

Wasted septal work in left ventricular dyssynchrony: a novel principle to predict response to cardiac resynchronization therapy

J. Vecera^{1,2}, M. Penicka², M. Eriksen¹, K. Russell¹, J. Bartunek², M. Vanderheyden², and O.A. Smiseth^{1*}

¹Division of Cardiovascular and Pulmonary Diseases, Department of Cardiology and Institute for Surgical Research, Center for Cardiological Innovation, Center for Heart Failure Research and KG Jebsen Cardiac Research Centre Oslo, Oslo University Hospital and University of Oslo, Rikshospitalet, N-0027 Oslo, Norway; and ²Cardiovascular Center Aalst, OLV Clinic, Aalst, Belgium

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Aims

Cardiac resynchronization therapy (CRT) in heart failure is limited by many non-responders. This study explores whether degree of wasted left ventricular (LV) work identifies CRT responders.

Methods and results

Twenty-one patients who received CRT according to guidelines were studied before and after 8 ± 3 months. By definition, segments that shorten in systole perform positive work, whereas segments that lengthen do negative work. Work was calculated from non-invasive LV pressure and strain by speckle tracking echocardiography. For each myocardial segment and for the entire LV, wasted work was calculated as negative work in percentage of positive work. LV wall motion score index (WMSI) was assessed by echocardiography. Response to CRT was defined as $\geq 15\%$ reduction in end-systolic volume (ESV). Responder rate to CRT was 71%. In responders, wasted work for septum was $117 \pm 102\%$, indicating more negative than positive work, and decreased to $14 \pm 12\%$ with CRT ($P < 0.01$). In the LV free wall, wasted work was $19 \pm 16\%$ and showed no significant change. Global LV wasted work decreased from 39 ± 21 to $17 \pm 7\%$ with CRT ($P < 0.01$). In non-responders, there were no significant changes. In multiple linear regression analysis, septal wasted work and WMSI were the only significant predictors of ESV reduction ($\beta = 0.14$, $P = 0.01$; $\beta = 1.25$, $P = 0.03$). Septal wasted work together with WMSI showed an area under the curve of 0.86 (95% confidence interval 0.71–1.0) for CRT response prediction.

Conclusion

Wasted work in the septum together with WMSI was a strong predictor of response to CRT. This novel principle should be studied in future larger studies.

Keywords

Heart failure • Strain • Dyssynchrony

Introduction

Cardiac resynchronization therapy (CRT) has become an important treatment option for heart failure patients with left ventricular (LV) dyssynchrony. The therapy is restricted to patients who have abnormally wide QRS in the electrocardiogram and preferably left bundle branch block (LBBB) morphology as signs of electrical conduction delay.¹ A significant limitation of CRT, however, is that 30–40% of the patients who receive a device based on these criteria experience no improvement in symptoms after device implantation. This may

reflect that the electrocardiographic criteria for dyssynchrony are sub-optimal. A number of imaging-based dyssynchrony markers that measure timing of contraction have been proposed, but none of these has proved to increase CRT responder rate when studied in prospective clinical trials. Therefore, current guidelines do not recommend assessment of dyssynchrony by echocardiography or by any other imaging modality in the diagnostic work-up when patients are evaluated for CRT.¹ The failure of echocardiographic timing indices to improve CRT responder rate suggests that other approaches should be explored. As the ultimate problem with in-coordinated contractions is mechanical

* Corresponding author. Tel: +47 23070000/+47 23073271; Fax: +47 23073917. E-mail: otto.smiseth@ous-hf.no

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inefficiency, we hypothesized that the amount of wasted myocardial energy caused by mechanical dyssynchrony predicts response to CRT.

Normally, all LV segments contract in a synchronized fashion and contribute to ejection of blood into the aorta. When there is electrical conduction delay, however, early and late activated segments contract at different times and energy is wasted in stretching opposing segments.² As observed typically in LBBB, the early activated septum contracts prior to aortic valve opening and stretches the LV lateral wall, and contraction in the late activated lateral wall causes a variable degree systolic lengthening of the septum. The negative work during systolic lengthening makes no contribution to LV ejection and therefore represents a waste. We suggest that the amount of wasted work in the dyssynchronous ventricle reflects the potential for recovery of function with CRT. This concept was tested in the present study, in which we calculated negative and positive work for each LV segment and expressed wasted work as negative work in percentage of positive work for each segment and globally for the entire LV.

Methods

Patients and study protocol

Forty-two consecutive patients with heart failure (age 72 ± 12 years, 74% males) who were scheduled for implantation of a CRT device were prospectively included between March 2011 and December 2012. Patients were selected according to current recommendations for CRT: that is, severe heart failure [New York Heart Association (NYHA) classes II–IV] with severely depressed LV ejection fraction (EF) ($<35\%$) and QRS duration >130 ms.

Twenty-one patients were excluded from our analysis due to atrial fibrillation ($n = 8$), multiple bigeminies ($n = 1$), right ventricular pacing ($n = 3$), and poor image quality ($n = 8$), and one patient died after implantation and could not be followed.

At baseline and at a median of 8 months (interquartile range 6–13) after device implantation, clinical status was evaluated and echocardiographic measurements were performed. Measurements included arterial cuff blood pressure and two-dimensional transthoracic echocardiography to determine LV volumes, EF, to define timing of aortic and mitral valve events, and to calculate LV myocardial strain by speckle tracking echocardiography (STE).

