Original Article

Investigating the clinical utility of global and regional myocardial work parameters in predicting response to cardiac resynchronization therapy in patients with heart failure and reduced ejection fraction

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Background: Previous studies have indicated that despite adhering to current patient selection guidelines, there remains a 30% to 40% subset of patients who do not experience improvement in heart failure (HF) after receiving cardiac resynchronization therapy (CRT). We aim to utilize echocardiographic myocardial work parameters to serve as predictors of responsiveness to CRT in patients with heart failure and reduced ejection fraction (HFrEF).

Methods: We prospectively recruited patients who underwent CRT at Sun Yat-sen Memorial Hospital from June 2019 to September 2022. Comprehensive preoperative information, clinical laboratory data, conventional echocardiographic parameters and myocardial work were collected for all participants, as well as follow-up data 6 months after CRT.

Results: Twenty-five patients (67.6%) showed response to CRT treatment, while twelve patients (32.4%) had no response. Compared with the non-response group, the response group had larger region constructive work [RCW: the sum of constructive work (CW) in the 9 segments of the basal, mid, and apical segments of the anterior, lateral, and posterior walls], region wasted work [RWW: the sum of wasted work (WW) in the 6 segments of the basal and mid segments of the anterior septum, posterior septum and anterior walls], and the combination of RCW and RWW (RCW + RWW) in baseline (RCW: 9,695.68±2,955.40 *vs.* 5,219.50±2,207.68 mmHg%, P<0.001; RWW: 3,612.08±1,723.80 *vs.* 1,674.33±995.23 mmHg%, P=0.001; RCW + RWW: 13,307.76±3,857.71 *vs.* 6,893.83±2,592.83 mmHg%, P<0.001). Furthermore, global constructive work (GCW), global wasted work (GWW), GCW + GWW, RCW, RWW, and RCW + RWW had areas under the receiver operating characteristic curve (AUCs) of 0.870, 0.770, 0.860, 0.890, 0.870, and 0.910, respectively, for predicting CRT responsiveness.

Conclusions: The global and regional myocardial work parameters are associated with CRT response in CRT candidates. Particularly regional myocardial work parameters appear to be promising parameters to improve selection for CRT of patients with HFrEF.

Keywords: Heart failure (HF); cardiac resynchronization therapy (CRT); echocardiography; speckle-tracking; myocardial work

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Introduction

Heart failure (HF) is a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion (1). Cardiac resynchronization therapy (CRT) is an indispensable technique and modality in the management of HF which improves symptoms and the quality of life and reduces complications and the risk of death (2,3). However, despite adhering to current guideline recommendations for patient selection, approximately 30% to 40% of patients with HF and reduced ejection fraction (HFrEF) do not experience improvements, a phenomenon known as non-response to CRT (4-6). These observations suggest that the current guideline recommendations for CRT indication have certain limitations. Therefore, it is of utmost importance to identify reliable parameters for predicting CRT responsiveness.

CRT aims to enhance cardiac function by coordinating left and right ventricular as well as intraventricular contraction to ameliorate cardiac dyssynchrony. Myocardial work analysis is a novel approach that uses speckle tracking technology to assess left ventricular motion coordination and function. By quantifying myocardial work at both the segmental and global levels throughout the cardiac cycle, this method holds the potential to identify early and sensitive changes in regional and global myocardial mechanics (7-11). Regarding the prediction of CRT responsiveness, previous investigations have primarily focused on global parameters. Nevertheless, the evaluation of local myocardial contraction has been relatively overlooked in prior studies. It is plausible that incorporating parameters related to regional myocardial work may address this limitation.

The primary objective of this study is to employ comprehensive global and regional myocardial work analysis techniques to compare and evaluate the clinical value of various parameters in predicting CRT responsiveness. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-393/rc).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Institution Review Board of Sun Yat-sen Memorial Hospital (No. 2019-KY-056). Written informed consent was obtained from all participants.

Study population

This study was a prospective study that enrolled patients who underwent CRT at Sun Yat-sen Memorial Hospital between June 2019, and September 2022. The inclusion criteria were as follows: (I) left ventricular ejection fraction (LVEF) ≤35%; (II) ventricular depolarization complex (QRS) duration ≥130 ms; (III) symptomatic patients with New York Heart Association (NYHA) functional class II, III and ambulatory IV (12); (IV) Patients who received standardized medical treatment for HF for a minimum of 3 months before CRT. All the patients included in the study were undergoing device implantation for the first time. The exclusion criteria were as follows: (I) patients with concurrent diseases (assessed through medical history, significant liver or kidney abnormalities) or those with an expected lifespan of less than 1 year. (II) Patients planning to undergo other cardiovascular interventions or cardiac surgeries, such as coronary artery stenting or bypass surgery, during the follow-up period. (III) Patients who expressed difficulties in follow-up during the initial interview. Comprehensive preoperative information, clinical laboratory data, conventional echocardiographic parameters and myocardial work were collected for all participants, as well as follow-up data 6 months after CRT.

