



# The value of non-invasive myocardial work indices derived from left ventricular pressure-strain loops in predicting the response to cardiac resynchronization therapy

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**Background:** Non-invasive left ventricular (LV) pressure-strain loops (PSLs), which are generated by combining LV longitudinal strain with brachial artery blood pressure, provide a novel method of quantifying global and segmental myocardial work (MW) indices with potential advantages over conventional echocardiographic strain data, which suffers from being load-dependent. This method has been recently introduced in echocardiographic software, enhancing the efficiency of MW calculations. This study aimed to evaluate the role of non-invasive MW indices derived from LV PSLs in predicting cardiac resynchronization therapy (CRT) response.

**Methods:** A total of 106 heart failure (HF) patients scheduled for CRT were included in the MW analysis. Global and segmental (septal and lateral at the mid-ventricular level) MW indices were assessed before CRT and at a 6-month follow-up. Response to CRT was defined as  $\geq 15\%$  reduction in LV end-systolic volume and  $\geq 1$  NYHA functional class improvement at 6-month follow-up compared to baseline.

**Results:** CRT response was observed in 78 (74%) patients. At baseline, the global work index (GWI) and global constructive work (GCW) were significantly higher in CRT responders than in non-responders (both  $P < 0.05$ ). Furthermore, responders exhibited significantly higher mid lateral MW and mid lateral constructive work (CW) (both  $P < 0.001$ ), but significantly lower mid septal MWI and mid septal myocardial work efficiency (MWE) than non-responders (all  $P < 0.01$ ). Baseline mid septal MWE (OR 0.975, 95% CI: 0.959–0.990,  $P = 0.002$ ) and mid lateral MWI (OR 1.003, 95% CI: 1.002–1.004,  $P < 0.001$ ) were identified as independent predictors of CRT response in multivariate regression analysis. Mid septal MWE  $\leq 42\%$  combined with mid lateral MWI  $\geq 740$  mmHg% predicted CRT response, with an optimal sensitivity of 79% and specificity of 82% [area under the receiver operating characteristic curve (AUC) = 0.830,  $P < 0.001$ ].

**Conclusions:** Assessment of MW indices before CRT could identify the marked imbalance in LV MW distribution and can be widely used as a reliable complementary tool for guiding patient selection for CRT in clinical practice.

**Keywords:** Cardiac resynchronization therapy (CRT); myocardial work; non-invasive; pressure-strain loop; segmental heterogeneity

Submitted Jun 13, 2020. Accepted for publication Nov 13, 2020.

doi: 10.21037/qims-20-754

View this article at: <http://dx.doi.org/10.21037/qims-20-754>

## Introduction

Cardiac resynchronization therapy (CRT) is a well-established treatment for symptomatic patients with dyssynchronous heart failure (HF) (1); however, nearly 30% of patients undergoing CRT do not respond favorably to therapy (2). As strain suffers from being load-dependent (3,4), its application is limited in this special HF population characterized by left ventricular (LV) dyssynchrony, as early and late activated segments contract at different times in different loading states. LV dyssynchrony is mainly associated with marked imbalance in segmental myocardial work (MW) distribution. Therefore, analysis of global and segmental MW may provide novel insights into the cardiac mechanics of patients with dyssynchronous HF, and may be useful for guiding patient selection for CRT. The MW derived from invasive LV pressure-volume/strain loops measured during coronary angiography have been developed for many years. Nevertheless, its invasive nature limits its widespread use in clinical practice.

Recently, a new non-invasive approach to evaluate MW was introduced in echocardiographic software. MW augments speckle tracking echocardiography by taking dynamic LV pressure into account, which further facilitates the interpretation of LV longitudinal strain (LS) traces concerning LV pressure dynamics by providing excellent visualization of pressure-strain loops (PSLs). It also adds an important dimension to the evaluation of LV function. The inclusion of afterload data in the assessment of myocardial performance has the advantage of limiting the variability induced by loading status (5). Both animal experiments and clinical studies have demonstrated the validity of this method (6,7).

The present study aimed to explore the role of baseline MW indices derived from non-invasive LV PSLs in the prediction of CRT response and to evaluate the changes in MW indices at follow-up after CRT.

## Methods

### *Study population*

A total of 106 consecutive HF patients who were first scheduled for CRT were retrospectively recruited from August 2018 to May 2019. The indication for CRT based on the 2016 European Society of Cardiology (ESC) guidelines (8) were as follows: symptomatic HF patients in sinus rhythm with a QRS duration  $\geq 130$  ms and left ventricular ejection fraction (LVEF)  $\leq 35\%$ , and New

York Heart Association (NYHA) functional class II-IV despite optimal medical treatment. Patients were excluded from the study for the following reasons: LV outflow tract obstruction (for example, obstructive hypertrophic cardiomyopathy), aortic stenosis, prosthetic aortic valve replacement, and any other cardiac pathologies that could induce a pressure gradient between the aorta and the LV, atrial fibrillation, narrow QRS, a history of acute myocardial infarction or cardiac surgery, absence of clinical follow-up, and/or poor echocardiographic image quality. MW analysis was feasible in 98% of patients, and only 2 patients were excluded for incomplete MW analysis due to acquisition with inadequate imaging quality. Left bundle branch block (LBBB) was diagnosed according to the criteria proposed by the 2013 ESC guidelines (9) of the Class 1 Recommendation for CRT, namely, a wide QRS duration with QS or rS in V1, broad (frequently notched or slurred) R wave in leads I, aVL, V5, or V6, and absence of q waves in leads V5 and V6.

All HF patients, being on stable and optimal medical treatment according to the ESC guidelines (8), underwent baseline and 6-month follow-up evaluations. Response to CRT was defined as a reduction of left ventricular end-systolic volume (LVESV)  $\geq 15\%$  and  $\geq 1$  NYHA functional class improvement at the 6-month follow-up (10,11). All responders at the 6-month follow-up satisfied 2 conditions simultaneously: a reduction of LVESV  $\geq 15\%$  and  $\geq 1$  NYHA functional class improvement. Patients were classified as non-responders at follow-up after CRT if they showed no improvement in NYHA functional class, were re-hospitalized, underwent cardiac transplantation, had worsening HF, or died.