Echocardiography

A Vivid E9 ultrasound scanner (GE Vingmed Ultrasound AS, Horten, Norway) was used to record conventional two-dimensional greyscale images of LV apical two-, four-, and three-chamber views for assessing volumes, EF, and strain by STE. Narrow sector two-dimensional imaging over valves in parasternal long-axis view was used to define timing of opening and closure of the mitral and aortic valves; this was required for calculation of an estimated LV pressure curve.²

Calculation of segmental work

Segmental LV work was assessed as described previously.³ In brief, work was calculated in a representative heartbeat for each of up to 17 individual segments ($n = 13.1 \pm 2.7$). Peak systolic LV pressure was assumed to be equal to peak arterial pressure measured with a cuff manometer, as the average of three recordings. Segments with poor image quality (mostly apical) were excluded from the analysis. Work was calculated as a function of time throughout the cardiac cycle from the strain recordings and estimated LV pressure. This was performed by calculating the rate of segmental shortening (strain rate) by differentiation of the strain curve and multiplying this with

instantaneous LV pressure. 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 segment elongation represents energy loss and was defined as negative work in contrast to positive work performed during segmental shortening. In order to characterize energetic efficacy of each segment, the ratio between negative and positive work was calculated. This ratio $\times 100\%$, which we report as wasted work, was calculated for each segment (segmental wasted work) and was also reported as a global measure (wasted work global) calculated from the sum of work for all segments. Wasted work of 100% means that negative work equals positive work, and ratios $>100\%$ indicate that negative work exceeds positive work. Septal work analysis was based on four-segment analysis (basal inferoseptal, basal anteroseptal, mid-inferoseptal, and mid-antroseptal) as good speckle tracking data from apical segments were often difficult to obtain.

The clinical part of the study was done in Aalst, and recordings were brought to Oslo for the work analysis, and this was done by a co-author who was blinded to clinical and echocardiographic data.

The study was approved by the Regional Committee for Medical Research Ethics. All subjects gave written informed consent.

Definitions

Response to CRT

A positive response to CRT was defined as $\geq 15\%$ reduction in LV end-systolic volume (ESV) at follow-up.

LV systole, isovolumic contraction (IVC), and relaxation times (IVR)

The time interval from mitral valve closure to mitral valve opening, both based on timing of opening and closure of valve cusps, was used for work calculations. IVC timing was defined as the time interval from mitral valve closure to aortic valve opening and IVR timing as the time interval from aortic valve closure to mitral valve opening.

LBBB

LBBB was defined as QRS ≥ 120 ms in combination with broad, notched, or slurred R wave in I, aVL, V5, and V6 and absent q waves in I, V5, and V6 (in the absence of a large anterior-apical infarction).^{4,5}

Echocardiographic wall motion score index (WMSI)

Regional LV function includes evaluated WMSI by echocardiography. As recommended by the European Association of Cardiovascular Imaging,⁶ a 17-segment model was used for LV segmentation. This model consists of six segments at both the basal and mid-ventricular levels and five segments at the apex. The attachment of the right ventricular wall to the LV defines the septum, which is divided at basal and mid-LV levels into anteroseptum and inferoseptum. Continuing counterclockwise (viewed from apex), the remaining segments at both basal and mid-ventricular levels are labelled as inferior, inferolateral, anterolateral, and anterior. The apex includes apical cap and septal, inferior, lateral, and anterior segments. Each segment was analysed individually and scored on the basis of its motion and systolic thickening. Each segment's function was confirmed in multiple views. Segments were scored as: normal or hyperkinesis = 1, hypokinesis = 2, akinesis = 3, and dyskinesis (or aneurysmatic) = 4. WMSI was derived as the sum of all scores divided by the number of segments visualized.

End-diastolic LV volume index (LV EDVix) and end-systolic LV volume index (LV ESVix)

LV volumes were measured using biplane Simpson's method and indexed to body surface calculated using Mosteller formula and expressed in mL/m² of the body surface area.⁶

Table 1 Baseline clinical, echocardiographic, and haemodynamic characteristics

	Responders, <i>n</i> = 15	Non-responders, <i>n</i> = 6	<i>P</i> -value
Age (years)	70.6 ± 11.6	72.7 ± 6.7	0.69
Sex (% females)	33	0	0.26
Diabetes mellitus, <i>n</i> (%)	4 (27)	5 (83)	0.046
Coronary artery disease, <i>n</i> (%)	6 (40)	4 (67)	0.36
Epicardial leads, <i>n</i> (%)	9 (60)	5 (83)	0.61
NYHA class	2.7 ± 0.4	2.6 ± 0.5	0.68
NT-proBNP (pg/mL)	6131 ± 7589	3734 ± 3645	0.52
Glomerular filtration rate (mL/min)	54 ± 22	54 ± 13	0.99
QRS width (ms)	176 ± 24	165 ± 20	0.36
EF-LV (%)	28 ± 8	29 ± 11	0.81
LV EDVix (mL/m ²)	117 ± 28	116 ± 36	0.95
LV ESVix (mL/m ²)	85 ± 25	85 ± 42	0.99
Mitral regurgitation, moderate <, <i>n</i> (%)	8 (53)	2 (33)	0.64
Systolic blood pressure (mmHg)	122 ± 18	113 ± 10	0.24
WMSI, <i>n</i>	2.7 ± 0.4	2.5 ± 0.5	0.54
sPAP (mmHg)	35 ± 12	32 ± 16	0.7
LBBB pattern, <i>n</i> (%)	15 (100)	3 (50)	0.015
Wasted work LV global (%)	39 ± 22	26 ± 17	0.19
Wasted work interventricular septum (%)	117 ± 102	45 ± 34	0.11
Wasted work lateral wall (%)	18.8 ± 15.6	18.9 ± 10.1	0.99

WMSI, wall motion score index; sPAP, systolic pulmonary arterial pressure; EDVix, end-diastolic volume index; ESVix, end-systolic volume index; LV, left ventricle; LBBB, left bundle branch block; NT-proBNP, N-terminal fragment of brain natriuretic peptide; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.