A total of 39 patients were initially considered for inclusion, and 2 patients were excluded due to poor quality of echocardiographic images. Ultimately, 37 patients were included in the study, and all of them provided written informed consent. In this study, the response to CRT was defined as ≥15% decrease in left ventricular end systolic volume (LVESV) at follow-up compared to baseline (13). The patients were categorized into two groups: the responsive group and the non-responsive group. The responsive group was defined as individuals who exhibited ≥15% decrease in LVESV compared to the preliminary cardiac resynchronization therapy (pre-CRT) value. Conversely, the non-responsive group included patients who did not meet these specified criteria. The primary objective of this study was to compare and analyze the differences and similarities in both conventional parameters and echocardiographic parameters before and after CRT between these two distinct groups.

CRT implantation procedure

Device implantations were performed according to the current standards by using a transvenous approach method (12). Patients received a conventional right ventricular lead (usually positioned in the right ventricular apex) and a right atrial lead. Transvenous LV lead deployment was guided by fluoroscopic coronary sinus venography. For patients with unsuccessful coronary sinus electrode implantation, Left Bundle Branch Pacing-CRT (LBBP-CRT) implantation was performed (14). After successful positioning of the leads, electrical parameters such as pacing, sensing, and impedance values were measured and also registered.

Echocardiography

Echocardiograms were obtained by experienced echocardiographers using a Vivid E95 commercial ultrasound scanner (GE Healthcare, Horten, Norway) with a phased-array transducer (M5S-D) on the day before CRT implantation and at 6-month follow-up for the assessment of response to CRT. Noninvasive blood pressure values were recorded using a brachial artery sphygmomanometer at the time of transthoracic echocardiography. Standard echocardiographic measurements were performed according to the American Society of Echocardiography for comprehensive transthoracic echocardiographic examination in adults (15).

Myocardial work assessment

For image analysis and parameter acquisition, the GE Echopac 204 workstation was utilized. Firstly, the spectral Doppler images of the mitral valve and aortic valve were selected, and the timing of key events, such as mitral valve opening (MVO), mitral valve closure (MVC), aortic valve opening (AVO), and aortic valve closure (AVC), were annotated. Subsequently, the automated functional imaging mode was activated, and dynamic images of the apical three-chamber, four-chamber, and two-chamber views were sequentially analyzed. The software automatically traced the left ventricular endocardial contour, with manual adjustments to be made if necessary. Within the analysis section, the global longitudinal strain (GLS) of the left ventricle was calculated, and the peak strain dispersion (PSD) of the 18 segments was recorded. Furthermore, utilizing the myocardial work feature, the systolic and diastolic pressures of the subjects were entered, resulting in the computation of myocardial work parameters. Advanced functions provided access to left ventricular pressure-strain loops (LVPSL), overall myocardial work parameters, as well as constructive work (CW), wasted work (WW), work index (WI), and work efficiency (WE) for each of the 18 segments based on the left ventricular model.

We defined region constructive work (RCW) as the sum of CW in the 9 segments of the basal, mid, and apical segments of the anterior, lateral, and posterior walls. Additionally, region wasted work (RWW) was defined as the sum of WW in the 6 segments of the basal and mid segments of the anterior and posterior septum, as well as the basal and mid segments of the anterior wall. The combination of RCW and RWW (RCW + RWW) was used as an evaluation of the local myocardial function of the left ventricle.

Statistical analysis

A database was established using Microsoft Excel software, and statistical analysis was conducted using SPSS 25.0 software (IBM, Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation (SD). The comparisons of means within-group were performed using paired *t*-tests for normally distributed data or Wilcoxon signed-rank tests for non-normally distributed data. The comparisons of means between-group were analyzed using independent samples t-tests for normally distributed data or Mann-Whitney U tests for non-normally distributed data. Categorical variables were reported as frequencies and percentages, and between-group comparisons were assessed using the Chi-squared test. Pearson correlation analysis was applied to explore the correlation between variables and

ΔLVEF, aiming to identify the parameters most strongly associated with ΔLVEF. Receiver operating characteristic (ROC) curve analysis was conducted for binary variables to evaluate the predictive value, sensitivity, and specificity of various parameters in predicting CRT responsiveness.

Results

Baseline patient characteristics

This study enrolled a cohort of 37 patients with HF who underwent CRT at our hospital between June 2019, and September 2022. Among the participants, 23 (62.2%) were male and 14 (37.8%) were female, with ages ranging from 33 to 85 years (mean age: 62.51±10.96 years). Twenty-five patients (67.6%) demonstrated a positive response to CRT, while 12 patients (32.4%) did not. The rate of HF hospitalization was 18.9% and no patients died during follow-up. we included a total of 27 patients with left bundle branch block (LBBB) in the study, with 19 cases in the responsive group and 8 cases in the non-responsive group. There were no statistically significant differences in baseline characteristics, including gender and age between the two groups (*Table 1*).