### *Echocardiographic acquisition*

With a synchronous ECG connected, all patients underwent standard transthoracic echocardiography using a Vivid E9 or E95 ultrasound system (GE Healthcare, Horten, Norway) equipped with a 3S or M5S transducer. Non-invasive cuff blood pressure values were measured and recorded with brachial artery sphygmomanometry immediately before echocardiography. The following parameters were obtained according to the American Society of Echocardiography guidelines (12,13): (I) left ventricular end-diastolic volume (LVEDV); (II) LVESV; (III) LVEF measured using biplane Simpson's method; (IV) interventricular mechanical delay (IVMD); (V) septal-posterior wall motion delay (SPWMD); and (VI) Yu index.

### Offline MW analysis

Standard two-dimensional apical views (long-axis, four-chamber, and two-chamber) acquired with at least 60 frames per second were digitized during 5 consecutive cardiac cycles in cine-loop format. Views were imported to the dedicated workstation (EchoPAC Version 203, GE Vingmed Ultrasound) for the offline analysis using a vendor-specific module within the Automated Function Imaging (AFI) software.

Following the identification of the timing points of the aortic and mitral valve opening and closure using pulsed-wave Doppler recordings in the LV outflow and inflow tract, speckle tracking analysis was performed using 3 standard apical views (long-axis, four-chamber, and two-chamber). The software presented the results of segmental and global LS. Global longitudinal strain (GLS) was calculated from the weighted average of the peak systolic LS of all LV segments. Mechanical dispersion (MD) was calculated as the standard deviation of the time to peak systolic LS of the 17 LV segments.

After strain analysis was completed, the “Myocardial Work” module in AFI was selected to continue the MW analysis. LV strain and systolic blood pressure data were then synchronized through the alignment of valvular timing events, and the software generated global and segmental PSLs automatically. The loop area served as an index of global and segmental MW, namely, the myocardial work index (MWI).

Work was evaluated from mitral valve closure to the mitral valve opening, or in other words, mechanical systole, including isovolumetric relaxation (IVR). During the LV ejection period, MW performed during segmental shortening represented constructive work (CW) of that segment, whereas work performed by the myocardium during segmental elongation represented energy loss, which was defined as wasted work (WW) of that segment. During IVR, this definition was reversed, such that MW during shortening was considered segmental WW, and work during lengthening was considered segmental CW. LV global work index (GWI), global constructive work (GCW), and global wasted work (GWW) were calculated as the average of all segmental values. LV global work efficiency (GWE) was calculated as the sum of CW in all LV segments, divided by the sum of CW and WW in all LV segments, expressed as a percentage. A bull’s eye using the 17-segment model with the values of the segmental MWI and myocardial work efficiency (MWE) was provided (*Figure 1*).

Segmental MWI was calculated for each LV segment as the difference between the work performed during the shortening of the segment and the work performed during the segment’s elongation. Also, a set of values of segmental MW additional indices were provided and could be exported from the software:

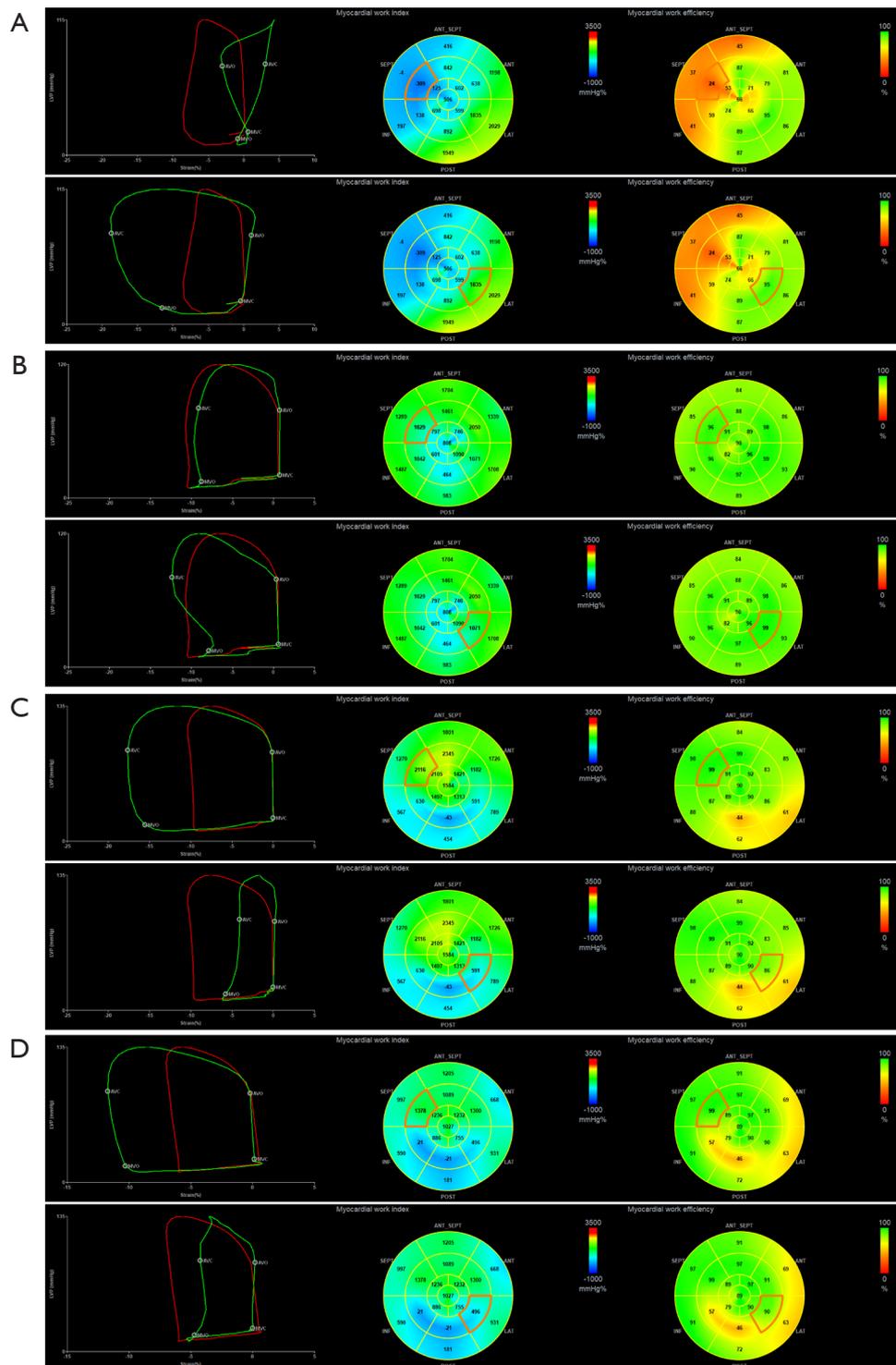
- ❖ CW was defined as work performed by a segment during shortening in systole adding negative work during IVR lengthening.
- ❖ WW was defined as negative work performed by a segment during lengthening in systole adding work performed during shortening in IVR. Although a negative number by definition, WW was presented as a positive number.
- ❖ MWE was defined as the ratio between CW and the sum of CW and WW measured at each segment  $[CW/(CW + WW)]$ , expressed as a percentage.

