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CLINICAL RESEARCH
Heart failure

Imaging predictors of response to cardiac resynchronization therapy: left ventricular work asymmetry by echocardiography and septal viability by cardiac magnetic resonance

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Aims Left ventricular (LV) failure in left bundle branch block is caused by loss of septal function and compensatory hyperfunction of the LV lateral wall (LW) which stimulates adverse remodelling. This study investigates if septal and LW function measured as myocardial work, alone and combined with assessment of septal viability, identifies responders to cardiac resynchronization therapy (CRT).

Methods and results In a prospective multicentre study of 200 CRT recipients, myocardial work was measured by pressure-strain analysis and viability by cardiac magnetic resonance (CMR) imaging ($n = 125$). CRT response was defined as ≥15% reduction in LV end-systolic volume after 6 months. Before CRT, septal work was markedly lower than LW work ($P < 0.0001$), and the difference was largest in CRT responders ($P < 0.001$). Work difference between septum and LW predicted CRT response with area under the curve (AUC) 0.77 (95% CI: 0.70–0.84) and was feasible in 98% of patients. In patients undergoing CMR, combining work difference and septal viability significantly increased AUC to 0.88 (95% CI: 0.81–0.95). This was superior to the predictive power of QRS morphology, QRS duration and the echocardiographic parameters septal flash, apical rocking, and systolic stretch index. Accuracy was similar for the subgroup of patients with QRS 120–150 ms as for the entire study group. Both work difference alone and work difference combined with septal viability predicted long-term survival without heart transplantation with hazard ratio 0.36 (95% CI: 0.18–0.74) and 0.21 (95% CI: 0.072–0.61), respectively.

Conclusion Assessment of myocardial work and septal viability identified CRT responders with high accuracy.

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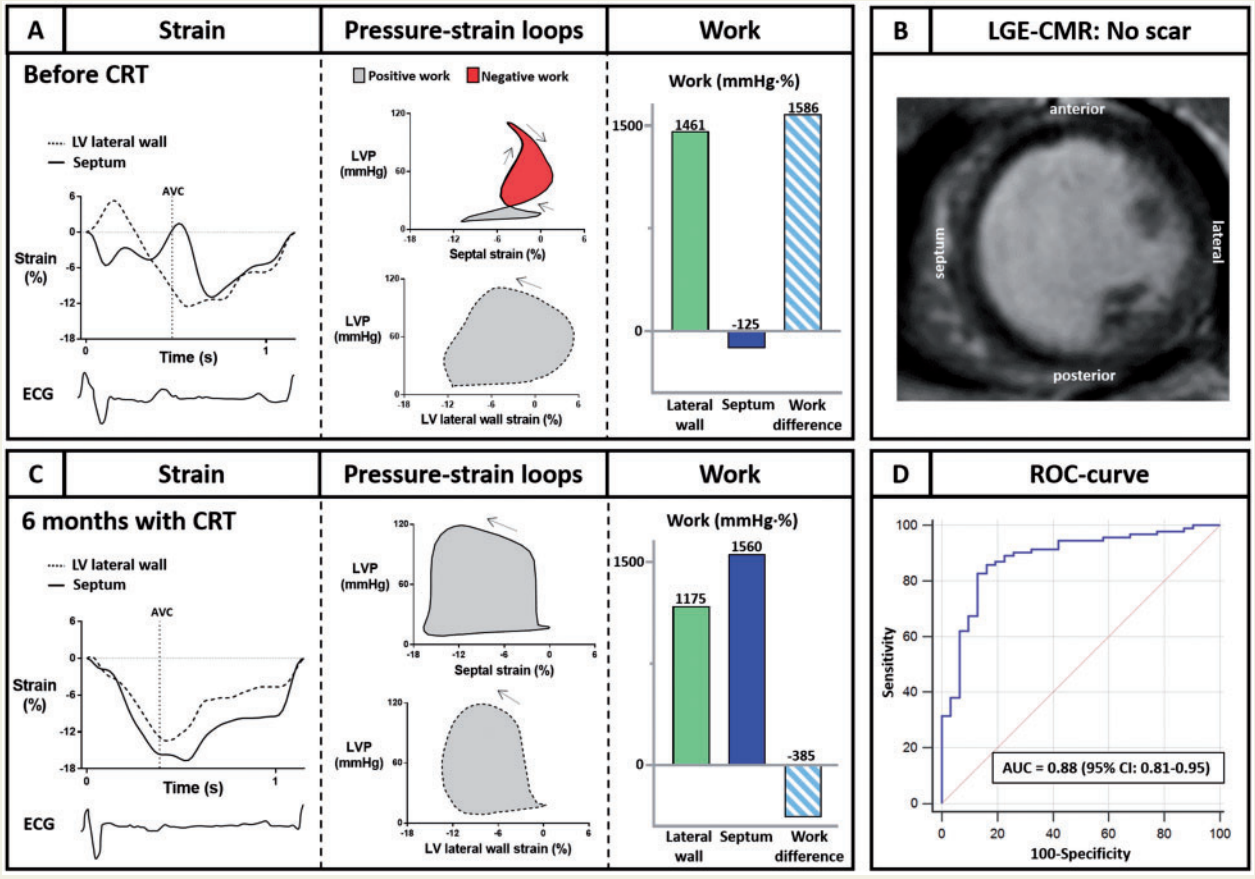
Graphical Abstract



Keywords Cardiac resynchronization therapy • Dyssynchrony • Heart failure • Left bundle branch block • Myocardial scar • Myocardial work

Introduction

Cardiac resynchronization therapy (CRT) is indicated in patients with symptomatic heart failure, reduced left ventricular (LV) ejection fraction (EF) and wide QRS in the electrocardiogram (ECG). A significant limitation of CRT is that 30–40% of patients show no improvement. In an effort to improve selection of patients for CRT, a number of echocardiographic measures of LV dyssynchrony have been tested, but none of these are proven to improve responder rate.[1] Therefore, current guidelines do not recommend echocardiographic measures of dyssynchrony or any other imaging tool when evaluating patients for CRT.[2]

In patients with left bundle branch block (LBBB), there is typically reduced contractile function of the interventricular septum which has a direct negative effect on global LV function, and there is compensatory hyperfunction of the LV lateral wall (LW) which stimulates adverse remodelling.[3] It was proposed by Prinzen *et al.*[3,4] that asymmetry in workload between the LW and septum could be a diagnostic indication for success of CRT. Furthermore, since restoration of septal function is important for recovery of LV function, we suggest septal viability as another determinant of response to electrical resynchronization. Therefore, in addition to work asymmetry between LW and septum, which reflects the disturbance of LV function in LBBB, we suggest assessment of septal viability to determine the potential for recovery of LV function with CRT.