Conventional echocardiographic parameters

Comparison of conventional echocardiographic parameters before and after CRT, between responsive and non-responsive groups before CRT are displayed in Appendix 1, Tables S1,S2. This paper focused on the study of myocardial work parameters.

Comparison of myocardial work parameters before and after CRT

Compared to preoperative values, the responsive group showed a significant decrease in GWW at 6 months postoperatively (203.12±87.18 *vs.* 393.20±158.52 mmHg%, P<0.001). However, the non-responsive group only demonstrated a slight decrease in GWW without statistical significance (252.25±66.76 *vs.* 286.08±165.20 mmHg%, P=0.475) (*Table 2*).

The responsive group showed a significant increase in GCW + GWW at 6 months after CRT (1,825.20±349.59 *vs.* 1,190.28±303.12 mmHg%, P<0.001). Conversely, the non-responsive group only exhibited a slight post-CRT increase without statistical significance (988.58±317.94 *vs.* 844.17±351.73 mmHg%, P=0.255) (*Table 2*).

Figure 1 presents myocardial work for a responsive patient before and 6 months after CRT.

Comparison of myocardial work parameters between responsive and non-responsive groups before CRT

Overall myocardial work parameters

The responsive group demonstrated a significantly higher pre-CRT GCW (797.08±226.30 *vs.* 558.08±243.85 mmHg%, P<0.001) and GWW (393.20±158.52 *vs.* 286.08±165.20 mmHg%, P=0.023) than the non-responsive group (*Table 2*).

The responsive group exhibited a significantly higher pre-CRT GCW + GWW (1190.28±303.12 *vs.* 844.17±351.73 mmHg%, P<0.001) as compared to the non-responsive group (*Table 2*).

Regional myocardial work parameters

Regarding the regional myocardial work parameters, there were significant differences in CW observed in 9 myocardial segments, including the basal, mid, and apical segments of the anterior, lateral, and posterior walls, between the responsive and non-responsive groups. Similarly, significant differences in WW were observed in 6 segments, including the basal and mid segments of the anterior and posterior septum, as well as the basal and mid segments of the anterior wall. In these segments with significant differences, the responsive group had higher values of CW and WW compared to the non-responsive group before CRT (*Table 3*, *Figure 2*).

In comparison to the non-responsive group, the responsive group exhibited significantly higher values of RCW, RWW, and RCW + RWW before CRT (9,695.68±2,955.40 *vs.* 5,219.50±2,207.68 mmHg%, P<0.001; 3,612.08±1,723.80 *vs.* 1,674.33±995.23 mmHg%, P=0.001; 13,307.76±3,857.71 *vs.* 6,893.83±2,592.83 mmHg%, P<0.001) (*Table 4*).

Correlation analysis of parameters with the change in left ventricular ejection fraction (ΔLVEF)

LVEDV and LVESV demonstrated a negative correlation with ΔLVEF, while the absolute value of GLS, GCW, GWW, GCW + GWW, RCW, RWW, and RCW + RWW exhibited positive correlations (*Table 5*). Notably, RCW + RWW showed the strongest correlation with ΔLVEF, with an R-value of 0.670.

Table 1 Baseline clinical characteristics of patients with responsive and non-responsive groups

Characteristics	Responsive group (n=25)	Non-responsive group (n=12)	P
Age (years)	62.32±10.90	62.92±11.56	0.882
Number of male cases	14 (56)	9 (75)	0.277
Height (cm)	158.76±13.60	164.83±7.36	0.087
Weight (kg)	60.13±14.00	57.46±7.69	0.543
Heart rate (bpm)	74.50±15.79	81.92±14.92	0.184
Systolic blood pressure (mmHg)	117.24±17.88	109.75±13.44	0.208
Diastolic blood pressure (mmHg)	71.48±8.43	66.25±7.19	0.073
NYHA functional classification	2.4±0.82	2.67±0.78	0.352
QRS duration (ms)	155.72±21.27	148.67±16.18	0.216
Number of cases with LBBB	19 (76)	8 (66.7)	0.696
Number of cases with LBBP-CRT	7 (28)	3 (25)	0.421
NT-proBNP level (pg/mL)	4,822.36±5,219.20	4,554.43±4,886.42	0.882
Comorbidities			
Hypertension	9 (36)	2 (17)	0.206
Diabetes	5 (20)	3 (25)	0.738
COPD	2 (8)	1 (8)	0.973
Renal insufficiency	2 (8)	1 (8)	0.973
Ischemic cardiomyopathy	7 (28)	3 (25)	0.853
Medication use			
Digoxin	14 (56)	4 (33)	0.207
Furosemide	22 (88)	10 (83)	0.707
Spironolactone	23 (92)	12 (100)	0.161
Ivabradine	21 (84)	9 (75)	0.352
Entresto	24 (96)	11 (92)	0.597
Beta blockers	17 (68)	10 (83)	0.466

Data are presented as mean ± SD, or number (%). NYHA, New York Heart Association; QRS, ventricular depolarization complex; LBBB, left bundle branch block; LBBP-CRT, left bundle branch pacing cardiac resynchronization therapy; NT-proBNP, N-terminal pro-B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; SD, standard deviation.