Table 2 Selected variables: baseline and after CRT at FU visit (*n* = 21)

Variable	Baseline	CRT, FU	<i>P</i> -value
LVEF (%)	28.2 ± 8.3	37.5 ± 12.2	0.0007
NT-proBNP (pg/mL)	5532 ± 6809	4497 ± 8298	0.48
6MWT (min)	288 ± 86	345 ± 125	0.0038
NYHA class	2.6 ± 0.5	2.2 ± 0.6	0.0077
LV ESVix (mL/m ²)	163 ± 61	121 ± 60	0.0001
QRS width (ms)	171 ± 21	151 ± 22	0.0001
Wasted work global (%)	36 ± 21	19.0 ± 10	0.0023
Wasted work septum (%)	96 ± 93	17 ± 19	0.0011
Wasted work lateral wall (%)	19 ± 14	33 ± 38	0.09
WMSI	2.6 ± 0.5	2.1 ± 0.6	0.0002

All abbreviations are explained in Table 4.

Table 3 Selected variables: baseline and after CRT in responders (*n* = 15)

Variable	Baseline	CRT, FU	<i>P</i> -value
LVEF (%)	27.9 ± 7.7	41.9 ± 11.1	<0.0001
NT-proBNP (pg/mL)	6131 ± 7589	4185 ± 8955	0.1
6MWT (min)	301 ± 79	376 ± 117	0.0064
NYHA class	2.5 ± 0.5	2.0 ± 0.4	0.0013
LV ESVix (mL/m ²)	159 ± 52	104 ± 44	<0.0001
QRS width (ms)	174 ± 21	148 ± 22	<0.0001
Wasted work global (%)	39 ± 21	17 ± 7	0.0015
Wasted work septum (%)	117 ± 102	14 ± 12	0.0016
Wasted work lateral wall (%)	19 ± 16	27 ± 20	0.16
WMSI	2.5 ± 0.5	1.9 ± 0.6	0.0001

All abbreviations are explained in Table 4.

Biventricular pacemaker implantation

CRT was provided by the clinician's decision with transvenous or epicardial lead implantation. In all patients, CRT devices with defibrillation capabilities (CRT-D) were implanted. The LV lead was inserted into lateral branches of coronary sinus in two, posterolateral branches in four, and anterolateral branch in one patient. In 14 patients, the lead was placed epicardially via a left minithoracotomy, where the lead was positioned in the posterolateral region of the LV at the site with maximum delay from QRS onset according to epicardial signal mapping. After implantation, the atrioventricular (AV) delay was adjusted for optimal filling by

Doppler echocardiographic assessment of mitral inflow, resulting in AV delays of 139 ± 26 ms. Left-right ventricle (V-V) timing of stimulation was adjusted according to the best LV stroke volume based on velocity–time–integral measurements in LV outflow tract with Doppler echocardiography (LV before RV of 27 ± 17 ms). In all patients, biventricular stimulation was present >95% of time.

Statistical analysis

Continuous variables with normal distribution are expressed as mean ± SD. Dichotomous data are expressed as percentages.

Table 4 Selected variables: baseline and after CRT in non-responders ($n = 6$)

Variable	Baseline	CRT, FU	P-value
LVEF (%)	28.9 ± 10.7	28.8 ± 8.8	0.98
NT-proBNP (pg/mL)	3734 ± 3644	5970 ± 7664	0.59
6MWT (min)	261 ± 104	278 ± 127	0.18
NYHA class	2.8 ± 0.4	2.7 ± 0.8	0.36
LV ESVix (mL/m ²)	171 ± 84	163 ± 78	0.07
QRS width (ms)	163 ± 21	160 ± 22	0.54
Wasted work global (%)	26 ± 17	25 ± 13	0.75
Wasted work septum (%)	45 ± 34	25 ± 32	0.12
Wasted work lateral wall (%)	18.9 ± 10.1	48.2 ± 64.4	0.27
WMSI	2.7 ± 0.4	2.6 ± 0.4	0.3

6MWT, six-minute walking test; WMSI, wall motion score index; LV ESVix, left ventricular end-systolic volume index; ESVix, end-systolic volume index; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal fragment of brain natriuretic peptide.

To compare numerical data between two groups, paired and unpaired Student's tests were used when appropriate. Dichotomized comparisons were assessed by χ^2 test or Fisher's exact test. Receiver-operating characteristic (ROC) curves [area under the curve (AUC)] were determined to evaluate the diagnostic performance of LV dyssynchrony indices to detect responders to CRT. An optimal cutoff value for the diagnosis of responders was chosen to maximize the Youden index (sensitivity + specificity - 1). Pearson's correlation analysis was used to find a parameter that correlates the best with ESV relative reduction. We used univariate linear regression analysis to find predictors for the amount of ESV reduction after CRT. Stepwise linear regression was used to identify the parameters that best predicted the reduction in ESV. The limited number of patients in the studied group allowed us to test only two variables at a time. As the only independent predictor in univariate analysis was septal wasted work, we tested the additive value of other clinically relevant characteristics, and the best prediction was found by a linear weighted combination of septal wasted work and WMSI. For the ROC analysis, the values for each patient found by evaluating the regression formula $66.46 + (0.14 \times \text{septal wasted work}) - (1.32 \times \text{WMSI})$ were then used. P-values of less than 0.05 were considered significant (SPSS 20.0, SPSS, Chicago, IL, USA).

