart failure, MHFQ= Minnesota HF questionnaire, LBBB= left bundle branch block, LVEDD= left ventricular end-diastolic diameter, LVESD= Left ventricular end-systolic diameter, LVEDV= left ventricular end-diastolic volume, LVESV= Left ventricular end-systolic volume, EF= Ejection fraction, MR= Mitral regurgitation, RVD= Right ventricular diameter FAC= Fractional area change, TAPSE= Tricuspid annular systolic plane excursion, S'= Tissue Doppler–derived tricuspid lateral annular systolic velocity, MPI= Myocardial performance index, RVSP= Right ventricular systolic pressure, TR= Tricuspid regurgitation.

Table 2. Comparison between pre- and post-CRT data in the study cohort

Variable	Pre-CRT	Post-CRT	P-value
NYHA	3.2 ± 0.4	2.1 ± 0.7	0.0001
MHFQ	70.8 ± 15.1	43.8 ± 22.9	0.0001
LVEDD, mm	71.5 ± 9.1	67.9 ± 8.5	0.002
LVESD, mm	62.6 ± 9	55.6 ± 10.1	0.0001
LVEDV, ml	223.9 ± 73.1	205.4 ± 63.8	0.06
LVESV, ml	166.1 ± 60.5	138.3 ± 56.4	0.002
EF, %	25.9 ± 5.9	33.8 ± 10.7	0.0001
MR grade	1.8 ± 0.8	1.5 ± 1	0.01
RV basal diameter, mm	43.8 ± 9.5	39.7 ± 11.8	0.0001
RV mid diameter, mm	28.9 ± 6.4	26.8 ± 9.9	0.12
RV longitudinal diameter, mm	82.7 ± 13.6	75.6 ± 15.4	0.001
FAC, %	37.4 ± 9.1	41.0 ± 12.8	0.01
TAPSE, mm	14.8 ± 5.6	19.5 ± 6.9	0.002
S', cm/s	11.3 ± 3	12.8 ± 4.2	0.0001
MPI	0.46 ± 0.1	0.44 ± 0.12	0.15
RVSP, mmHg	39.3 ± 10.5	8.8 ± 9.73	0.16
TR grade	1.53 ± 0.7	1.51 ± 0.7	0.88

Data are presented as mean ± SD.

NYHA= New York heart association, HF= heart failure, MHFQ= Minnesota HF questionnaire, LVEDD= left ventricular end-diastolic diameter, LVESD= Left ventricular end-systolic diameter, LVEDV= left ventricular end-diastolic volume, LVESV= Left ventricular end-systolic volume, EF= Ejection fraction, MR= Mitral regurgitation, RVD= Right ventricular diameter FAC= Fractional area change, TAPSE= Tricuspid annular systolic plane excursion, S'= Tissue Doppler–derived tricuspid lateral annular systolic velocity, MPI= Myocardial performance index, RVSP= Right ventricular systolic pressure, TR= Tricuspid regurgitation

On a further ROC curve analysis, FAC >30% (100% sensitivity and 80% specificity; p = 0.003), TAPSE >18 mm (90% sensitivity and 80% specificity; p < 0.0001), S' >8 cm/s (100% sensitivity and 70% specificity; p< 0.0001) and MPI < 0.52 (100% sensitivity and 70%; p < 0.0001) were identified as the baseline cut-off values for such parameters to predict appropriate CRT response (**Figure 1**).

Multivariate logistic regression analysis including all the significant baseline clinical and echocardiographic parameters in a step-wise fashion revealed baseline RV S' as the single independent predictor of successful response to CRT (odds ratio (OR): 3.21, 95% CI: 1.32 to 7.82, p= 0.01). Based on this finding, we chose S' > 8 cm/s as a cutoff to stratify the population into 2 groups. At baseline, 23 out of 30 patients (76.6%) had an S' value >8 cm/s. CRT response was observed in 20 patients with S' value >8 cm/s versus none with S' ≤ 8 cm/s.