### Inter- and intra-observer variability

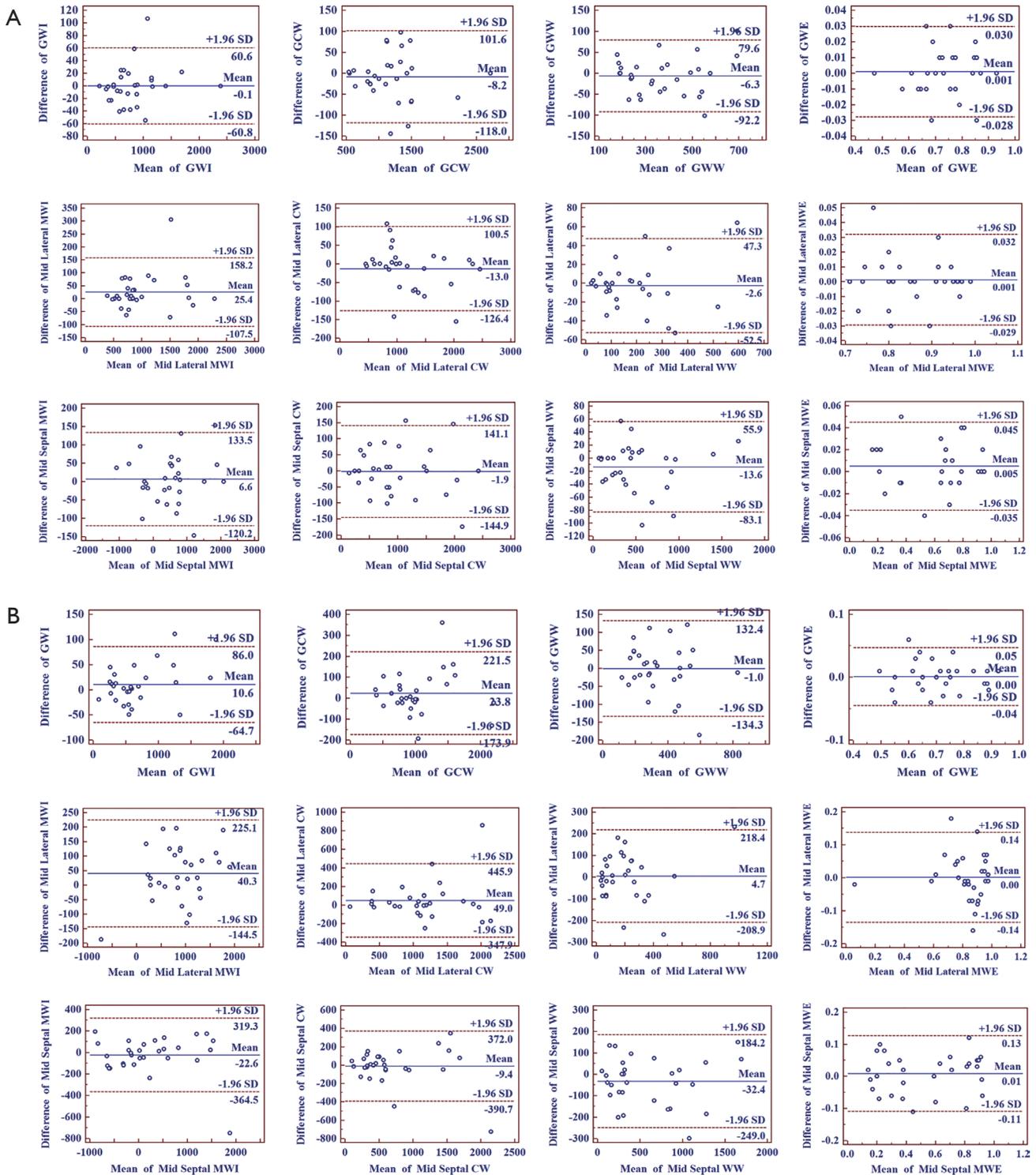
Inter- and intra-observer variability of MW indices was assessed using Bland-Altman plots (*Figure 2*) with data from 30 randomly selected patients. Data was examined twice by one observer who was blinded to the results of the previous measurements, and by a second observer who was blinded to the values obtained by the first observer, respectively.