ROC curve analysis of parameters for predicting responsiveness to CRT (Table 6)

Among the conventional echocardiographic parameters, the LVEDV cut-off of 218.0 ml was found to predict non-response CRT with a sensitivity of 83.3% and specificity of 72.0% [the area under the ROC curve (AUC) =0.808, P<0.05]. The LVESV cut-off of 192.5 mL was shown to predict non-response CRT with a sensitivity of 75.0% and specificity of 88.0% (AUC =0.835, P<0.05).

In terms of speckle tracking parameters, the GLS absolute value cut-off of 5.5% was shown to predict response to CRT with a sensitivity of 76.0% and specificity of 83.3% (AUC =0.855, P<0.05)

Regarding global myocardial work parameters, the GCW cut-off of 695.5 mmHg% predicted response to CRT with a sensitivity of 68.0% and specificity of 91.7% (AUC =0.870, P<0.05). The GWW cut-off of 272.5 mmHg% predicted response to CRT with a sensitivity of 88.0% and specificity

Table 2 Comparison of myocardial work parameters between responsive and non-responsive groups

Characteristics	Responsive group (n=25)			Non-responsive group (n=12)			P value[a]
	Before CRT	After CRT	P value	Before CRT	After CRT	P value	
GCW (mmHg%)	797.08±226.30	1,622.08±335.31	<0.001	558.08±243.85	736.33.08±281.10	0.092	<0.001
GWW (mmHg%)	393.20±158.52	203.12±87.18	<0.001	286.08±165.20	252.25±66.76	0.475	0.023
GWE (%)	63.63±9.45	88.68±5.48	<0.001	62.83±9.58	69.33±7.56	0.031	0.094
GWI (mmHg%)	492.00±209.12	1,369.84±331.70	<0.001	335.00±210.48	513.42±172.84	0.042	0.009
GCW + GWW (mmHg%)	1,190.28±303.12	1,825.20±349.59	<0.001	844.17±351.73	988.58±317.94	0.255	<0.001

Data are presented as mean ± SD. P value[a], comparison between the two groups before CRT. CRT, cardiac resynchronization therapy; GCW, global constructive work; GWW, global wasted work; GWE, global work efficiency; GWI, global work index; GCW + GWW, the combination of GCW and GWW; SD, standard deviation.