The present study investigates the hypothesis that LW-to-septal work asymmetry and septal viability determines response to CRT. We used regional LV work rather than shortening indices to measure function since work quantifies the asymmetry in workload between LW and septum which is typical for LBBB. Myocardial work was assessed by a method innovated by the group of Smiseth, which uses a non-invasive estimate of LV pressure (LVP) in combination with myocardial strain by speckle-tracking echocardiography (STE).[5] Absolute rather than relative difference in work between LW and septum was used since septal work is often near zero in LBBB which results in large relative differences even when little work is done in the LW. Furthermore, the method takes into account reduced LW function due to LW scar, which is associated with non-response to

CRT.[6] To address the second part of the hypothesis, that viable septum is important for CRT response, we used late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) imaging to assess myocardial scar.

A previous small feasibility study[5] and retrospective single-centre studies suggest that the work method may have a role in selection of patients for CRT.[7,8] The present study is the first clinical testing of the work method in a prospective multicentre study and investigates if myocardial work alone and combined with viability by LGE-CMR identifies responders to CRT with added value to current guidelines.

Methods

Study population

A total of 236 heart failure patients referred for CRT were prospectively included from Oslo University Hospital, Norway ($n = 101$), University Hospitals Leuven, Belgium ($n = 50$), Rennes University Hospital, France ($n = 71$), OLV Hospital Aalst, Belgium ($n = 11$), and Karolinska University Hospital, Sweden ($n = 3$) between August 2015 and November 2017. This constitutes about one-third of patients who received CRT in the main contributing centres during the study period. Inclusion criterion was indication for CRT according to 2013 European Society of Cardiology (ESC) guidelines.[9] Exclusion criteria contained recent myocardial infarction, recent cardiac surgery, and severe aortic stenosis. Thirty-six patients were excluded from the final analysis due to CRT not implanted ($n = 24$), study withdrawal ($n = 4$), lack of echocardiographic data ($n = 7$) or lead extraction due to endocarditis ($n = 1$). LGE-CMR was obtained in 125 of 200 remaining patients. Main reasons for not undergoing LGE-CMR were CMR non-compatible cardiac device ($n = 42$) and estimated glomerular filtration rate <45 mL/min/1.73m^2 ($n = 11$). For the remaining patients ($n = 22$), reasons included claustrophobia, intracranial metal implants, and logistical causes. Left bundle branch block was defined according to ESC guidelines.[9]

The study was approved by the respective Regional Ethics Committees and written informed consent was obtained from all study participants. The study was registered at clinicaltrials.gov (identifier NCT02525185).

Echocardiography and strain analysis

Echocardiography (Vivid E9 or E95 scanner, GE Vingmed Ultrasound AS, Horten, Norway) was performed before and 7 ± 1 months after CRT implantation. Recordings included two-dimensional (2D) grey-scale images from LV apical views for STE and timing of valvular events. Ventricular volumes and LVEF were obtained by biplane Simpson's method and blood pressure by the brachial cuff method at beginning of the examination.

Longitudinal strain was measured by STE and is presented as absolute values. In patients with atrial fibrillation, we analysed beats with approximately average heart rate. Frame rate was 66 ± 11/s.

Estimation of regional work

Myocardial work was calculated by a previously validated method.[5] The work index (mmHg·%) was calculated by multiplying rate of segmental shortening (strain rate) with instantaneous LVP. This resulted in a measure of instantaneous power, which was integrated over time to give work as a function of time in systole, defined as the time interval from mitral valve closure to mitral valve opening. Work performed during segmental shortening (i.e. counter-clockwise rotation of the pressure-strain loop) was defined as positive and work during segmental lengthening (i.e. clockwise rotation) as negative. Net myocardial work was calculated as the sum of positive (constructive) and negative (wasted) work for the given segment and globally as an average for all segments.

Regional work in the septum and LW was calculated as the average value of work from the respective basal and mid-ventricular segments in the apical four-chamber view. The absolute difference between net work in LW and septum (LW-S work difference) was used as a measure of asymmetry in workload. Myocardial work analysis was performed in Oslo by an observer blinded to volumetric measurements.

Alternative approaches

Septal flash[10] and apical rocking[11] were assessed visually in Leuven by two experienced readers. A visual reader interpretation of scar burden[12] was not performed. Systolic stretch index[13] was calculated from longitudinal strain traces as the sum of early-systolic stretch in the LW and septal systolic stretch.

Cardiac magnetic resonance and scar analysis

Prior to CRT implantation, patients were scanned with a 1.5 or 3.0 Tesla unit. LGE images were obtained after intravenous injection of either 0.15 or 0.20 mmol/kg gadoterate meglumine or 0.15 mmol/kg gadobenate dimeglumine. An experienced CMR radiologist made decision regarding presence of scar and, if positive, scar size was quantified semi-automatically in Segment software v2.0 R5270 from a stack of short-axis slices using a 17 segment model. We utilized the automatic algorithm EWA (expectation maximization, weighted intensity, a priori information).[14] Myocardial scar was reported regionally as percentage of total amount of tissue per wall and globally as percentage of total amount of tissue in the left ventricle. All scars were analysed and reported the same way independent of underlying aetiology.

Cardiac resynchronization therapy implantation

Patients underwent standard implantation of a biventricular pacing system. The implanting electrophysiologist had access to CMR images but was blinded to myocardial work data. Coronary venography was used to optimize placement of the LV lead in a lateral or posterolateral vein. The device was programmed in a conventional biventricular pacing mode and retested prior to hospital discharge.

Endpoints

Primary endpoint was reverse remodelling defined as at least 15% reduction in LV end-systolic volume (ESV) indexed to body surface area at 6 (7 ± 1) months follow-up. Reverse remodelling was chosen as it provides both a qualitative and quantitative endpoint, can be acquired in almost all patients, and is closely related to mortality.[15] To optimize precision, all volumes were measured independently in three different centres (Rennes, Leuven, and Oslo) and a majority decision was used in cases of disagreement on response. The pre-specified secondary endpoint was death at 12 months after CRT, but follow-up was extended and heart transplantation included to increase the number of events. Therefore, secondary endpoint was heart transplantation or death of any cause at 35 ± 11 (interquartile range 14) months after CRT implantation. As another measure of clinical response,[16] we assessed improvement in Packer clinical composite score[17] at 6 months.

Statistical analysis

All analyses involving myocardial scar were confined to the group of patients undergoing LGE-CMR. Values are presented as mean ±

Table 1 Baseline characteristics

	All patients ($n = 200$)	Responders ($n = 135$)	Non-responders ($n = 65$)	*P*-value
Age (years)	67 ± 11	68 ± 11	65 ± 11	0.041
Gender (%)				
Male	71	65	83	0.009
Weight (kg)	79 ± 16	75 ± 14	85 ± 17	<0.001
Heart failure aetiology (%)				
Non-ischaemic	65	76	43	<0.001
Ischaemic	35	24	57	<0.001
Medication (%)				
ACE-inhibitor/ARB	95	97	89	0.023
Beta-blocker	90	89	92	0.450
Aldosterone antagonists	41	39	46	0.304
Diuretics	71	69	77	0.263
Rhythm (%)				
Sinus	82	86	72	0.020
Atrial fibrillation	6	4	8	0.345
Paced	13	11	20	0.041
QRS configuration (%)				
LBBB	86	90	78	0.033
Non-LBBB	14	10	22	0.033
QRS duration (ms)	167 ± 21	168 ± 19	166 ± 24	0.497
Upgrades (%)	22	16	35	0.002
Systolic blood pressure (mmHg)	124 ± 21	126 ± 21	119 ± 20	0.020
Diastolic blood pressure (mmHg)	69 ± 11	70 ± 12	68 ± 10	0.318
NYHA functional class	2.4 ± 0.6	2.3 ± 0.6	2.5 ± 0.6	0.030
Mitral regurgitation (0–3)	1.2 ± 0.8	1.1 ± 0.8	1.4 ± 0.9	0.053