### Statistical analysis

Continuous data were presented as mean  $\pm$  standard deviation, and dichotomous data were presented as numbers and percentages. Comparisons of continuous variables between responders and non-responders were carried out using the independent-samples t-test, while intragroup comparisons were performed using the paired-samples t-test. Categorical variables were compared using Chi-square tests or Fisher’s exact tests when appropriate. Correlations between two continuous variables were analyzed using Pearson’s correlation coefficient test. Binary logistic regression analysis was employed to determine the independent predictors of CRT response. The prediction accuracy assessment was conducted by constructing a receiver operating characteristic (ROC) curve. A two-sided P value  $<0.05$  was accepted as indicating statistical significance. All analyses were performed with SPSS version 24.0 (SPSS Inc., IBM, Chicago, IL, USA) and MedCalc version 12.5.0.0 (MedCalc Software, Mariakerke, Belgium).



**Figure 1** LV PSLs (left), MWI (middle), and MWE (right) of individual examples from CRT responders and non-responders before CRT and at 6-month follow-up after CRT. (A) A CRT responder before CRT; (B) a CRT responder at 6-month follow-up after CRT; (C) a CRT non-responder before CRT; (D) a CRT non-responder at 6-month follow-up after CRT. LV, left ventricular; PSL, pressure-strain loop; MWE, myocardial work efficiency; MWI, myocardial work index; CRT, cardiac resynchronization therapy.



**Figure 2** Bland-Altman analysis for intra-observer variability (A) and inter-observer variability (B) of MW indices. Solid line represents bias, and dotted lines represent 95% limits of agreement for measurements performed in 30 patients. Bias was assessed by the mean of 30 differences of 2 measurements. The 95% CI: was calculated as  $\pm 1.96$  SD from the mean. CI, confidence interval; CW, constructive work; GCW, global constructive work; GWE, global work efficiency; GWI, global work index; GWW, global wasted work; MW, myocardial work; MWE, myocardial work efficiency; MWI, myocardial work index; SD, standard deviation; WW, wasted work.

**Table 1** Baseline clinical characteristics of CRT responders versus non-responders

Variable	Responders (n=78)	Non-responders (n=28)	P
Age (years)	63.29±10.76	59±12.21	0.085
Gender, female	27 (35%)	6 (21%)	0.196
NYHA functional class			
II	19 (24%)	4 (13%)	0.400
III	51 (65%)	15 (54%)	0.269
IV	8 (10%)	9 (32%)	0.007
HF duration (years)	4.41±4.64	6.16±4.13	0.082
LBBB morphology	69 (89%)	20 (71%)	0.035
Ischemic etiology	8 (10%)	5 (18%)	0.293
Coronary artery disease	31 (40%)	7 (25%)	0.163
Hypertension	39 (50%)	11 (39%)	0.330
Diabetes	22 (28%)	6 (21%)	0.485
Renal insufficiency	8 (10%)	4 (14%)	0.818
Medication			
ACEI/ARBs	72 (92%)	27 (96%)	0.757
Beta-blockers	71 (91%)	27 (96%)	0.609
Diuretics and/or spironolactone	75 (96%)	27 (96%)	1.000
Serum biomarkers			
NT-proBNP (pg/mL)	2,891.75±3,840.21	3,477.61±2,547.57	0.456
cTnT (ng/mL)	0.06±0.15	0.04±0.03	0.402
CK-MB (U/L)	13.08±4.43	14.75±13.78	0.565
CK-MM (U/L)	74.24±55.43	57.87±54.39	0.227
Cre (μmol/L)	106.11±103.98	99.88±39.1	0.767
Uric acid (μmol/L)	439.19±127.22	471.85±140.16	0.280
hs CRP (mg/L)	7.41±14.34	7.94±21.47	0.895

Data are expressed as mean ± standard deviation or number (%). ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CK-MB, creatine kinase MB fraction; CK-MM, creatine kinase MM fraction; Cre, creatinine; CRT, cardiac resynchronization therapy; cTnT, cardiac troponin T; HF, heart failure; hs CRP, high-sensitive C-reactive protein; LBBB, Left bundle branch block; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide; NYHA, New York Heart Association.

## Results

### *Baseline evaluation and changes at follow-up*

At 6-month follow-up, CRT response was found in 78 (74%) patients, while the other 28 (26%) patients were classified as non-responders. Baseline clinical characteristics from the overall population are summarized in *Table 1* based on CRT response. No significant differences in general clinical

characteristics were observed between CRT responders and non-responders, except patients in NYHA functional class IV were more likely to be non-responders ( $P=0.007$ ), and LBBB was more prevalent in CRT responders ( $P=0.035$ ). Comparisons of other characteristics between CRT responders and non-responders at baseline and at follow-up are shown in *Table 2*.