Reproducibility

Previous studies have tested the reproducibility of the non-invasive estimate of myocardial work by pressure-strain loop area, and the studies by Russell *et al.*² and Boe *et al.*⁷ showed good inter- and intra-observer reproducibility for estimates of work.

Results

At the time of follow-up, 15 patients (71%) were responders and 6 (29%) were non-responders.

In the non-responders group ($n = 6$), there were three episodes of heart failure decompensation, one sustained ventricular tachycardia during follow-up, and no patient claimed improvement in terms of functional capacity. In contrast, in the responders ($n = 15$), 12

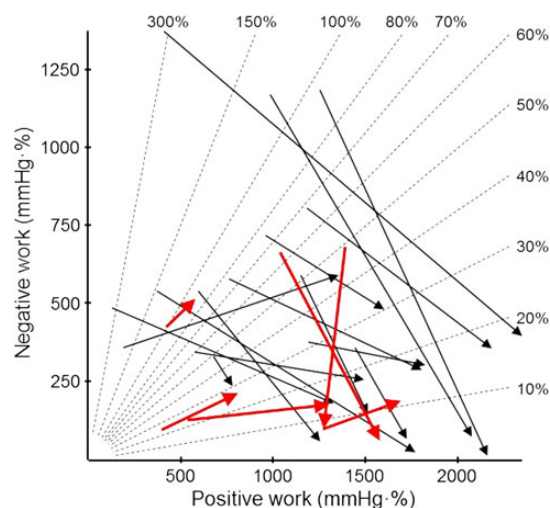


Figure 1 Individual data showing effect of CRT on septal work: percentage of wasted work is indicated by the dashed lines. CRT responders (black thin arrows) demonstrated a shift towards more positive work with reduction in the wasted work. The non-responders (red thick arrows) showed no consistent shift.

patients (80%) claimed significant improvement in terms of quality of life or functional status. When episodes of heart failure, ventricular tachycardia, and acute renal failure were taken into the analysis, these were significantly more frequent in non-responders than in the responder group (67 vs. 13%, $P = 0.03$).

At baseline, non-responders and responders were similar with regard to all measured variables except for higher prevalence of diabetes mellitus in non-responders and there was more often LBBB pattern in ECG in responders (Table 1). Table 2 shows changes in key parameters for the entire study population. In the responder group, CRT caused significant improvement in NYHA class and EF and there was a decrease in ESV (Table 3). Furthermore, there was a reduction in global wasted work from 39 ± 21 to $17 \pm 7\%$ ($P < 0.01$) and for the septum, there was a reduction in wasted work from 117 ± 102 to $14 \pm 12\%$ ($P < 0.01$), indicating less waste of myocardial energy. In the non-responder group, there was no significant change in NYHA class, EF, ESV, or in wasted work (Table 4). Individual data displayed in Figures 1 and 2 show a shift towards more positive work in the responders, whereas non-responders showed no consistent shift.

In the LV free wall, there was no significant difference in wasted work between responders and non-responders at baseline or at follow-up (Tables 1 and 2).

Prior to CRT, the majority of responders had higher levels of wasted work compared with non-responders (Table 1), but variability was substantial and the difference was not statistically significant. Reduction in wasted work with CRT, however, was observed only in responders (Tables 3 and 4).

In univariate linear regression analysis, the only independent predictor for the amount of ESV reduction after CRT was the level of wasted work of the interventricular septum at baseline [95% confidence interval (CI) 0.015–0.206, $P = 0.028$] (Table 5). In multiple

linear regression analysis, septal wasted work and WMSI together were the only significant predictors of the ESV reduction (septal wasted work: $\beta = 0.14$, $P = 0.004$; WMSI: $\beta = 1.32$, $P = 0.0012$) (Table 6). Stepwise linear regression analysis with these significant variables showed reasonable predictive value with $r^2 = 0.46$ and $\sigma_{\text{est}} = 16.3$ (RMS residual error) [ESV reduction = $66.46 + (0.14 \times \text{septal wasted work}) - (1.32 \times \text{WMSI})$] for the ESV reduction with CRT therapy (Figure 3 and Table 7).

In AUC analysis, wasted work in septal segments together with LV WMSI showed an AUC of 0.86 (CI 0.71–1.0) for CRT response prediction (Figure 4).

In univariate correlation analysis, the strongest correlation was found also for the combined variable of wasted work in septal segments together with WMSI taken from stepwise multivariate analysis ($r = 0.68$, $P < 0.05$) (Table 8). Thus, higher degree of wasted work in the septum and preserved regional LV function were the best predictors at baseline and were significantly associated with more pronounced reduction in ESV with CRT.

Discussion

CRT is a well-established non-pharmacological therapy for patients with systolic heart failure and wide QRS, preferably LBBB.¹ Due to the risks and costs associated with CRT, it is important to avoid device implantation in patients who are unlikely to benefit. This is a major clinical challenge, and the cardiology community has so far not been able to come up with imaging approaches, which may improve patient selection. Rather than focusing on indices measuring timing of contraction, which was studied extensively and with little success in the past, we address the issue of mechanical efficiency and how this may help to identify responders to the therapy. The observations in this study suggest that the response to CRT is related to the degree of energy loss that results from in-coordinated LV contractions.