Continuous variables are given as mean ± standard deviation. *P*-value for comparison of responders vs. non-responders.
ACE-inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LBBB, left bundle branch block; NYHA, New York Heart Association.

standard deviation or confidence intervals (CIs). Comparisons between two groups were performed using Student's *t*-test or chi-square test as appropriate. Univariate and multivariate linear regression analyses were used to identify predictors of reverse remodelling. Receiver operating characteristic (ROC) curves with area under the curve (AUC) values were used to determine discriminative ability. To combine assessment of two parameters, we used logistic regression to calculate a linear combination of the parameters, which was then used for ROC curves. The DeLong method or, when more appropriate, the Hanley and McNeil method (both MedCalc Software 2019) were used to compare ROC curves. Survival data are presented as hazard ratios (Cox regression) and Kaplan–Meier curves with log-rank test. As input, we used cut-off values from the primary endpoint analysis. Bland–Altman plot, Pearson correlation coefficient, intra-class correlation coefficient (ICC), and Cohen's kappa were used for reproducibility. If not otherwise stated, $P < 0.05$ was considered significant and IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp was used for analysis.

Reproducibility

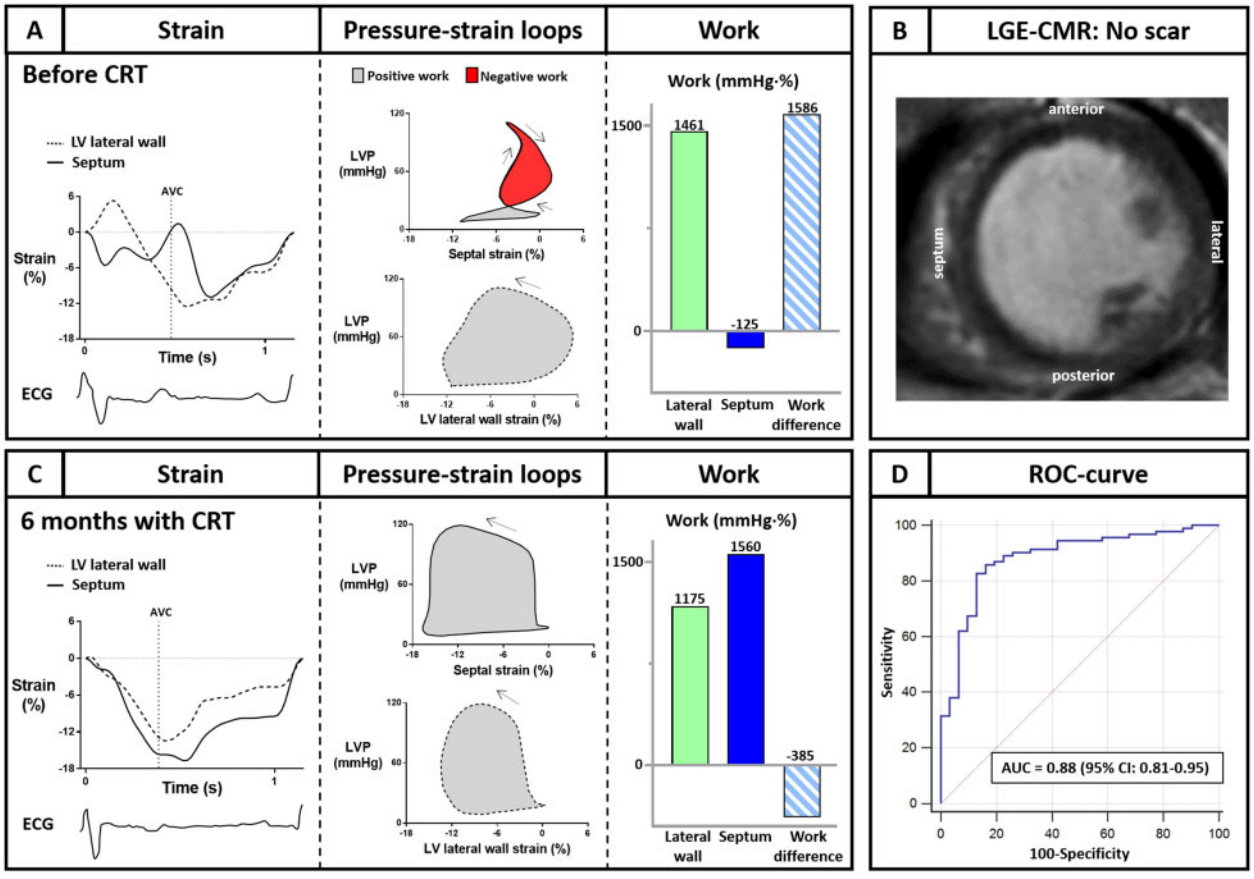
Excellent intra- and interobserver reproducibility for myocardial work has been reported previously.[5] Intercentre variability for myocardial work, septal flash, and apical rocking was studied in 38 randomly selected patients.

Results

At 6 months follow-up, there were three deaths, one heart transplantation and one LV assist device implantation, and these five patients were considered non-responders. The primary endpoint of ≥15% reduction in LV ESV index was achieved in 135 of 195 remaining patients, which gives 68% responder rate to CRT. Among responders, there were more females, patients in sinus rhythm and patients with non-ischaemic cardiomyopathy and a lower number of upgrades compared with non-responders (*Table 1*).

At follow-up, LVEF, GLS, and global work improved substantially in responders, while in non-responders there were no significant changes (*Figure 1A and B*, Supplementary material online, *Tables S1 and S2*).

The *Take home figure* is from a CRT responder with characteristic large lateral wall-to-septal work difference and viable septal myocardium. Prior to CRT, this patient has LV contraction pattern typical for LBBB with highly inefficient septal contractions due to substantial negative work, which was converted to positive work with CRT. The figure also illustrates how CRT reduced workload on the LW. Figure 2 shows a non-responder with essentially similar echocardiographic findings prior to CRT, but with significant septal scar indicating limited potential for septal



Take home figure Left ventricular work asymmetry combined with septal viability identifies cardiac resynchronization therapy responders. (*A*–*C*) The panels are from the same patient and illustrate how the lateral-to-septal work difference is used in combination with viability by LGE-CMR to identify cardiac resynchronization therapy responders. Before cardiac resynchronization therapy (*A*) there is dominantly negative septal work, as indicated by the red-coloured pressure-strain loop area, but compensatory increase in left ventricular lateral wall work, which gives a large lateral-to-septal work difference. Viable septum (*B*) indicates potential for recovery of septal function. After 6 months with cardiac resynchronization therapy (*C*), there is fine recovery of septal function. The highly inefficient septal contractions before cardiac resynchronization therapy are converted to positive work throughout systole. The improvement in septal function was accompanied by reduced workload on the lateral wall. (*D*) ROC curve displaying combined assessment of work difference and septal viability for cardiac resynchronization therapy response prediction (n = 123). AUC, area under curve; AVC, aortic valve closure; CI, confidence interval; LGE-CMR, late gadolinium enhancement cardiac magnetic resonance; LVP, left ventricular pressure; ROC, receiver operating characteristic.

recovery. Following CRT, there was only a moderate improvement of septal function.