At baseline evaluation, CRT responders showed

**Table 2** Comparisons between CRT responders and non-responders at baseline and at follow-up

Variable	Baseline		Follow-up		Baseline versus follow-up		
	Responders (n=78)	Non-responders (n=28)	P value	Responders (n=78)	Non-responders (n=28)	P value (responders)	P value (non-responders)
SBP (mmHg)	118.6±14.81	115.14±15.08	0.294	123.76±14.46	112.32±16.5	0.001	0.212
DBP (mmHg)	74.92±8.31	70.25±9.74	0.017	79.55±7.88	71.11±10.29	0.000	0.621
Heart rate (beats/min)	73.99±13.05	72.14±21.1	0.667	69.14±10.55	70.93±15.19	0.498	0.712
QRS duration (ms)	166.26±24.1	155.67±24.53	0.088	128.46±25.41	123.71±30.22	0.487	0.000
Conventional echocardiographic data							
Mitral regurgitation grade	2.6±0.77	2.71±0.8	0.492	1.65±0.73	2.57±1.07	0.000	0.310
LVEDV (mL)	219.26±76.77	300.18±120.72	0.002	140.97±63.72	289.11±122.49	0.000	0.143
LVESV (mL)	162.59±66.49	230.57±100.96	0.002	79.33±48.69	222.14±104.24	0.000	0.145
LVEF (%)	26.87±7.31	24.39±8.97	0.151	46.63±9.67	24.11±8.58	0.000	0.827
IVMD (ms)	64.88±23.1	43.43±32.98	0.000	39.83±28.52	34.82±34.73	0.454	0.248
SPWMD (ms)	72.14±115.24	71.82±132.92	0.990	16.41±85.75	33.39±100.26	0.392	0.189
Yu index (ms)	55.79±22.57	60.96±21.7	0.303	55.29±20.31	64.14±26.82	0.073	0.743
GLS (%)	-6.91±2.27	-5.48±2.73	0.008	-10.37±3.34	-5.41±2.33	0.000	0.882
MD (ms)	129.96±38.93	139.93±39.59	0.250	76.71±29.98	116.11±46.53	0.000	0.023
Mid lateral LS (%)	-9.92±5.22	-5.18±4.09	0.000	-9.99±5.95	-4.25±6.35	0.000	0.409
Mid septal LS (%)	-2.45±6.34	-4.11±5.21	0.179	-9.74±5.07	-3.75±4.73	0.000	0.641
Myocardial work							
GWl (mmHg%)	581.56±287.35	424.54±349.77	0.021	1,134.67±482.33	444.61±308.45	0.000	0.663
GCW (mmHg%)	930.51±340.5	740.54±363.58	0.014	1,511.74±483.3	733.89±311.75	0.000	0.906
GWW (mmHg%)	378.82±144.5	323.18±177.72	0.104	341.73±172.73	309.57±175.78	0.402	0.655
GWE (%)	68±9	66±10	0.366	80±9	69±11	0.000	0.284
Mid lateral MWI (mmHg%)	1,056.74±479.37	565±339.51	0.000	1,140.55±573.07	469.32±527.21	0.000	0.252
Mid lateral CW (mmHg%)	1,284.86±566.05	742.32±400.39	0.000	1,388.82±558.88	687.36±437.68	0.000	0.477
Mid lateral WW (mmHg%)	190.25±162.9	154.61±107.27	0.285	208.29±266.02	225.61±309.23	0.778	0.221
Mid lateral MWE (%)	84.12±15.84	81.18±10.65	0.366	85.76±14.24	74.75±26.66	0.045	0.164
Mid septal MWI (mmHg%)	-200.71±431.21	123.79±548.31	0.002	1,004.33±572.74	272.18±557.08	0.000	0.075

**Table 2** (continued)

Table 2 (continued)

Variable	Baseline		Follow-up		Baseline versus follow-up	
	Responders (n=78)	Non-responders (n=28)	Responders (n=78)	Non-responders (n=28)	P value (responders)	P value (non-responders)
Mid septal CW (mmHg%)	452.58±290.18	523.61±486.88	1,324.4±578.45	561.32±525.74	0.000	0.560
Mid septal WW (mmHg%)	845.35±426.6	436.21±352.16	278.36±234.62	303.89±274.22	0.000	0.022
Mid septal MWE (%)	35.97±20.28	52.82±25.17	81.21±14.95	61.57±25.29	0.000	0.126

Data are expressed as mean ± standard deviation. CRT, cardiac resynchronization therapy; CW, constructive work; DBP, diastolic blood pressure; GCW, global constructive work; GLS, global longitudinal strain; GWE, global work efficiency; GWI, global work index; GWW, global wasted work; IVM, interventricular mechanical delay; LS, longitudinal strain; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MD, mechanical dispersion; MW, myocardial work; MWE, myocardial work efficiency; MWI, myocardial work index; SBP, systolic blood pressure; SPWMD, septal-posterior wall motion delay; WW, wasted work; Yu index, the standard deviation of time from QRS to peak systolic velocity in ejection phase for 12 LV segments.

significantly higher diastolic blood pressure (P=0.017), smaller LVEDV and LVESV (both P=0.002), as well as larger IVMD, GLS, and mid lateral LS (all P<0.01). Concerning MW indices, GWI and GCW were significantly higher in CRT responders than in non-responders (both P<0.05). Also, CRT responders exhibited significantly higher mid lateral MWI and mid lateral CW (both P<0.001), but significantly lower mid septal MWI and mid septal MWE than non-responders (both P<0.01). At 6-month follow-up, significant improvements in mid septal MWI, mid septal CW, and mid septal MWE (all P<0.001), as well as a significant reduction in mid septal WW (P<0.001) were observed in CRT responders, accompanied by significant improvements in GWI, GCW, and GWE (all P<0.001).

**Correlations between advanced MW indices and conventional echocardiographic parameters**

The increased values of global MW indices (ΔGWI, ΔGCW, and ΔGWE) and mid septal MW indices (Δmid septal MWI, Δmid septal CW, and Δmid septal MWE) at 6-month follow-up were significantly correlated with improvements in the magnitudes of conventional echocardiographic parameters (ΔLVESV%, ΔLVEF, and ΔGLS, all P<0.001, Table 3).

Also, the improved values of global MW indices (ΔGWI and ΔGCW) at 6-month follow-up showed good correlations with the increased magnitudes of corresponding mid septal MW indices (Δmid septal MWI and Δmid septal CW, r=0.772 and r=0.789, respectively, both P<0.001, Figure 3).