We utilized a novel clinical method that was introduced and validated by Russell et al.^{2,3} to measure how much work is wasted in ventricles with dyssynchronous contractions. This energy waste

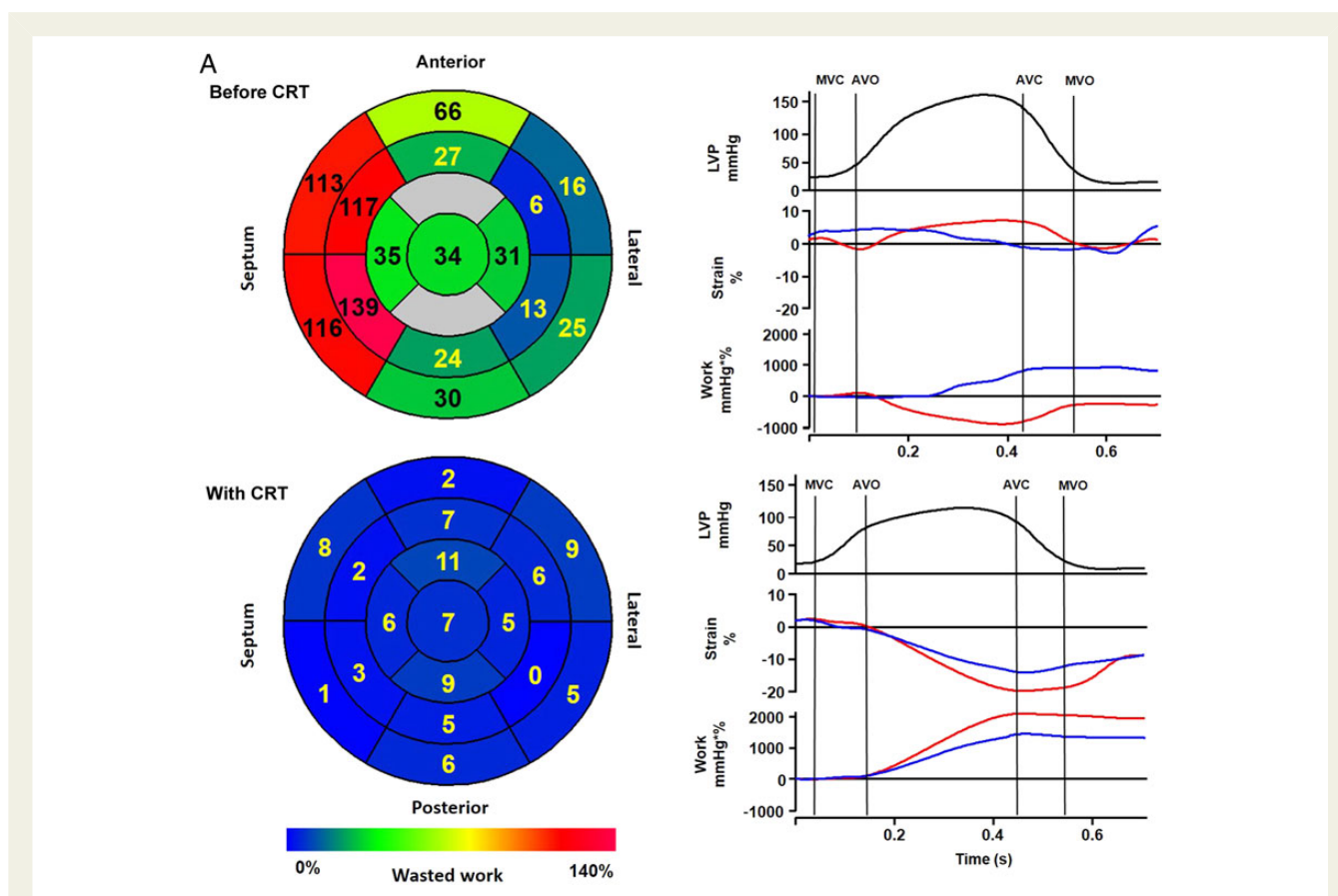


Figure 2 Calculation of wasted work in individual examples from a responder and a non-responder before and after CRT. To the right are traces of estimated LV pressure, septal strains, and calculated work. The red and blue curves represent average strain values from the four basal and mid-segments of the septum and the LV lateral wall, respectively. The left panels display bull's eye plot of LV segmentation where each number reflects the amount of wasted work (%). As shown in the right panels, when the work level drops below 0, it reflects segment elongation, as indicated by the strain trace, and means that work is wasted. (A) Example—CRT responder: note substantial amount of wasted work in septal segments before CRT (upper bull's eye) and a marked drop in wasted work in these segments with CRT (lower bull's eye). (B) Example—CRT non-responder: the amount of wasted work in septum is moderate before CRT and the drop is not as marked as in the responder in (A). AVC, aortic valve closure; AVO, aortic valve opening; MVC, mitral valve closure; MVO, mitral valve opening; LVP, left ventricular pressure.