Left ventricular work asymmetry

Large baseline LW-S work difference was associated with good CRT response both in the whole study population (*Figure 1B*) and when excluding patients with septal or LW scars. Univariate analysis revealed a direct relation between LW-S work difference and reverse remodelling ($r = 0.44$, $P < 0.0001$), where larger work difference was associated with more extensive reverse remodelling (*Figure 3*). Furthermore, in multivariate analysis, work difference together with heart failure aetiology (ischaemic or non-ischaemic) and QRS duration, but not QRS morphology (LBBB or non-LBBB), were independent predictors of reverse remodelling ($P < 0.0001$ for work difference) (*Table 2*). Work difference was somewhat larger in non-ischaemic as compared with ischaemic patients (1349 ± 702 vs. 955 ± 887 mmHg·%, $P < 0.001$).

AUC for LW-S work difference as predictor of CRT response in the entire study population was 0.77 (95% CI: 0.70–0.84) and was similar in the subgroup of patients with sinus rhythm and non-ischaemic aetiology. In comparison, AUC for QRS morphology (LBBB or non-LBBB) as predictor of CRT response was 0.56 (95% CI: 0.47–0.64) and for QRS duration 0.54 (95% CI: 0.45–0.63). Work difference ≥860 mmHg·% showed accuracy of 75% (95% CI: 68–81) for CRT response (*Figure 4A*, Supplementary material online, *Table S3*) and was a predictor of reduced risk for heart transplantation or death at long-term follow-up [hazard ratio 0.36 (95% CI: 0.18–0.74)] (*Figure 5A*). Furthermore, work difference was an independent predictor of improved Packer clinical composite score (Supplementary material online, *Table S4*). Assessment of work difference was feasible in 195 patients (98% feasibility).

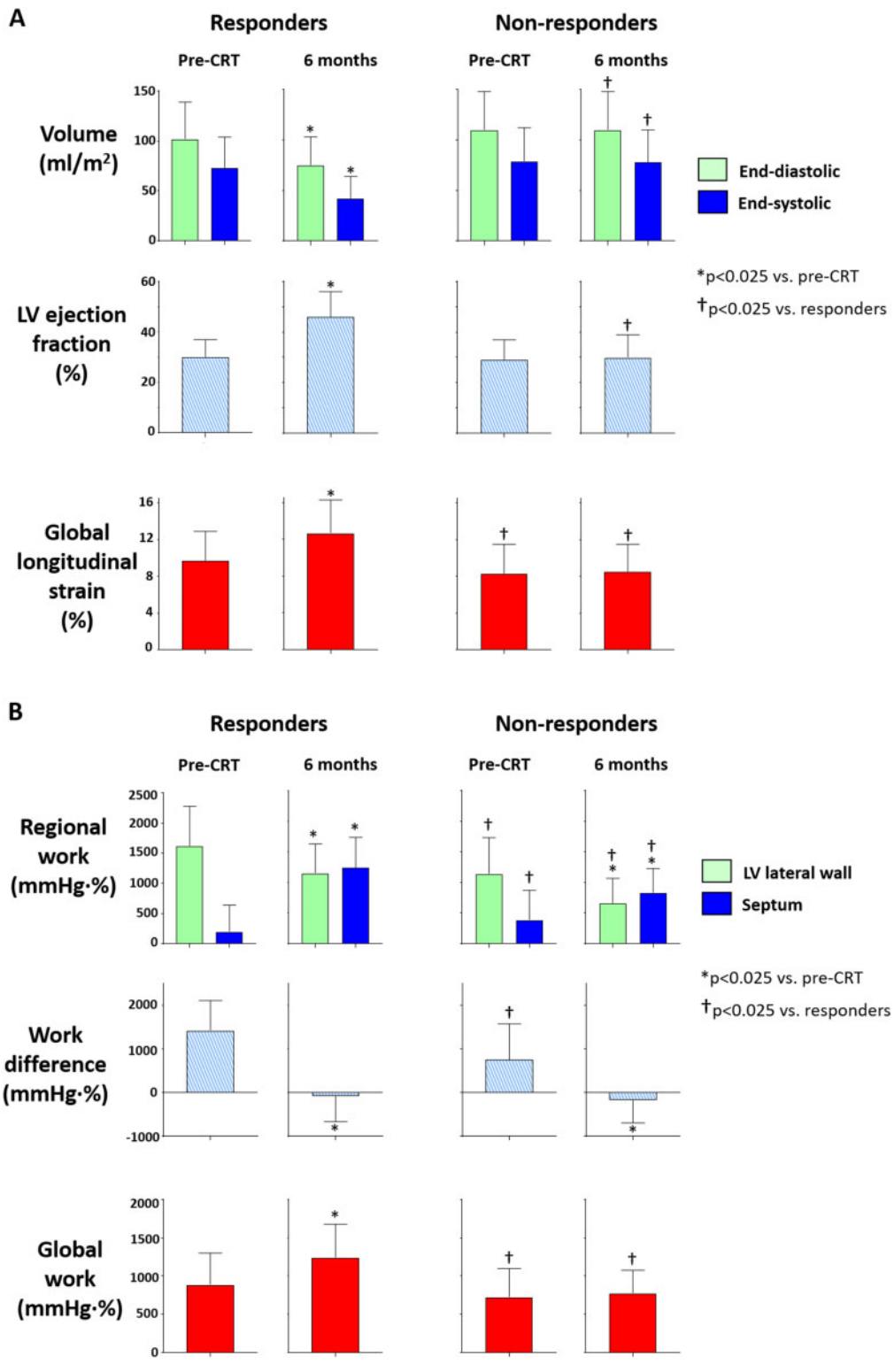


Figure 1 Left ventricular systolic function and work asymmetry. (*A*) Effect of cardiac resynchronization therapy on left ventricular volumes and function: Volumes and ejection fraction were similar in responders and non-responders before cardiac resynchronization therapy, but improved significantly only in responders. (*B*) Effects of cardiac resynchronization therapy on work: Before cardiac resynchronization therapy, responders have more work in the left ventricular lateral wall and less in the septum than non-responders (upper panels). This is reflected in a larger lateral-to-septal work difference (mid-panels). With cardiac resynchronization therapy, lateral wall work is reduced and septal work increased in both groups. Among responders, however, reduction in lateral wall work was far exceeded by increased septal work and explains why only responders showed improved global work (lower panels). One standard deviation indicated.