**Analyses to identify baseline predictors of response to CRT**

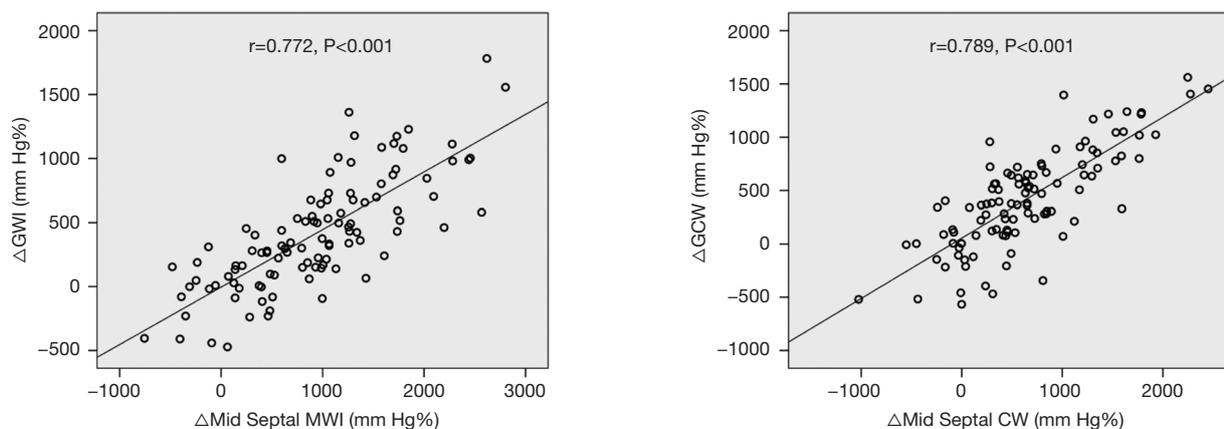
Logistic regression analysis was performed to identify the independent predictors of response to CRT (Table 4). All variables significantly associated with CRT response in the univariate analysis were involved in the multivariate logistic regression analysis. In the multivariate analysis, baseline mid septal MWE [odds ratio (OR) 0.975, 95% confidence interval (CI): 0.959–0.990, P=0.002] and mid lateral MWI (OR 1.003, 95% CI: 1.002–1.004, P<0.001) were identified as independent predictors of response to CRT.

ROC analysis identified the optimal cutoff value of mid septal MWE as 40% [sensitivity, 71%; specificity, 71%; area under the ROC curve (AUC) =0.713, P<0.001] and the optimal cutoff value of mid lateral MWI as 634 mmHg%

**Table 3** Correlations between changes in myocardial work indices and changes in conventional echocardiographic parameters at follow-up in comparison with baseline values

Variable	$\Delta$ LVESV %		$\Delta$ LVEF		$\Delta$ GLS	
	r	P	r	P	r	P
$\Delta$ GWI	0.619	0.000	0.631	0.000	0.843	0.000
$\Delta$ GCW	0.654	0.000	0.669	0.000	0.745	0.000
$\Delta$ GWE	0.464	0.000	0.424	0.000	0.662	0.000
$\Delta$ Mid septal MWI	0.657	0.000	0.590	0.000	0.650	0.000
$\Delta$ Mid septal CW	0.610	0.000	0.554	0.000	0.623	0.000
$\Delta$ Mid septal MWE	0.547	0.000	0.446	0.000	0.472	0.000

$\Delta$  indicates change;  $\Delta$ LVESV%, the percentage change in left ventricular end-systolic volume; GCW, global constructive work; GLS, global longitudinal strain; GWE, global work efficiency; GWI, global work index; LVEF, left ventricular ejection fraction; CW, constructive work; MWE, myocardial work efficiency; MWI, myocardial work index.

**Figure 3** Correlations between changes in global MW indices and changes in mid septal MW indices.  $\Delta$  indicates change; GCW, global constructive work; GWI, global work index; CW, constructive work; MW, myocardial work; MWI, myocardial work index.

(sensitivity, 85%; specificity, 71%; AUC =0.807,  $P<0.001$ ) for predicting response to CRT. The combination of the 2 predictors, mid septal MWE  $\leq 42\%$  and mid lateral MWI  $\geq 740$  mmHg%, yielded sensitivity of 79%, specificity of 82%, and AUC =0.830 ( $P<0.001$ ) (Figure 4).

## Discussion

Non-invasive MW indices derived from LV PSLs, which were generated by combining LV LS measured by speckle tracking echocardiography with brachial artery blood pressure measured by sphygmomanometry, provide incremental clinical value for decision making in the selection of HF patients for CRT. In the present study, we evaluated the global and segmental MW indices in

CRT candidates and demonstrated that the abnormal but reversible segmental heterogeneous distribution of MW at baseline was significantly associated with favorable CRT response. The lower mid septal MWE and the higher mid lateral MWI at baseline were also identified as independent predictors of CRT response. Additionally, their combination could further improve the prediction accuracy of response to CRT, which indicates that the assessment of the potentially recoverable reserves in the septum and residual myocardial contractile performance in the lateral wall before CRT could be useful in the identification of responders.

The proportion of patients with coronary heart disease in our study population was not high. A degree of coronary artery stenosis can result in myocardial ischemia, and the

**Table 4** Analyses to identify the baseline predictors of positive response to CRT

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
NYHA functional class IV	0.241	0.082–0.71	0.010			0.055
LBBB	3.067	1.047–8.982	0.041			0.593
DBP	1.065	1.010–1.122	0.020			0.447
LVEDV	0.991	0.986–0.996	0.001			0.334
LVESV	0.990	0.984–0.996	0.001			0.369
IVMD	1.034	1.013–1.055	0.002			0.061
GLS	0.757	0.612–0.936	0.010			0.497
Mid lateral LS	0.827	0.746–0.917	0.000			0.995
GWI	1.002	1.000–1.004	0.025			0.701
GCW	1.002	1.000–1.003	0.018			0.837
Mid lateral MWI	1.003	1.001–1.004	0.000	1.003	1.002–1.004	0.000
Mid lateral CW	1.002	1.001–1.003	0.000			0.689
Mid septal MWI	0.999	0.998–1.000	0.006			0.386
Mid septal MWE	0.969	0.950–0.988	0.002	0.975	0.959–0.990	0.002
Mid septal WW	1.003	1.001–1.004	0.000			0.312