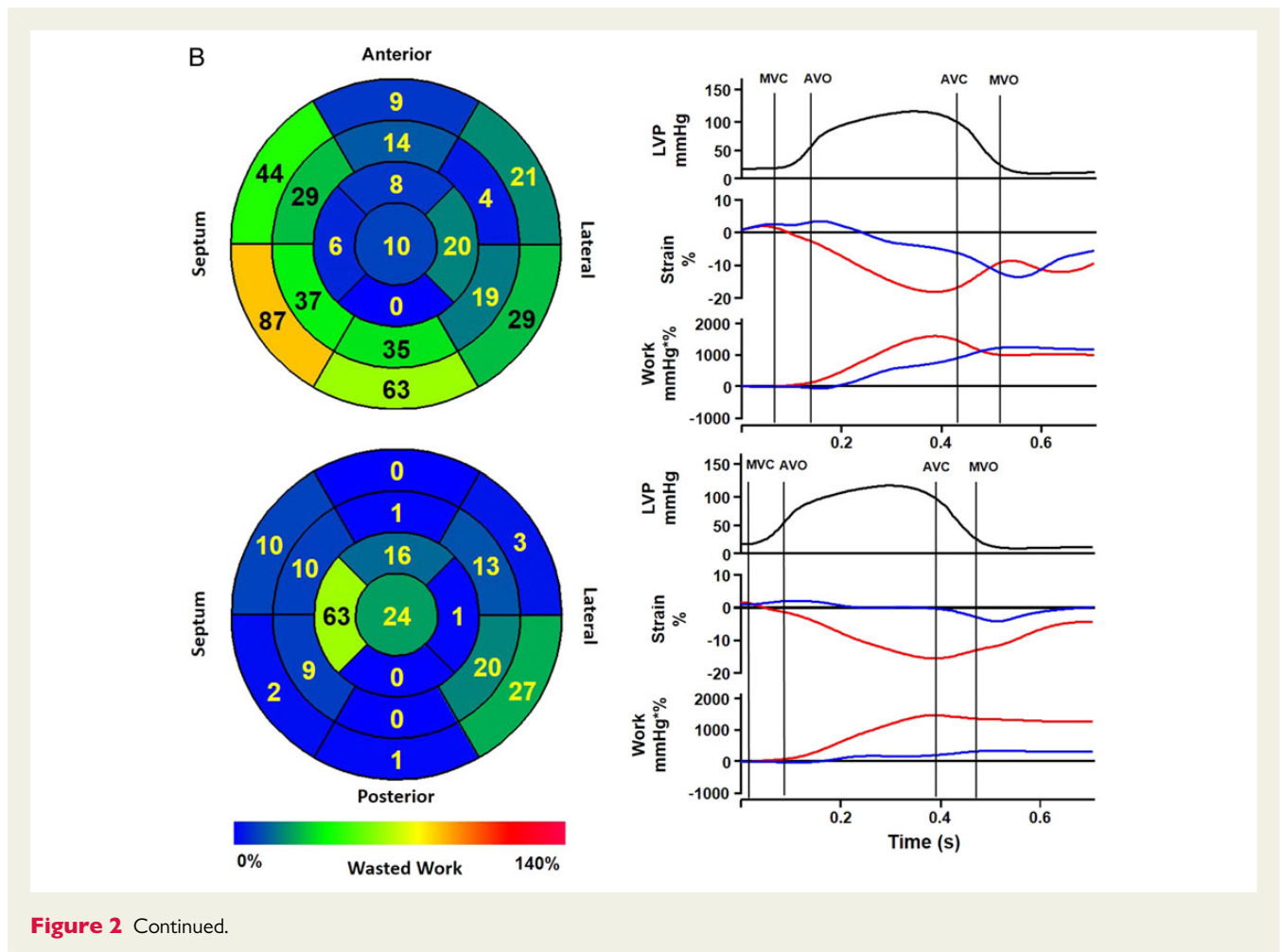


Figure 2 Continued.

Table 5 Univariate linear regression analysis, dependent variable: LV end-systolic volume change with CRT

Variable	β	B	95% CI for B		P-value
EF-LV (%)	0.6	0.153	-1.064	1.369	0.796
DM	-0.133	-5.557	-25.46	14.306	0.564
WMSI	-0.360	-0.966	-2.167	0.235	0.109
LV EDVix (mL/m ²)	-0.49	-0.035	-0.377	0.307	0.834
Age (years)	-0.394	-0.810	-1.717	0.097	0.077
NT-proBNP (pg/mL)	0.000	-0.091	-0.002	0.001	0.695
QRS width (ms)	-0.103	-0.95	-0.533	0.344	0.657
LV perfusion defect rest (SPECT), %	-0.274	-0.444	-1.193	0.305	0.230
Wasted work septum baseline (%)	0.485	0.110	0.015	0.206	0.026

All abbreviations are explained in Table 7.

was measured as work consumed during segmental lengthening (negative work) in percentage of work during segmental shortening (positive work) and was named wasted work. In a normal heart, there are only minor physiological differences in timing of LV segmental contraction, and the global wasted work in a normal heart is on average <10%, which means that more than 90% of the energy generated during systolic contraction is utilized for work.² In the present study, the responder group had global wasted work of

39% prior to CRT, which means that more than one-third of the energy generated during systolic contraction was wasted. In the septum, the average wasted work was near 100%, which indicates that the septum absorbed as much work as it generated and therefore made essentially no contribution to LV ejection and stroke volume. In the responder group, the global as well as the septal wasted work approached normal values with CRT, indicating a major improvement in coordination of LV contractions. In the

Table 6 Multiple linear regression analysis, dependent variable: LV end-systolic volume change with CRT

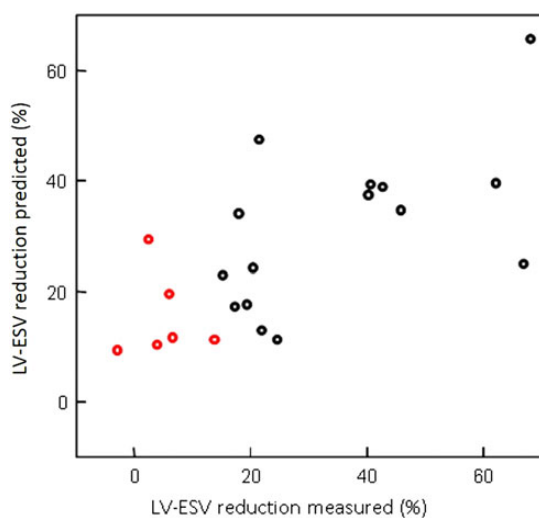
Baseline variable	B	P-value
Constant term	66.546	0.003
Wasted work septum	0.135	0.004
WMSI	-1.316	0.012

All abbreviations are explained in Table 7.