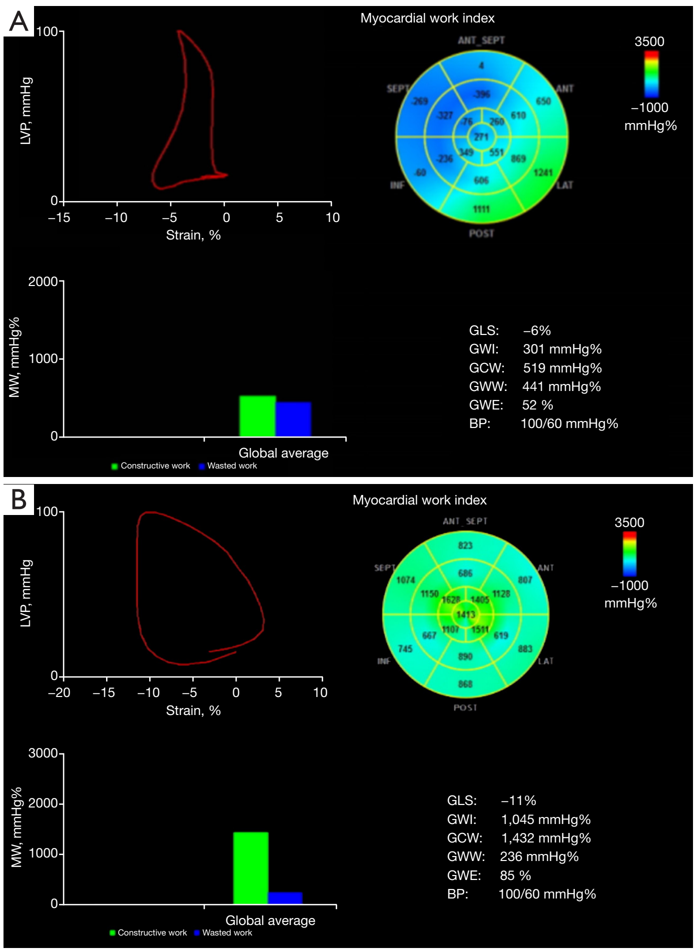

Figure 1 Myocardial work parameters before and 6 months after CRT therapy in a responsive patient. (A,B) Myocardial work parameters before (A) and 6 months after CRT therapy (B) in a responsive patient respectively. The myocardial work bull's eye shows areas of negative work as blue, green indicates normal values. LVP, left ventricular pressure; MW, myocardial work; ANT_SEPT, anteroseptal; ANT, anterior; LAT, lateral; POST, posterior; INF, inferior; SEPT, posteroseptal; GLS, global longitudinal strain; GWI, global work index; GCW, global constructive work; GWW, global wasted work; GWE, global work efficiency; BP, blood pressure; CRT, cardiac resynchronization therapy.

Table 3 Comparison of segmental constructive work and segmental waste work between responsive and non-responsive groups before CRT treatment

Characteristics	Segmental constructive work			Segmental waste work		
	Responsive group (mmHg%)	Non-responsive group (mmHg%)	P	Responsive group (mmHg%)	Non-responsive group (mmHg%)	P
Anterior septum						
Basal segment	237.48±241.50	246.92±182.64	0.905	727.80±472.07	347.58±173.55	0.001*
Mid-segment	364.44±369.38	486.50±269.58	0.315	736.48±531.41	284.92±344.19	0.011*
Apical segment	774.80±513.68	525.58±271.1	0.057	269.80±236.56	233.00±309.65	0.691
Posterior septum						
Basal segment	263.12±238.77	338.08±335.22	0.439	663.48±306.90	308.42±254.23	0.001*
Mid-segment	320.40±279.35	305.75±264.70	0.880	877.52±500.69	433.08±339.10	0.009*
Apical segment	803.56±388.52	785.58±377.64	0.895	431.60±430.21	250.92±470.28	0.254
Anterior wall						
Basal segment	921.84±492.09	505.50±291.50	0.001*	369.32±331.94	209.83±127.03	0.043*
Mid-segment	237.48±225.79	90.50±79.78	0.009*	869.68±444.49	548.00±255.38	0.007*
Apical segment	917.32±432.86	621.75±278.68	0.038*	198.92±134.82	182.58±180.16	0.759
Lateral wall						
Basal segment	1,258.08±462.82	724.17±469.16	0.002*	303.60±250.83	373.25±244.55	0.431
Mid-segment	1,036.96±482.86	446.08±303.04	<0.001*	202.76±168.83	196.92±157.58	0.920
Apical segment	1,120.92±448.87	553.92±389.46	0.001*	145.96±129.28	131.00±142.33	0.752
Posterior wall						
Basal segment	1,505.24±586.19	960.08±403.47	0.006*	335.08±198.73	361.33±405.40	0.791
Mid-segment	1,067.72±568.99	386.00±316.21	<0.001*	287.80±258.77	220.33±126.61	0.401
Apical segment	997.92±462.82	474.00±288.90	0.001*	174.96±165.97	236.25±283.43	0.412
Inferior wall						
Basal segment	547.60±379.44	503.83±333.56	0.735	397.88±248.54	283.25±292.27	0.223
Mid-segment	418.40±300.78	231.83±225.11	0.065	358.84±220.79	295.58±274.13	0.456
Apical segment	959.44±519.43	667.50±334.29	0.085	349.92±259.03	274.58±234.56	0.400

Data are expressed as mean ± SD. *, P<0.05. CRT, cardiac resynchronization therapy; SD, standard deviation.

of 75.0% (AUC =0.770, P<0.05). The GCW + GWW cut-off of 1,113.5 mmHg% predicted response to CRT with a sensitivity of 60.0% and specificity of 100.0% (AUC =0.860, P<0.05).

As for regional myocardial work parameters, the RCW cut-off of 8,204.0 mmHg% predicted response to CRT with a sensitivity of 68.0% and specificity of 100.0% (AUC =0.890, P<0.05). The RWW cut-off of 2,170.0 mmHg% predicted response to CRT with a sensitivity of 83.3% and specificity of 92.0% (AUC =0.870, P<0.05). The RCW + RWW cut-off of 10,534.0 mmHg% predicted response to CRT with a sensitivity of 80.0% and specificity of 92.0% (AUC =0.910, P<0.05).

Remarkably, RCW + RWW exhibited the highest AUC of 0.910, while both GCW + GWW and RCW demonstrated a specificity of 100% in predicting CRT responsiveness.