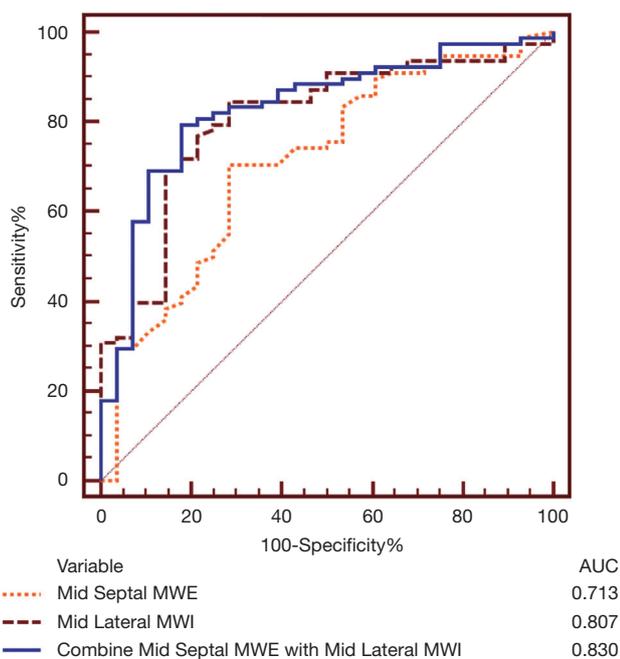
CRT, cardiac resynchronization therapy; CI, confidence interval; CW, constructive work; DBP, diastolic blood pressure; GCW, global constructive work; GLS, global longitudinal strain; GWI, global work index; IVMD, interventricular mechanical delay; LBBB, left bundle branch block; LS, longitudinal strain; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MW, myocardial work; MWE, myocardial work efficiency; MWI, myocardial work index; WW, wasted work; OR, odds ratio; NYHA, New York Heart Association.

etiology of heart failure may be attributed to the impact of myocardial ischemia over the long-term. Patients with severe myocardial ischemia have low myocardial viability and often fail to respond to CRT, especially those with a history of acute myocardial infarction, which develops into heart failure due to segmental wall motion abnormalities rather than dyssynchrony. For patients with significant coronary artery disease, percutaneous coronary intervention (PCI) is recommended over CRT.

Existing studies have also reported some predictors for CRT response. For example, Maass *et al.* (14) demonstrated that apical rocking and IVMD were significantly associated with the amount of reverse ventricular remodeling, and could predict clinical outcomes after CRT. Although visual assessment of apical rocking is a feasible and reproducible approach for identifying CRT responders, qualitative evaluation can be problematic for non-expert readers. IVMD was previously proposed to be useful for predicting CRT response (1); however, subsequent studies

have produced conflicting results on its ability to predict CRT response. Most evidence suggests that IVMD is not as useful in predicting response to CRT (12). Previous studies have also shown that LBBB is associated with a favorable response to CRT. CRT responders in our study also exhibited a significantly higher prevalence of LBBB at baseline. However, in addition to the presence of LBBB, residual LV myocardial viability, which represents the substrate for CRT response, is another important determinant of prognosis (15). Therefore, LBBB was not an independent predictor in our multivariate logistic regression analysis.

Invasive LV pressure-volume loops (PVLs) measured during coronary angiograms, as first demonstrated in experiments by Suga and Sagawa (16), have been used to quantify global LV function and segmental MW for over 40 years. However, the invasive LV pressure-volume/strain loops are not without risk to the patient. Developments toward a fully non-invasive assessment of MW were



**Figure 4** ROC curves for predicting response to CRT. The area under the ROC curve (AUC) for combined mid septal MWE and mid lateral MWI was greater than that of mid septal MWE or mid lateral MWI. CRT, cardiac resynchronization therapy; ROC, receiver operating characteristic; MWE, myocardial work efficiency; MWI, myocardial work index.

therefore made in the hope of improving its clinical applicability. Russell *et al.* (6,7) proposed a simple method to non-invasively estimate LV pressure, which was based on the measurement of brachial artery cuff pressure and the timing of valvular events, then the LV strain data combined with this non-invasively estimated LV pressure was used to construct LV pressure-strain loops (PSLs). The area within the non-invasive LV PSLs showed excellent correlation and good agreement with the invasive measurements (6,7).

Recently, this non-invasive MW analysis was introduced as a new vendor-specific module into the AFI software within the EchoPAC workstation (GE Vingmed Ultrasound), which is also the only currently available commercial system that can provide echocardiographic software to calculate MW. This new software has been applied under normal physiological conditions, and in some pathological LV remodeling. The Normal Reference Ranges for Echocardiography (NORRE) study (17), accredited by the European Association of Cardiovascular Imaging (EACVI), has provided useful normal reference

ranges for novel non-invasive global MW indices. Furthermore, the NORRE sub-study (18) evaluated the correlations between global MW indices and traditional two-dimensional echocardiographic parameters, including LV size, and LV systolic and diastolic functional parameters. Considering that the study population was entirely composed of healthy subjects, leading to restricted LV size and function value ranges, these correlations were not all strong and were not observed for all MW indices. In our study with a HF population, the improved values for global and segmental MW indices at 6-month follow-up showed good correlations with the improved magnitudes of conventional echocardiographic parameters.

Moreover, the correlations in our study were stronger than those in the NORRE sub-study, as LV remodeling and dysfunction are usually tightly correlated, especially in advanced HF. Hedwig *et al.* (19) demonstrated the new GWI correlated with established prognostic parameters in HF patients.  $GWI < 500 \text{ mmHg}\%$  was a predictor of severely impaired ejection fraction, very low exercise capacity, and strongly elevated NT-pro-BNP, suggesting a poor prognosis. Also, non-invasive MW indices have shown more promising results in the diagnosis and prognostication of some cardiovascular diseases than strain alone (20-25).