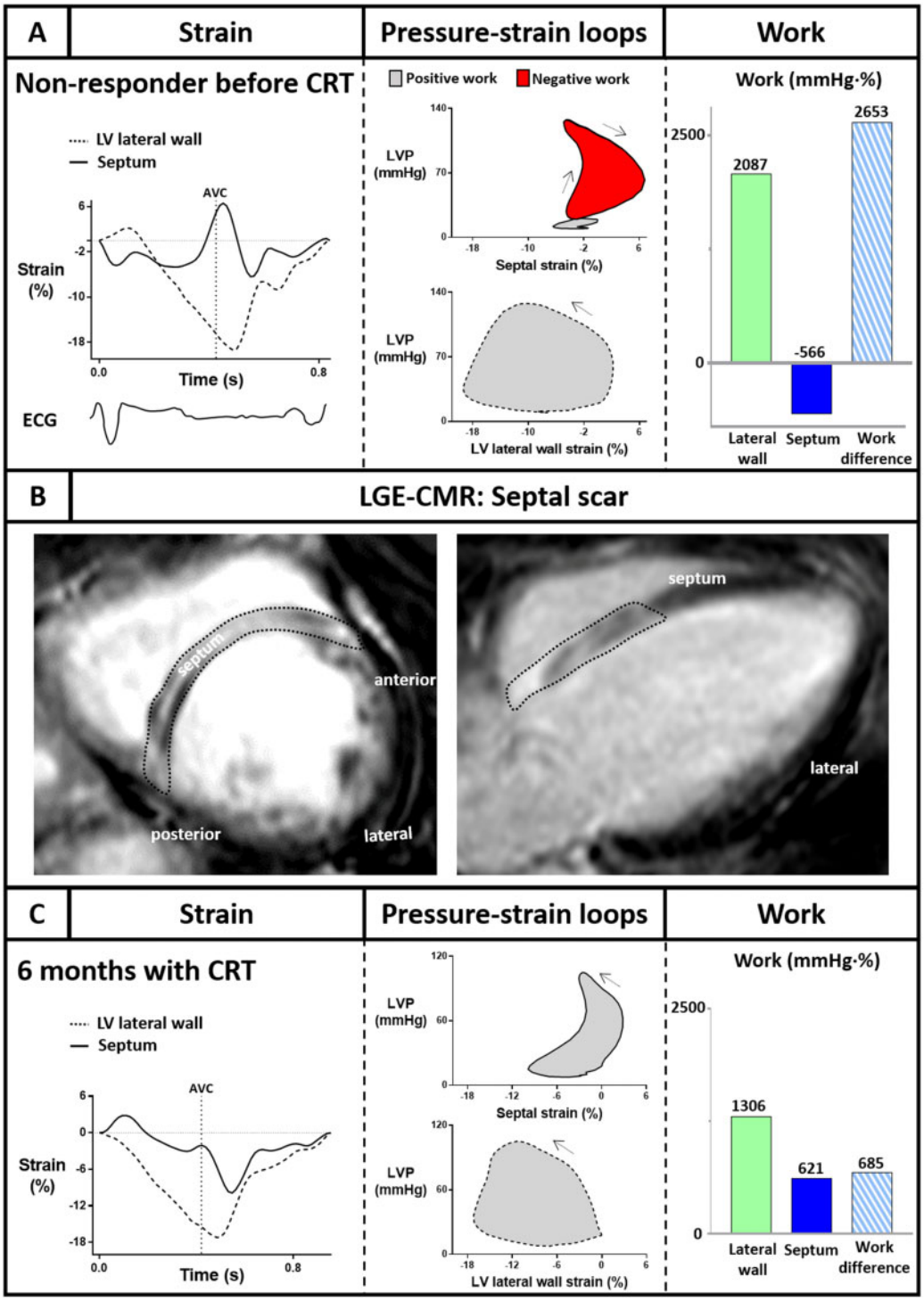


Figure 2 Septal scar identifies non-responder to cardiac resynchronization therapy. (*A*) Strain traces (left), pressure-strain loops (middle), and regional work (right) in a representative non-responder (with non-ischaemic cardiomyopathy) prior to cardiac resynchronization therapy. Similar to the patient in the *Take home figure*, there are highly inefficient septal contractions with predominantly negative work (red-coloured pressure-strain loop area), which leads to a large lateral-to-septal work difference. (*B*) LGE-CMR revealed extensive septal scar with limited potential for recovery of septal function with cardiac resynchronization therapy. (*C*) After 6 months with cardiac resynchronization therapy, there is only moderate recovery of septal function and, despite reduced workload on the left ventricular lateral wall, still significant lateral-to-septal work difference. AVC, aortic valve closure; LGE-CMR, late gadolinium enhancement cardiac magnetic resonance; LVP, left ventricular pressure.

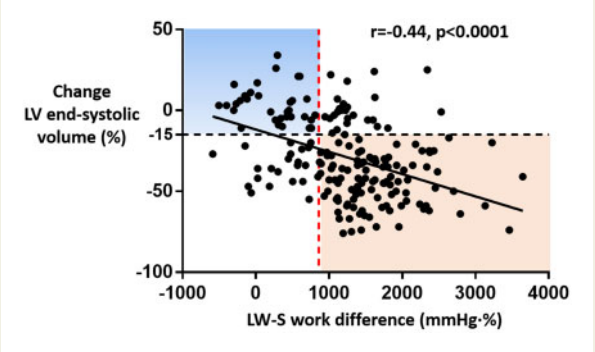


Figure 3 Regional work and reverse remodelling. Lateral-to-septal work difference correlates with degree of reverse remodelling following cardiac resynchronization therapy. The black-dotted line represents 15% reduction in left ventricular end-systolic volume index, whereas the red-dotted line represents the proposed cut-off value for work difference of 860 mmHg·%. LW-S, lateral-to-septal.

Scar

LGE-CMR was performed in 125 patients, in whom scar was present in 61. Forty-six patients had some degree of scar in the anterior wall, 57 in the septum, 55 in the inferior wall, and 37 in the LW (Supplementary material online, *Table S5*). In univariate analysis, there was inverse correlation between total scar burden and reverse remodelling (r = -0.54, $P < 0.0001$).

Multivariate analysis including the percentage of anterior, septal, inferior, and lateral scar revealed that septal scar was a significant predictor of reverse remodelling (*Table 3*). Furthermore, the presence of any scar in the septum showed sensitivity of 81% (95% CI: 63–93) for non-response to CRT. AUC was 0.79 (95% CI: 0.69–0.89) (Supplementary material online, *Figure S2*).

Combining work and viability

There was inverse correlation between LW-S work difference and total scar burden (r = -0.43, $P < 0.0001$). In multivariate analysis including percentage of septal scar, LW-S work difference, QRS duration, and QRS morphology, only septal scar and work difference were significant predictors of reverse remodelling (both $P < 0.0002$) (*Table 4*). Furthermore, septal scar and work difference showed significant incremental value to a multivariate model for CRT response including QRS duration, heart failure aetiology and LV ESV index. In patients with septal scars, there was less improvement in septal work with CRT as compared to patients without scar ($P < 0.001$).