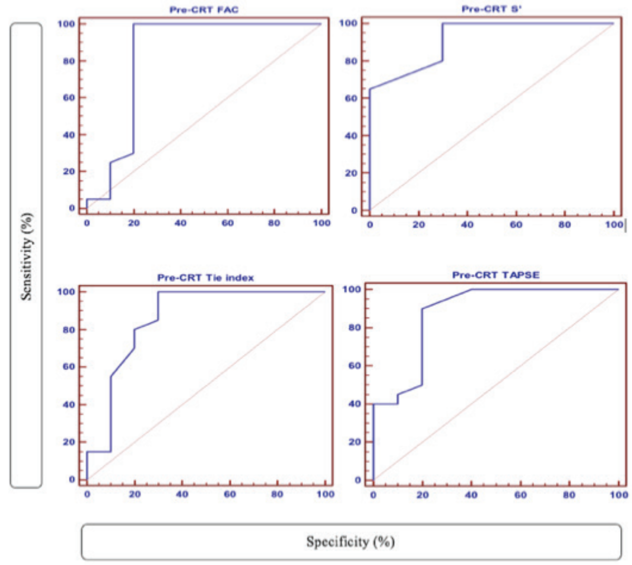

Figure 1. Receiver operating characteristic curves for pre-CRT FAC, TAPSE, S' and MPI (Tie) index and relation to CRT response.

Discussion

In the current single-center, prospective study of 30 patients, we demonstrated baseline echocardiographic RV function parameters to be significant predictors of CRT response in HF. Our study showed that at follow-up of 6 months, CRT resulted in significant improvement in the clinical symptoms, NYHA class, MHFQ score and echocardiographic measures of LV and RV function. Baseline criteria that were associated with improved CRT response included LBBB, increased QRS duration, lower MR severity, smaller RV basal and transverse diameters, and higher RV FAC, TAPSE, S' and MPI. However, RV S' was the single independent predictor of CRT response on multivariate analysis. An S' cut off value of >8 cm/s was 100% sensitive, and 70% specific in predicting a satisfactory CRT response.

CRT is the recommended line of treatment for patients with systolic HF on maximally tolerated guideline-based medical therapy and has been proven to reinstitute ventricular syn-

Table 3. Degree of change in echocardiographic RV parameters in CRT responders and non-responders

Variable	Responders					Non-Responders					P value Δ-Δ
	Pre-CRT		Post-CRT		Δ	Pre-CRT		Post-CRT		Δ	
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		
RVD, basal (mm)	40.7	8.6	33.6	7.1	-7.1	50.1	8.4	52	9.8	1.9	<0.0001
RVD, mid (mm)	27	6.1	21.4	4.9	-5.6	32.6	5.9	37.6	8.4	5	<0.0001
RVD, longitudinal (mm)	81.2	15	68.3	10.8	-12.9	85.9	10.1	90.4	12.5	4.5	<0.0001
FAC (%)	40.9	6.4	47.7	7.3	6.8	30.4	10.1	27.5	10.7	-2.9	<0.0001
TAPSE (mm)	22.1	4.9	25.2	4.6	3.1	15.2	3.9	14	4	-1.2	<0.0001
S' (cm/s)	12.8	2.3	15.3	2.3	2.5	8.4	1.8	7.9	2.3	-0.5	<0.0001
MPI	0.41	0.07	0.37	0.06	-0.04	0.54	0.09	0.59	0.05	-0.04	<0.0001
TR	1.4	0.68	1.2	0.44	-0.2	1.8	0.78	2.2	0.91	0.4	0.03

RVD= Right ventricular diameter, FAC= Fractional area change, TAPSE= Tricuspid annular systolic plane excursion, S'= Tissue Doppler–derived tricuspid lateral annular systolic velocity, MPI= Myocardial performance index, RVSP= Right ventricular systolic pressure, TR= Tricuspid regurgitation chrony and improve LV function [1,2]. The effect of CRT on RV function is, however, still a topic of debate. Significant reverse remodeling, reduction of RV diameters, as well as improvement of RV function were demonstrated in prior studies [10,13]. The effect of CRT on RV systolic function was observed earlier to the changes in RV dimensions [14]. Other studies failed to find a significant improvement in the RV function in conjunction with the observed improvement in LV function [15]. We aimed in this study to perform a comprehensive study of RV parameters and were able to demonstrate a significant improvement in the parameters of RV function in patients who responded to CRT.