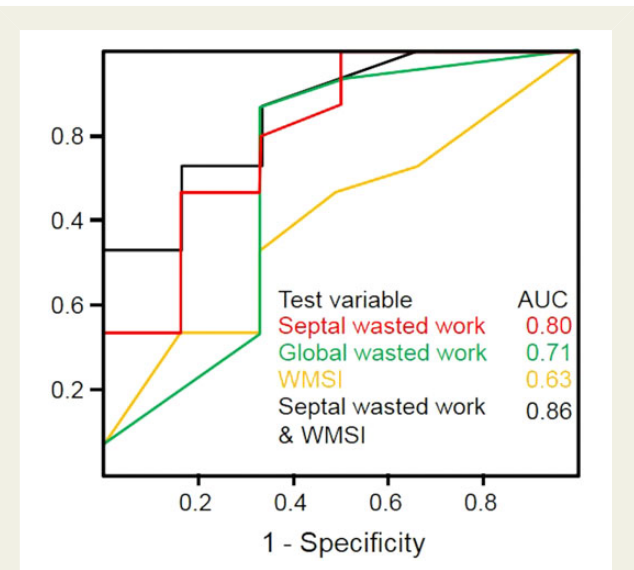
Table 7 Stepwise linear regression analysis, dependent variable: LV end-systolic volume change with CRT [$r^2 = 0.46$, $\sigma_{est} = 16.3$ (RMS residual error)]

Baseline variable	β	P-value
Constant term	66.46	0.00
Wasted work septum	0.14	0.00
WMSI	-1.32	0.01

DM, diabetes mellitus; WMSI, wall motion score index; EDVix, end-diastolic volume index; ESVix, end-systolic volume index; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal fragment of brain natriuretic peptide.

**Figure 3** Stepwise logistic regression analysis-based scatter plot showing predicted vs. measured LV-ESV reduction with CRT; prediction equation: LV-ESV reduction = $66.46 + (0.14 \times \text{septal wasted work}) - (1.32 \times \text{WMSI})$. Red symbols, non-responders; black symbols, responders. LV-ESV, left ventricular end-systolic volume; WMSI, wall motion score index; LV-ESV reduction, relative reduction with CRT expressed in percentage.

non-responder group, there was much less wasted work globally and in the septum at baseline, and the changes with CRT were less marked than in the responders. The observation that the largest waste of myocardial work was located to the septum is consistent

**Figure 4** AUC analysis for selected variables for CRT response prediction. WMSI, wall motion score index; AUC, area under the curve; CRT, cardiac resynchronization therapy.**Table 8** Univariate correlation analysis: LV-ESV change with CRT is correlated variable

Baseline variable	R	P-value
Wasted work global	0.05	0.83
Wasted work septum	0.49	0.03
WMSI	-0.36	0.11
QRS width	-0.10	0.66
Wasted work septum and WMSI ^a	0.68	0.00

WMSI, wall motion score index; LV-ESV, left ventricular end-systolic volume.

^aThe strongest correlation was found for the combined variable taken from stepwise multivariate analysis ($r = 0.68$, $P < 0.05$).

with well-described abnormalities in septal motion and deformation in patients with LBBB.⁸ When combining the degree of septal wasted work with LV wall motion score, the prediction of response to CRT was even better, suggesting that this combined approach may be useful.

A large fraction of the patient population had coronary artery disease as mechanism of heart failure, which often implies myocardial scarring. In principle, the proposed method for calculating wasted work cannot by itself differentiate between systolic lengthening which is due to electrical conduction delay as seen typically in the septum of patients with LBBB and systolic stretching of segments with transmural myocardial scar. The substantial variability in degree of wasted work between patients most likely in part reflects this mixed aetiology of systolic lengthening. For the septum at baseline, there was a large numerical difference between wasted work in responders and non-responders, but this difference did not reach statistical significance, probably reflecting both the relatively small size of the study and a variable contribution from myocardial scar to

wasted work. This mixed aetiology of wasted work probably explains why the combination of wasted work and WMSI was the best predictor of response to CRT.

The group of Prinzen and co-workers proposed to use the amount of myocardial stretch relative to shortening during LV ejection as a predictor of response to CRT.⁹ They used magnetic resonance imaging to measure strain and could show that the relative stretch, which they named the internal stretch fraction, was superior to time to peak shortening as predictor of response to CRT. Lim *et al.*¹⁰ introduced the concept of wasted work measured as the strain delay index, which was defined as the sum of the difference between peak and end-systolic strain across 16 LV segments. They showed that the strain delay index predicted response to CRT. The internal stretch fraction, the strain delay index or just measuring the ratio between septal lengthening and shortening, may be used to quantify discoordination. None of these parameters, however, incorporates a measure of wall stress. Pre-ejection septal shortening strain occurs in the early phase of IVC when there is only a small rise in LV pressure, whereas subsequent lengthening strain (rebound stretch) occurs when there is a more marked rise in LV pressure; therefore the ratio between shortening and lengthening strain is not the same as between positive and negative work.

We cannot claim that septal wasted work is superior to a pure strain-based analysis because such a comparison would require a larger study. The recent article by Risum *et al.*¹¹ suggests that combined analysis of septal and LV lateral wall strain patterns may be a useful approach for the identification of responders to CRT. As energy waste cannot be estimated by measuring strain or dimension only, the wasted work estimates represent a different concept than just measuring strain. Ultimately, however, the ability to best identify responders to CRT is what matters, and this issue was not resolved by the present study.

The response to CRT is not black and white, but it is a continuous variable when evaluated in terms of ESV changes. We found the amount of septal wasted work before CRT was the only significant predictor of the relative ESV change with CRT, and even in the non-responders group, there was a trend towards a reduction in septal wasted work, but the reduction in ESV was not large enough to put the patient in the responder group.