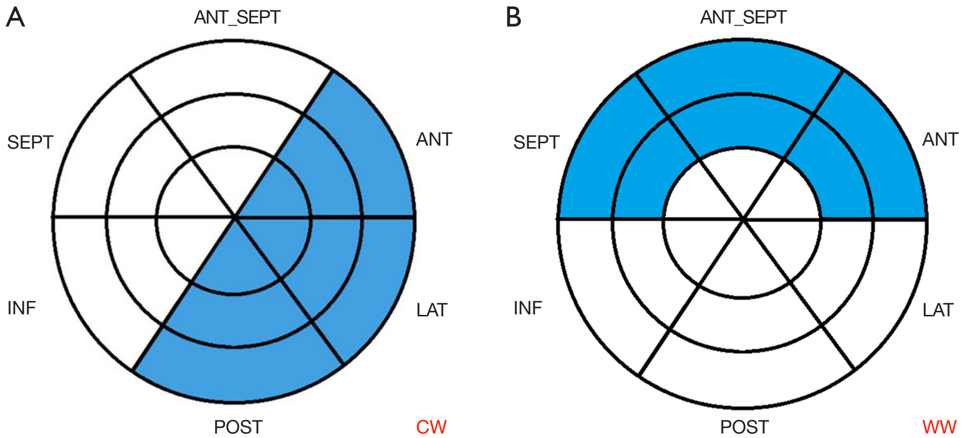

Figure 2 Illustrates the variations in myocardial work of left ventricular segments between the CRT responsive and non-responsive groups prior to CRT treatment. (A,B) CW and WW respectively. The blue color indicates statistically significant difference with the responsive group being greater than the non-responsive group before CRT treatment. ANT_SEPT, anteroseptal; ANT, anterior; LAT, lateral; POST, posterior; INF, inferior; SEPT, posteroseptal; CW, constructive work; WW, wasted work; CRT, cardiac resynchronization therapy.

Table 4 Comparison of regional myocardial work parameters between responsive and non-responsive groups before CRT

Characteristics	Responsive group (n=25)	Non-responsive group (n=12)	P
RCW (mmHg%)	9,695.68±2,955.40	5,219.50±2,207.68	<0.001
RWW (mmHg%)	3,612.08±1,723.80	1,674.33±995.23	0.001
RCW + RWW (mmHg%)	13,307.76±3,857.71	6,893.83±2,592.83	<0.001

Data are expressed as mean ± SD. CRT, cardiac resynchronization therapy; RCW, cumulative segmental useful work of the basal, mid, and apical segments of the anterior wall, lateral wall, and posterior wall (9 segments in total); RWW, cumulative wasted work of the basal and mid segments of the anterior and posterior septum, and basal segment of the anterior wall (6 segments in total); RCW + RWW, the combination of RCW and RWW; SD, standard deviation.

Table 5 The correlation analysis between various parameters and ΔLVEF

Characteristics	r	P
LVEDV (mL)	–0.538	0.001
LVESV (mL)	–0.528	0.001
|GLS| (%)	0.509	0.001
GCW (mmHg%)	0.535	0.001
GWW (mmHg%)	0.432	0.001
GCW + GWW (mmHg%)	0.592	<0.001
RCW (mmHg%)	0.630	<0.001
RWW (mmHg%)	0.544	<0.001
RCW + RWW (mmHg%)	0.670	<0.001

ΔLVEF, the change in left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; |GLS|, absolute value of global longitudinal strain; GCW, global constructive work; GWW, global wasted work; GCW + GWW, the combination of GCW and GWW; RCW, cumulative segmental useful work of the basal, mid, and apical segments of the anterior wall, lateral wall, and posterior wall (9 segments in total); RWW, cumulative wasted work of the basal and mid segments of the anterior and posterior septum, and basal segment of the anterior wall (6 segments in total); RCW + RWW, the combination of RCW and RWW.

Table 6 ROC curve analysis of parameters for predicting responsiveness to CRT

Characteristics	AUC	Cut-off value	Sensitivity (%)	Specificity (%)
LVEDV	0.808	218.0 mL	83.3	72.0
LVESV	0.835	192.5 mL	75.0	88.0
|GLS|	0.855	5.5%	76.0	83.3
GCW	0.870	695.5 mmHg%	68.0	91.7
GWW	0.770	272.5 mmHg%	88.0	75.0
GCW + GWW	0.860	1,113.5 mmHg%	60.0	100.0
RCW	0.890	8,204.0 mmHg%	68.0	100.0
RWW	0.870	2,170.0 mmHg%	83.3	92.0
RCW + RWW	0.910	10,534.0 mmHg%	80.0	92.0

ROC, receiver operating characteristic; CRT, cardiac resynchronization therapy; AUC, area under the ROC curve; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; |GLS|, absolute value of global longitudinal strain; GCW, global constructive work; GWW, global wasted work; GCW + GWW, the Combination of GCW and GWW; RCW, cumulative segmental useful work of the basal, mid, and apical segments of the anterior wall, lateral wall, and posterior wall (9 segments in total); RWW, cumulative wasted work of the basal and mid segments of the anterior and posterior septum, and basal segment of the anterior wall (6 segments in total); RCW + RWW, the combination of RCW and RWW.