It is estimated that approximately 30% of HF patients who receive a CRT device fail to show an appropriate response. Thus, novel methods to improve the CRT selection criteria and predict successful response are crucial, and RV parameters seem to be promising. Prior studies have demonstrated a significant correlation between echocardiographic indices of baseline RV function and the degree of LV reverse remodeling observed at 6-months follow up after CRT implantation in patients with HF [16]. Another study described pre-implant reduced RV systolic function to be a predictor of poor response to CRT [17]. TAPSE > 17 mm was also correlated with improved CRT response, however, only with the sensitivity of 68% and specificity of 54% in one study, and sensitivity of 64% and specificity of 60% in another [18]. In our study, we show for the first time that tissue Doppler-derived tricuspid annular systolic velocity is the most significant predictor of CRT response with a high degree of sensitivity and specificity.

The assessment of RV dimensions and function is clinically challenging owing to the complex geometry of the RV and difficult visualization on standard echocardiography [4,5]. Cardiac magnetic resonance (CMR) imaging has emerged as an accurate modality for RV assessment, but not feasible for all patients [19]. On contrary, RV S' is a reliable, reproducible, and easy to measure, way of RV function assessment [7]. Furthermore, it highly correlates with volumetric quantification of the RV systolic function on MRI [20], compared with 2D and 3D echocardiographic estimates of RV size and systolic function which display only a moderate correlation with MRI measurements of such parameters [21]. Despite these facts, the implementation of tissue Doppler-derived tricuspid lateral annular systolic velocity, known as RV S', as a predictor of CRT response was clearly under-represented in clinical trials.

To the best of our knowledge, our study is the first to-date to shed the light on RV S' as a reliable predictor of CRT response. The S' > 8 cm/s represents the highest sensitivity (100%), and specificity (70%) test, known in literature so far, to correlate with a successful CRT response. Such high sensitivity may offer physicians a possible reliable parameter to identify patients that will most probably not show adequate benefit to CRT device placement.

Strengths and Limitations

Strengths of our study include a prospective study design, systematic assessment of all available 2D RV echocardiographic parameters and analysis of a composite outcome of imaging and clinical parameters. However, we acknowledge several limitations in our study. First, a small number of patients were included in a single center. Since our study was only performed as a proof-of-concept, we highly encourage multicenter randomized clinical trials to validate these findings on a larger group of patients. Second, the study was open labeled however to reduce the risk of bias, the follow-up evaluation for patients was blinded from their baseline characteristics. Finally, a more accurate parameter to assess the RV size and function would be better if it were based on MRI. However, in our study, we had in mind to utilize simple, cheap and readily available parameters derived from the echocardiography.

Conclusion

In summary, the current study identifies RV S' (with cut-off value > 8cm/s) as a feasible and independent predictor of successful CRT response in HF patients.

Clinical Perspectives

Competency in Medical Knowledge: The utility of echocardiographic RV parameters on response to CRT in patients with HF is not well known. In a prospective study design, we demonstrate that various baseline RV function parameters significantly predict a positive response to CRT, irrespective of LV echocardiographic parameters. Among all available measures of RV function, tissue Doppler-derived tricuspid annular systolic velocity had the best predictive value of CRT response on ROC analysis. In addition, all patients with a positive CRT response had a concomitant improvement in RV function by TTE.

Translational Outlook: The findings of this prospective study are directly applicable to optimizing appropriate patient selection for CRT. Further larger studies validating these findings are encouraged.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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