AUC for combined assessment of septal viability and LW-S work difference for CRT response prediction was 0.88 (95% CI: 0.81–0.95) (*Figure 4B*), which was significantly better than work difference alone ($P < 0.02$). The proposed cut-off value for the combined approach (*Figure 4B*) provided 86% sensitivity, 84% specificity, and 85% accuracy for CRT response and was a strong predictor of reduced risk for heart transplantation or death at long-term follow-up [hazard ratio 0.21 (95% CI: 0.072–0.61)] (Figure 5B). Combined assessment of work and viability significantly predicted improvement in Packer clinical composite score.

Table 2 Multivariate linear regression analysis with left ventricular end-systolic volume reduction as dependent variable

Regression variable	*B*	VIF	95% CI	*P*-value
Constant term	22.3			
QRS morphology	4.67	1.09	-4.65 to 13.99	0.324
QRS duration	-0.165	1.00	-0.317 to -0.014	0.033
Heart failure aetiology	-15.9	1.07	-22.6 to -9.3	<0.0001
LW-S work difference	-0.011	1.15	-0.015 to -0.007	<0.0001

$N = 190$. $R^2 = 0.29$.
CI, confidence interval; LW-S, lateral wall-to-septal; VIF, variance inflation factors.

Alternative approaches

Septal flash, apical rocking, and systolic stretch index predicted CRT response with AUC 0.74 (95% CI: 0.66–0.82), 0.75 (95% CI: 0.68–0.83), and 0.73 (95% CI: 0.66–0.81), respectively. There was no significant difference when comparing the ROC curve for LW-S work difference with septal flash and apical rocking. Compared with systolic stretch index, however, work difference was superior ($P < 0.05$). LW-S work difference combined with septal viability was superior to both septal flash, apical rocking and systolic stretch index (all $P < 0.025$).

Intermediate QRS duration

A total of 44 patients had QRS duration 120–150 ms (including three patients with QRS 120–129 ms), and 25 of these responded to CRT. In multivariate analysis ($n = 43$) including QRS duration and heart failure aetiology, LW-S work difference was the only significant predictor of reverse remodelling ($P < 0.02$). AUC for LW-S work difference was 0.82 (95% CI: 0.68–0.95).

For patients with QRS duration 120–150 ms undergoing LGE-CMR ($n = 27$), AUC for the combined assessment of septal viability and work difference was 0.91 (95% CI: 0.81–1.00).

Reproducibility

Bland–Altman and linear regression plots for intercentre variability of LW-S work difference are displayed in Supplementary material online, *Figure S3*. The ICC between the three centres was 0.89 (95% CI: 0.82–0.94) for septal work, 0.92 (95% CI: 0.88–0.96) for LW work, and 0.90 (95% CI: 0.84–0.94) for LW-S work difference, indicating good reproducibility. Furthermore, average intercentre agreement for work difference ≥860 mmHg·% was 89% (kappa range 0.65–0.85). Average intercentre agreement for presence of septal flash was 68% (kappa range 0.16–0.46) and for apical rocking 70% (kappa range 0.25–0.69).

Discussion

The present multicentre study extends previous smaller studies on myocardial work and presents the novel finding that quantification of myocardial work by echocardiography in combination with viability by LGE-CMR accurately identifies patients who will respond to CRT

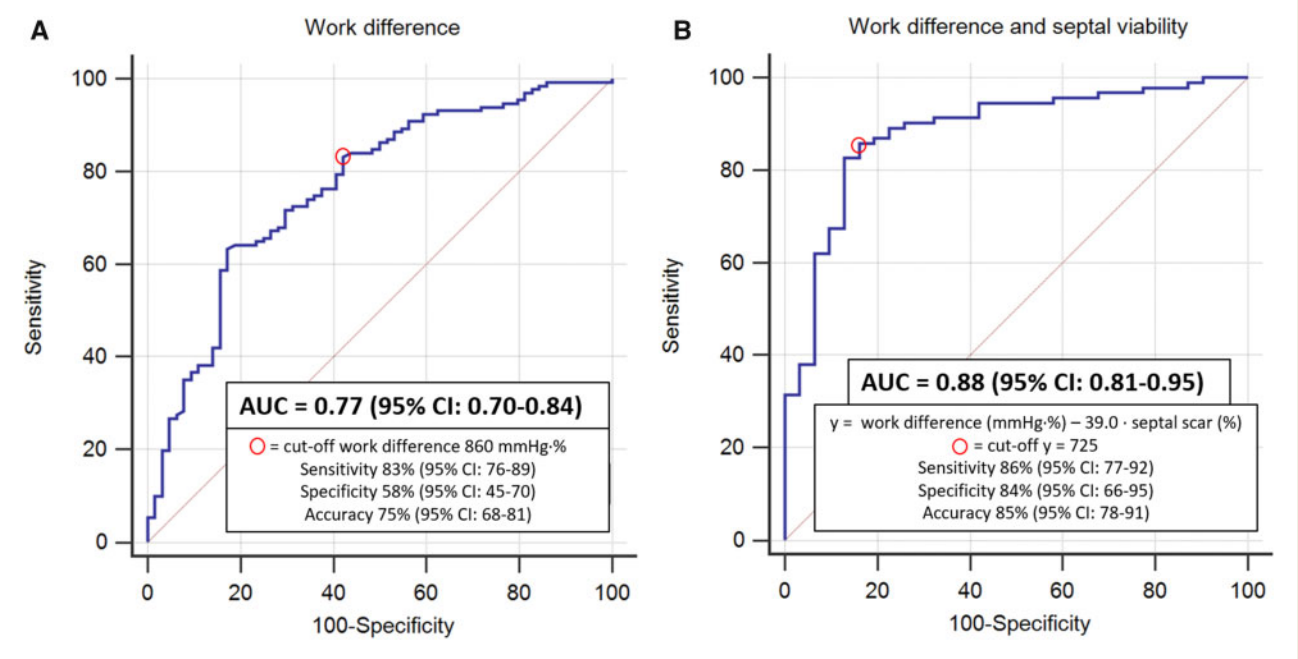


Figure 4 Work asymmetry and septal viability as predictors of cardiac resynchronization therapy response. (*A*) Receiver operating characteristic curve displaying lateral-to-septal work difference as predictor of cardiac resynchronization therapy response in the entire study population (n = 195). (*B*) Receiver operating characteristic curve displaying the combined assessment of lateral-to-septal work difference and septal viability as predictor of cardiac resynchronization therapy response (n = 123). AUC, area under curve; CI, confidence interval.