Intra- and inter-observer variability

Reproducibility and reliability analysis of myocardial work parameters were conducted prior to CRT. Intra-observer consistency was assessed by randomly selecting 12 samples and having the same experienced sonographer with over 5 years of experience to analyze the myocardial work parameters [global work index (GWI), GCW, GWW, and global work efficiency (GWE)] using the same methodology after a 2-week interval. The intra-class correlation coefficient (ICC) was 0.967, 0.952, 0.969, and 0.954, respectively, all significant at $P<0.05$. Inter-observer agreement was assessed by another cardiologist with over 5 years of experience in the field of echocardiography, who independently analyzed the myocardial work parameters (GWI, GCW, GWW, and GWE) for the same set of 12 samples. The interclass correlation coefficients (ICC) between the observers were found to be 0.964, 0.944, 0.947, and 0.948 for GWI, GCW, GWW, and GWE, respectively, all of which were statistically significant with a P value less than 0.05. According to the commonly accepted criteria, an ICC value of ≥0.75 indicates excellent agreement between observers, while values between 0.75 and 0.4 indicate relatively good agreement. ICC values less than 0.4 suggest a lower level of agreement between observers.

Discussion

Principles and effects of CRT in HF treatment

The 2021 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic HF recommends CRT as a Class I, Level A therapy for patients with HF who meet specific criteria, including sinus rhythm, LBBB, QRS duration ≥150 ms, and LVEF ≤35% (12). However, it is important to note that despite the guideline recommendations, a significant proportion of patients (30–40%) do not experience improved cardiac function or may even worsen after CRT, which is commonly referred to as non-response to CRT (4-6). This highlights the existing limitations in the current selection criteria for CRT and underscores the need to identify reliable predictors of CRT responsiveness. Identifying such predictors would enable the screening of patients who are more likely to benefit from CRT, leading to improved quality of life, alleviation of clinical symptoms, and better prognosis for HF patients.

Parameters for predicting CRT efficacy and their potential mechanisms

Previous studies have shown mixed results in predicting

CRT response in gender, non-ischemic cardiomyopathy, QRS duration, Mechanical Dyssynchrony index (YU index) and Septal to Posterior Wall Motion Delay (SPWMD) etc. (2,3,16-19). In this study, no significant differences were observed between the two groups in terms of these conventional parameters. However, we observed that the responsive group had smaller preoperative LVEDV and LVESV compared to the non-responsive group, which is in line with previous studies by Gasparini *et al.* (18,19). The smaller LVEDV and LVESV before CRT indicate an earlier stage of HF with less myocardial fibrosis and ventricular remodeling. Consequently, the benefits derived from correcting ventricular systolic dyssynchrony through CRT are more prominent in these patients. GLS has been recognized as sensitive and reliable parameters for assessing subclinical myocardial injury (20,21). In this study, the absolute value of GLS before operation in the responsive group was higher than that in the non-responsive group. This suggests that patients with better overall systolic function and greater potential for improvement in ventricular dyssynchrony may derive greater benefits from CRT.

Myocardial work parameters

Cardiac work technology is an emerging method based on speckle tracking imaging (STI) that aims to evaluate the coordination of left ventricular motion and assess left ventricular function. This innovative technique enables the quantification of myocardial work at both regional and global levels throughout the cardiac cycle, offering a sensitive and early detection of myocardial mechanical changes (7-11). Notably, previous studies have predominantly focused on global parameters, with findings suggesting that patients with higher values of GWW may have a greater likelihood of benefiting from CRT, as observed by Vecera *et al.* (10). Similarly, Galli *et al.* (22) identified GCW as an independent predictor of CRT response. Left ventricular regional mechanical nonuniformity is one of the important causes of HF. However, these investigations primarily focused on overall parameters and lacked a comprehensive assessment of regional myocardial contraction. Consequently, exploring parameters related to regional cardiac work may serve to complement existing knowledge and enhance our understanding of predicting CRT efficacy.