The novel echocardiography-based technique for non-invasive MW calculation has been used in the field of CRT. Galli *et al.* (26) showed that HF patients with higher GCW exhibited a favorable response to CRT, which was consistent with our results that GCW was significantly higher in CRT responders than in non-responders at baseline evaluation. Van der Bijl *et al.* (27) demonstrated that lower GWE before CRT was independently associated with better long-term outcomes in HF patients with a Class I indication for CRT according to current guidelines. However, in our study, GWE was comparable between CRT responders and non-responders at baseline. Possible reasons for these contradictory results may include the various patient clinical characteristics, for example, their study population only consisted of patients with a Class I indication for CRT, but our study enrolled a wider range of patients.

The prognostic implications of segmental MW indices in HF patients undergoing CRT have not been further explored. Our study extended prior work to explore the value of segmental MW indices in predicting CRT response, and evaluated the changes in segmental MW indices after CRT. The focus was on the septal and lateral mid-ventricular levels because LV mapping data in typical LV dyssynchrony

have shown that the mid septal region was electrically activated first and showed a U-shaped conduction pattern through the apical regions, with a prolonged activation time in the LV activation sequence, and was imposed between the LV septum and the lateral wall (28). Therefore, we believe that it enhances reproducibility since segmental heterogeneity is most evident between the septum and lateral wall, and mid-ventricular values could represent the complete myocardial wall and improve operability by simplifying the evaluation. In our study, CRT responders at baseline exhibited significantly lower mid septal MWI and mid septal MWE, and significantly higher mid lateral MWI and mid lateral CW than non-responders. The multivariate analysis identified baseline mid septal MWE and mid lateral MWI as independent predictors of CRT response. Baseline mid septal MWE, which presents potentially recoverable reserve, could play an important role in identifying possible responders to CRT. Baseline mid lateral MWI, which is an index of residual myocardial performance, is fundamental to CRT's success as myocardial substrates are related to the electrical response.

Dyssynchronous LV activation leads to unloading of the early activated regions, and a higher load in the late activated regions. As observed typically in patients with LBBB (29,30), the early activated septum contracts before aortic valve opening under low LV pressure, stretching the LV lateral wall simultaneously. The late activated lateral wall contracts during rising LV pressures, thus increasing regional workload and causing a variable degree of systolic lengthening of the septum at the same time. Septal work during systolic shortening is absorbed by pre-stretching of the LV lateral wall, and work during systolic lengthening does not contribute to LV ejection, both of which represent a waste. Consequently, compensatory mechanisms increase contractility of the lateral wall. Inhomogeneity of contraction resulted in the widely varied contribution of the septum to LV work in CRT candidates. Vecera *et al.* (31) proposed an assessment of wasted MW in the septum as a novel method to identify patients who may be responders of CRT. Our results indicated that the less efficiently the septum operates at baseline, the greater the potentially recoverable reserve, which translates into a favorable outcome. CRT responders show the preservation of LV lateral wall function at baseline, making it possible to provide myocardial substrates for a favorable response to CRT. Increased scar burden or LV free wall fibrosis was found to be associated with poor response and worse outcomes after CRT (32,33). Russell *et al.* (6) have shown

that regional differences in MWI assessed by PSLs have a strong correlation with the myocardial glucose metabolism evaluated by 18F-FDG PET, which supports the hypothesis that the differences in MWI detected by PSLs before CRT might correspond to myocardial residual metabolic activity, and might therefore explain the role of baseline mid lateral MWI in predicting CRT response.

MW indices could also be used to examine the impact of treatment on LV function. Our present study corroborated the finding that CRT induces the dyssynchronous heart to a more balanced distribution of work, thereby improving global cardiac function significantly and demonstrated that the improvement in LV global function mainly resulted from the increase in septal work efficiency following CRT.

### Limitations

First, for the non-invasive MW indices assessment, systemic arterial pressure was used as a substitute for LV pressure. This technique cannot be applied when systemic arterial pressure and LV pressure are discordant, for example, in patients with LV outflow obstruction or aortic stenosis, or any other cardiac pathologies that will induce a pressure gradient between the aorta and the LV. Second, atrial fibrillation, with significant beat-to-beat variability, inhibits the accurate and reliable assessment of MW indices in such patients. Third, this study is subject to the inherent limitations of a single-center, retrospective analysis. It would be ideal for retesting the cutoff values in a validation population. Larger scale multi-center studies are needed to evaluate the new parameters further to establish their clinical utility and prognostic implications in the field of CRT before they can be recommended as tools in clinical practice. Fourth, the non-invasive evaluation of MW was performed by estimating LV pressure, which is known to be imprecise. We are aware this method is somewhat imperfect; nevertheless, this parameter has the advantage of providing an automatic analysis of myocardial performance that is independent of LV afterload.

### Conclusions

The novel echocardiography-based technique allows the non-invasive assessment of MW indices rapidly and effectively, and therefore has the potential to be widely used as a promising tool for selecting CRT candidates in clinical practice. Lower mid septal MWE and higher mid lateral MWI at baseline were identified as independent predictors

of response to CRT, and their combination leads to more accurate and effective prediction than the individual parameters alone. Therefore, it is useful to improve patient selection for CRT to identify this abnormal but reversible segmental heterogeneity with the use of MW indices before CRT.

### Acknowledgments

This manuscript has not been previously published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium. The abstract of our manuscript was submitted to the 2020 ASE 31st Annual Scientific Sessions for scientific exchange and was accepted as a poster presentation. All accepted original science presentations have been published in the June issue of Journal of the American Society of Echocardiography, 2020.

*Funding:* This work was funded by the National Nature Science Foundation of China (Grant No. 82071933).

### Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/qims-20-754>). The authors have no conflicts of interest to declare.

*Ethical Statement:* This study was approved by the medical ethics committee of Zhongshan Hospital, Fudan University, and informed consent was obtained from all patients.

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**Cite this article as:** Zhu M, Wang Y, Cheng Y, Su Y, Chen H, Shu X. The value of non-invasive myocardial work indices derived from left ventricular pressure-strain loops in predicting the response to cardiac resynchronization therapy. *Quant Imaging Med Surg* 2021;11(4):1406-1420. doi: 10.21037/qims-20-754