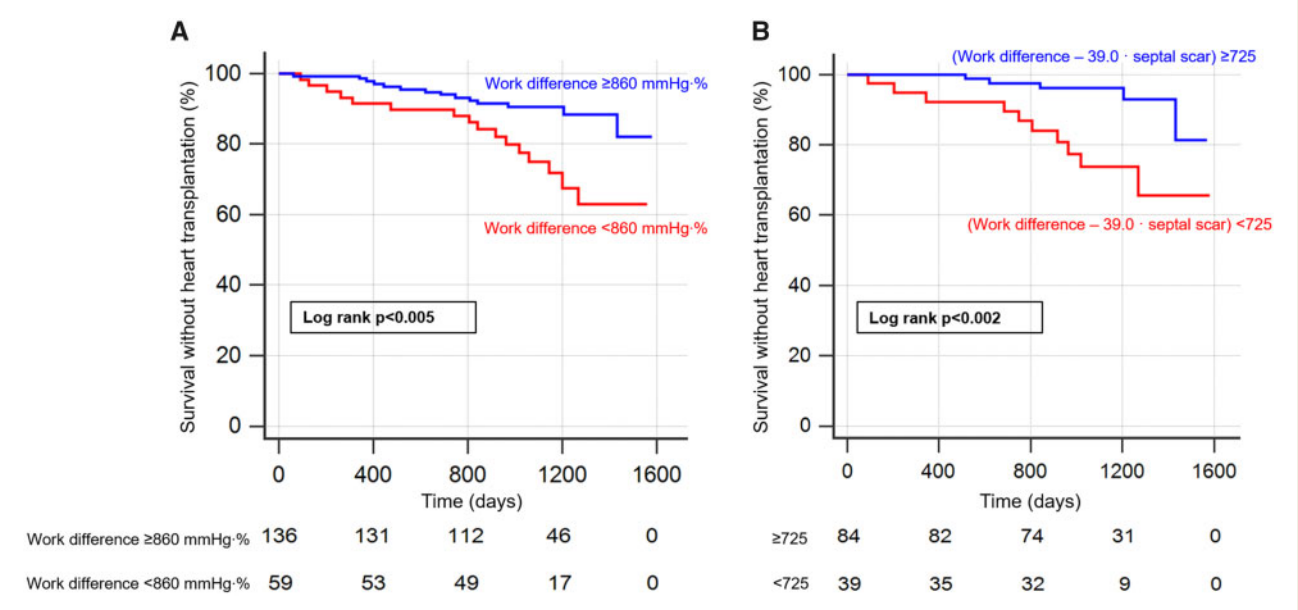


Figure 5 Association of work asymmetry and septal viability with long-term survival. (*A*) Kaplan–Meier curve stratified according to the proposed cut-off value for lateral-to-septal work difference. (*B*) Kaplan–Meier curve stratified according to the proposed cut-off value for lateral-to-septal work difference combined with septal viability.

Table 3 Multivariate linear regression analysis with left ventricular end-systolic volume reduction as dependent variable

Regression variable	B	VIF	95% CI	P-value
Constant term	-40.0			
Anterior wall scar	0.31	2.87	-0.05 to 0.66	0.088
Septal scar	0.42	3.17	0.04 to 0.80	0.029
Inferior wall scar	0.11	3.09	-0.22 to 0.45	0.503
Lateral wall scar	0.12	2.94	-0.21 to 0.45	0.479

$N = 122$. $R^2 = 0.33$. Regional scar was given as a continuous variable (%).
CI, confidence interval; VIF, variance inflation factors.

Table 4 Multivariate linear regression analysis with left ventricular end-systolic volume reduction as dependent variable

Regression variable	B	VIF	95% CI	P-value
Constant term	-1.15			
QRS morphology	8.70	1.13	-4.36 to 21.77	0.190
QRS duration	-0.15	1.07	-0.36 to 0.06	0.167
LW-S work difference	-0.009	1.13	-0.014 to -0.005	<0.0002
Septal scar	0.56	1.11	0.35 to 0.78	<0.0001

$N = 121$. $R^2 = 0.40$. Septal scar was given as a continuous variable (%).
CI, confidence interval; LW-S, lateral wall-to-septal; VIF, variance inflation factors.

with reverse LV remodelling and predicts long-term survival after CRT. The patient population represented all-comers referred for CRT, including upgrades from other pacemaker devices, atrial fibrillation and patients with poor echocardiographic image quality. When septal work was markedly reduced relative to LW work and septal myocardium was viable, the responder rate was high. When there was reduced septal work and septal scar, and therefore limited potential for improvement of septal function, the patients were unlikely to respond. Importantly, precision was very good in the subgroup of patients with QRS duration 120–150 ms where recommendation for CRT is weaker or even absent according to current guidelines.[2]

Work and viability

The work method provides a more comprehensive measure of contractile function than just measuring tissue velocities or strain since it incorporates the effect of abnormal regional loading conditions during dyssynchrony. The work method also provides a measure of contractile efficiency since both the positive and negative (wasted) work are taken into account. A variable degree of systolic lengthening is common in LBBB and reflects inefficient contractions where the septum absorbs energy as a result of contractions in the LV free wall. The work method incorporates this important feature of dyssynchrony.

It is well-known that total myocardial scar burden and, in particular, scars located in the LV posterolateral wall are associated with non-response to CRT.[6] The latter is believed to be caused by inefficient pacing delivery. Furthermore, as shown in a recent study from our group, LW scar tends to normalize septal contraction pattern in hearts with LBBB.[18] This reflects that systolic stretch and contractile inefficiency of the septum in LBBB is caused by vigorous contractions in the LW. Therefore, when there is reduced LW function, there is less impairment of septal function and therefore less potential for improvement with CRT.

The observation in the present study that septal scar is a predictor of non-response to CRT is in keeping with a small study of 23 patients who received CRT.[19] In our study, the presence of septal scar alone identified non-responders with relatively high sensitivity. Since a contraction pattern with impaired septal function and preserved LW function may be seen also in patients with septal infarcts, viability imaging is essential.

Alternative approaches

Septal flash, apical rocking, and systolic stretch in the septum and LW are well-known features of mechanical dyssynchrony, which have been shown to predict response and mortality in observational studies of CRT recipients.[12,13] An advantage of septal flash and apical rocking is the quick visual assessment on echocardiographic B-mode images, but their qualitative nature is a limitation. In a previous retrospective study, septal flash and apical rocking were combined with visual echocardiographic assessment of scar burden to optimize response prediction, and results were promising.[12] However, as indicated in the intercentre variability analysis, visual assessment of septal flash and apical rocking showed considerable variability which could depend on degree of training of the observers. It is likely that reproducibility of these methods can be improved by standardization of the diagnostic criteria and dedicated training. The systolic stretch index is based on myocardial strain and provides a quantitative assessment of dyssynchrony, but does not incorporate afterload. Taking into account results from the present and previous studies, it is likely that these parameters and myocardial work reflect the same phenomenon; i.e. the abnormal and inefficient septal contraction pattern during LBBB.

Clinical implications

The combined approach of work and viability offers a new, precise, and relatively simple approach for selection of CRT candidates. Myocardial work difference can be measured by acquisition of the apical four-chamber view only which can be obtained in nearly all patients. The addition of CMR represents an additional cost, but a large number of centres already perform LGE-CMR as routine investigation prior to CRT to avoid placing the LV lead in a scar. If CMR is not available, myocardial work difference may be useful as a standalone tool. Due to higher number of non-responders, the proposed approach appears especially valuable for patients with ischaemic cardiomyopathy and/or intermediate QRS duration.