In our study, we observed significant differences between the response and non-response groups in terms of both global and regional myocardial work parameters. Specifically, the response group exhibited larger values of preoperative GCW, GWW, and GCW + GWW compared to the non-response group. These parameters were positively correlated with ΔLVEF and served as predictive factors for CRT response. When analyzing regional myocardial work parameters, we found that there were significant differences in CW among various segments, particularly in the basal, mid-ventricular, and apical regions of the anterior, lateral, and posterior walls. Additionally, WW demonstrated differences primarily in the basal and mid-ventricular regions of the anterior and posterior septum. Previous studies have shown that in presence of dyssynchrony and wide QRS complex with LBBB, LV lateral region is activated with delay and systole can partially occur after AVC. But there was no significant difference in waste work of the lateral wall (before CRT treatment) between the non-responsive group and the responsive group in the study. This is because the AVC marks the beginning of left ventricular diastole, which includes the left ventricular isovolumetric relaxation period and the left ventricular filling period. The left ventricular filling phase occupies a large proportion of the left ventricular diastolic phase. At this point, the contraction of the left ventricular lateral region occurring after AVC is likely to overlap with the left ventricular filling phase. However, due to the inability to non-invasively obtain left ventricular end-diastolic pressure, the myocardial work, including waste work, during the left ventricular filling phase can not be evaluated. This is also a limitation in assessing myocardial work. In these segments with notable differences, the response group had higher values of CW and WW compared to the non-response group. Furthermore, RCW, RWW, and RCW + RWW also exhibited a positive correlation with ΔLVEF and served as predictive factors for CRT response. These findings suggest that both global and regional myocardial work parameters play a crucial role in predicting the response to CRT. By evaluating the overall and local myocardial function, these parameters provide valuable insights into the potential effectiveness of CRT and offer a more comprehensive assessment of cardiac performance. A newly published article indicates that patients with non-LBBB have low responsiveness to CRT, and speckle tracking techniques may be beneficial in the evaluation of such patients; besides, it suggests that combining electrocardiographic and echocardiographic parameters may help improve the prediction of responsiveness to CRT (23). Due to sample size limitations, non-LBBB patients were not analyzed separately in the study. We hope to have the opportunity for future research involving this subgroup of patients. ECG provides valuable information about electrical dyssynchrony, while echocardiography offers insights into mechanical dyssynchrony and myocardial function. Integrating these modalities provides a holistic view of the patient's condition. While the concept is promising, further research is needed to validate the efficacy and feasibility of this multiparametric approach in clinical practice. Other studies have also been conducted to assess CRT responsiveness. A previous study suggest that Ryanodine Receptor1 glycation >30% was identified as the optimum cut-off (maximum Youden's index) to predict a negative response to CRT (24). In terms of molecular cytography, a study has shown that miR-18, miR-145 and miR-181 play a role in adverse cardiac remodeling response to CRTd (25). Large-scale studies evaluating its predictive value and impact on patient outcomes are necessary to establish its utility and integration into routine CRT evaluation protocols. It has been suggested that the multipolar LV-pacing could increase the CRT response in high-risk patients as those with diabetes mellitus (26). Among the patients we enrolled, there were 17 patients with left bundle branch pacing, The remaining 20 patients were multipolar LV-pacing leads. Therefore, we have no further analysis and discussion in this paper. All patients in the responsive group showed an increase in LVEF exceeding 15%, which was identified as a criterion for CRT response in literature (27). In our study, we defined a reduction in LVESV greater than 15% as a criterion for response. We primarily observed changes in echocardiographic indices in the paper, thus not paying much attention to other clinical indicators.

CRT primarily works by synchronizing the contraction of the left and right ventricles as well as the intraventricular contraction to improve heart function. Aalen *et al.* (28) have previously proposed that the asymmetric loading between the left ventricular lateral wall and the interventricular septum could serve as an independent predictor of CRT response. In terms of global myocardial work parameters, we can reasonably infer that patients with a larger preoperative GCW have preserved stronger contractile capacity in their myocardium, allowing them to benefit more from CRT by maximizing their contraction potential. Conversely, GWW reflects the additional burden during cardiac systole and diastole, indicating a more severe cardiac dyssynchrony. Therefore, patients with higher preoperative GWW are more likely to benefit from CRT by improving systolic dyssynchrony. Similarly, by focusing on specific regions such as the anterior and lateral walls, which contribute significantly to left ventricular ejection, and considering areas like the anterior and posterior septum that better represent dyssynchrony, we can gain insights into how regional myocardial work parameters predict CRT responsiveness. The increase in RWW and RCW means that the left ventricular myocardia in the region have certain ability of contraction and diastole, but the timing is not appropriate. CRT can improve cardiac function by adjusting the timing of left ventricular contraction and diastole in this area, thereby improving left ventricular contraction and diastole coordination. By considering both global and regional myocardial work parameters, we can gain a better understanding of the underlying mechanisms of CRT response and tailor the treatment to individual patients, leading to improved outcomes.

Limitations

There is no uniform standard for the time point to determine whether CRT has a response. Previous literature has used time points of 6 months and 1 year. This study adopts the commonly used 6-month time point. Extending the follow-up period of this study may lead to more discoveries. It is important to acknowledge that this study was conducted at a single center with a limited sample size. Therefore, the generalizability of the findings may be limited. Further researches involving larger and more diverse populations, as well as multi-center studies, are warranted to confirm and extend these observations.

Conclusions

The global and regional myocardial work parameters are associated with CRT response in CRT candidates. Particularly regional myocardial work parameters appear to be promising parameters to improve selection for CRT of patients with HFrEF.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-24-393/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-393/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Institution Review Board of Sun Yat-sen Memorial Hospital (No. 2019-KY-056). Written informed consent was obtained from all participants.

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