Limitations

In a substantial number of patients, LGE-CMR is not feasible due to previous pacemaker device. This will be easier with wider use of CMR compatible devices.

Data on LV lead position were not available and may have provided additional insights.

The use of non-invasive LVP based on average brachial cuff pressure represents a limitation in patients with atrial fibrillation where LVP varies substantially from beat to beat. Furthermore, using pressure as a substitute for force in the work calculation represents a limitation to the methodology. It has previously been demonstrated, however, that the impact of such limitation is minor in LBBB.[5]

The present study was observational with a limited number of patients and the primary endpoint was reverse remodelling. Hence, there is need for a larger randomized trial with primarily clinical endpoints before considering to change clinical practice.

Conclusions

In the present study, assessment of LV function as the LW-S work difference by echocardiography identified CRT responders with good accuracy. When combining work difference with septal viability by CMR, the accuracy to identify CRT responders was further improved. Thus, marked work asymmetry with reduced septal function, but preserved septal viability, identified a contractile reserve which was activated by CRT.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: O.A.S. is co-inventor, but since May 24, 2017 no financial relations to the patent 'Method for myocardial segment work analysis', which was used to calculate myocardial work. The other authors report no conflicts.

References

1. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, Abraham WT, Ghio S, Leclercq C, Bax JJ, Yu CM, Gorcsan J 3rd, St John Sutton M, De Sutter J, Murillo J. Results of the predictors of response to CRT (PROSPECT) trial. *Circulation* 2008;**117**:2608–2616.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–2200.
3. Vernooy K, Cornelussen RNM, Verbeek X, Vanagt WYR, van Hunnik A, Kuiper M, Arts T, Crijns H, Prinzen FW. Cardiac resynchronization therapy cures dyssynchronopathy in canine left bundle-branch block hearts. *Eur Heart J* 2007;**28**:2148–2155.
4. Prinzen FW, Augustijn CH, Allessie MA, Arts T, Delhass T, Reneman RS. The time sequence of electrical and mechanical activation during spontaneous beating and ectopic stimulation. *Eur Heart J* 1992;**13**:535–543.
5. Russell K, Eriksen M, Aaberge L, Wilhelmsen N, Skulstad H, Remme EW, Haugaa KH, Opdahl A, Fjeld JG, Gjesdal O, Edvardsen T, Smiseth OA. A novel clinical method for quantification of regional left ventricular pressure-strain loop area: a non-invasive index of myocardial work. *Eur Heart J* 2012;**33**:724–733.
6. Bleeker GB, Kaandorp TA, Lamb HJ, Boersma E, Steendijk P, de Roos A, van der Wall EE, Schalij MJ, Bax JJ. Effect of posterolateral scar tissue on clinical and echocardiographic improvement after cardiac resynchronization therapy. *Circulation* 2006;**113**:969–976.
7. Vecera J, Penicka M, Eriksen M, Russell K, Bartunek J, Vanderheyden M, Smiseth OA. Wasted septal work in left ventricular dyssynchrony: a novel principle to predict response to cardiac resynchronization therapy. *Eur Heart J Cardiovasc Imaging* 2016;**17**:624–632.
8. Galli E, Leclercq C, Hubert A, Bernard A, Smiseth OA, Mabo P, Samset E, Hernandez A, Donal E. Role of myocardial constructive work in the identification of responders to CRT. *Eur Heart J Cardiovasc Imaging* 2018;**19**:1010–1018.
9. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt O-A, Cleland J, Deharo J-C, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J* 2013;**34**:2281–2329.
10. Parsai C, Bijnens B, Sutherland GR, Baltabaeva A, Claus P, Marciniak M, Paul V, Scheffer M, Donal E, Derumeaux G, Anderson L. Toward understanding response to cardiac resynchronization therapy: left ventricular dyssynchrony is only one of multiple mechanisms. *Eur Heart J* 2009;**30**:940–949.
11. Voigt JU, Schneider TM, Korder S, Szulik M, Gurel E, Daniel WG, Rademakers F, Flachskampf FA. Apical transverse motion as surrogate parameter to determine regional left ventricular function inhomogeneities: a new, integrative approach to left ventricular asynchrony assessment. *Eur Heart J* 2008;**30**:959–968.
12. Stankovic I, Prinz C, Ciarka A, Daraban AM, Kotrc M, Aarones M, Szulik M, Winter S, Belmans A, Neskovic AN, Kukulski T, Aakhus S, Willems R, Fehske W, Penicka M, Faber L, Voigt J-U. Relationship of visually assessed apical rocking and septal flash to response and long-term survival following cardiac resynchronization therapy (PREDICT-CRT). *Eur Heart J Cardiovasc Imaging* 2016;**17**:262–269.
13. Gorcsan J 3rd, Anderson CP, Tayal B, Sugahara M, Walmsley J, Starling RC, Lumens J. Systolic stretch characterizes the electromechanical substrate responsive to cardiac resynchronization therapy. *JACC Cardiovasc Imaging* 2019;**12**:1741–1752.
14. Engblom H, Tufvesson J, Jablonowski R, Carlsson M, Aletras AH, Hoffmann P, Jacquier A, Kober F, Metzler B, Erlinge D, Atar D, Arheden H, Heiberg E. A new automatic algorithm for quantification of myocardial infarction imaged by late gadolinium enhancement cardiovascular magnetic resonance: experimental validation and comparison to expert delineations in multi-center, multi-vendor patient data. *J Cardiovasc Magn Reson* 2016;**18**:27.
15. Gold MR, Daubert C, Abraham WT, Ghio S, St John Sutton M, Hudnall JH, Cerkvenik J, Linde C. The effect of reverse remodeling on long-term survival in mildly symptomatic patients with heart failure receiving cardiac resynchronization therapy: results of the REVERSE study. *Heart Rhythm* 2015;**12**:524–530.
16. Daubert C, Behar N, Martins RP, Mabo P, Leclercq C. Avoiding non-responders to cardiac resynchronization therapy: a practical guide. *Eur Heart J* 2017;**38**:1463–1472.
17. Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. *J Card Fail* 2001;**7**:176–182.
18. Aalen JM, Remme EW, Larsen CK, Andersen OS, Krogh M, Duchenne J, Hopp E, Ross S, Beela AS, Kongsgaard E, Bergsland J, Odland HH, Skulstad H, Opdahl A, Voigt JU, Smiseth OA. Mechanism of abnormal septal motion in left bundle branch block: role of left ventricular wall interactions and myocardial scar. *JACC Cardiovasc Imaging* 2019;**12**:2402–2413.
19. White JA, Yee R, Yuan X, Krahn A, Skanes A, Parker M, Klein G, Drangova M. Delayed enhancement magnetic resonance imaging predicts response to cardiac resynchronization therapy in patients with intraventricular dyssynchrony. *J Am Coll Cardiol* 2006;**48**:1953–1960.