Study limitations

The use of an estimate instead of a directly measured LV pressure implies that important details in pressure traces may be lost. The importance of this limitation was explored in a previous study by Russell *et al.*,² which validated the non-invasive method for estimating LV pressure and segmental work, including testing of how different LV systolic pressure profiles modified the work estimate. As expected, there were inaccuracies in the estimates of pressure during ejection in particular, but they did not play an important role because the impact on work of under- or overestimating LV pressure during the first part of the LV ejection phase was essentially compensated for by the opposite effect during the last part. If more subtle changes in LV pressure–loop area need to be detected, however, tonometrically recorded arterial pressure may be used.

In principle, work should be calculated using wall stress rather than pressure, and this would require measurement of local radius of curvature and wall thickness in each segment throughout systole.

Therefore, the values for segmental work used in the wasted work calculations are estimates and not direct measures of work. The observations that wasted work predicts response to CRT suggest that the method may be clinically useful in spite of this limitation.

A substantial number of patients were excluded due to irregular heart rate as this complicates the strain analysis, and we included only patients in sinus rhythm. Patients with atrial fibrillation represent a substantial fraction of the heart failure population, and future studies should determine whether the wasted work method may be applied in this group. Another potential limitation is patients with scarring in the ventricle as scar tissue will lengthen passively and show negative work. Potentially, the combination with assessment of LV wall motion score may help to identify the tissue that is non-contractile and therefore most likely represents scar. Other methods may also be used to identify scar, including cardiac magnetic resonance imaging.

In this study, the wasted work fraction was computed semi-automatically with special software, but in the future, there should be a software directly implemented into echo machines. The present study population was relatively small and therefore larger studies are needed to determine whether wasted work may serve as a supplementary method in patients who are evaluated for CRT.

The number of patients included in the present study does not allow comparison of wasted work with other proposed predictors of response to CRT, and further studies with larger patient populations are necessary for such analysis. Primarily, such a comparison was not the goal of our study because the power of prediction of previously suggested imaging-based parameters of CRT response has not shown added clinical value.

Conclusion

In this study, we propose assessment of wasted myocardial work as a novel principle to identify patients who may be responders to CRT. This principle needs to be tested in a larger study which should investigate whether wasted work and other measures of myocardial efficiency may be used to identify responders to CRT.

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IMAGE FOCUS

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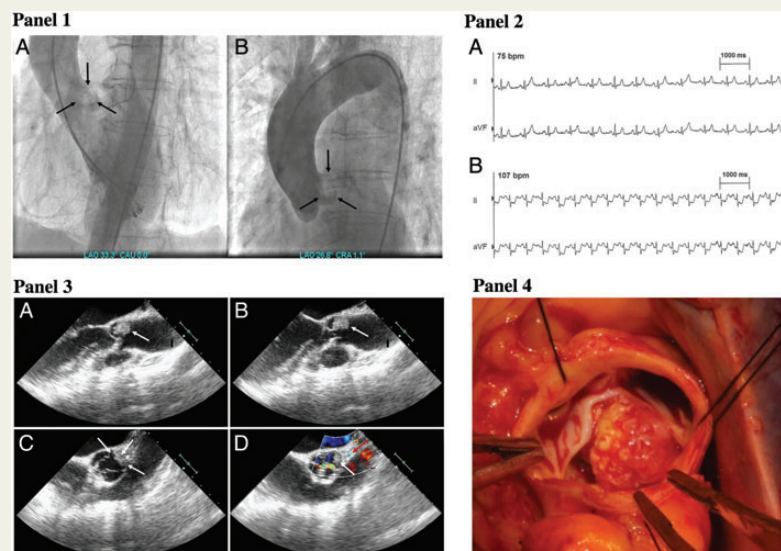
Papillary fibro-elastoma as a rare cause of rate-dependent angina: importance of diastolic coronary perfusion

Ief Hendrickx^{1*}, Philippe B. Bertrand¹, Mathias Vrolix¹, Bert Ferdinande¹, and Yves Cruysberghs²

¹Department of Cardiology, Ziekenhuis Oost-Limburg, Schiepse Bos 6, B-3600 Genk, Belgium; and ²Department of Cardiology, Ziekenhuis Maas en Kempen, B-3680 Maaseik, Belgium

* Corresponding author. Tel: +32 479 775 940. E-mail: iefhendrickx@hotmail.com

A 76-year-old woman presented with unstable angina pectoris. A diagnostic coronary angiography revealed single-vessel disease with a severe stenosis of the proximal left anterior descending coronary artery. However, aortography revealed a mobile mass located in the sinus of Valsalva (Panel 1A and B), obstructing the left main coronary artery in systole while diastolic coronary flow was maintained at normal heart rate (see Supplementary data online, Video S1). During ventriculography, an episode of relative tachycardia was induced (i.e. shorter diastole) causing significant LMCA obstruction (see Supplementary data online, Video S2), along with typical chest pain and significant ST depression on the ECG (left main equivalent) (Panel 2A and B). The chest pain caused discomfort and the patient developed reflex tachycardia further aggravating/maintaining symptoms of angina in a vicious circle. A transoesophageal echocardiography confirmed the mobile mass, which was attached to the free edge of the left coronary cusp (Panel 3A–C, see Supplementary data online, Videos S3 and S4) and systematically obstructed the LMCA during systole (Panel 3D, see Supplementary data online, Video S5). Because of ongoing myocardial ischaemia due to the LMCA obstruction, the patient underwent urgent surgery. Peri-operatively, the mass was shown to be attached to the free border of the left coronary cusp and was successfully removed while leaving the aortic valve structurally intact (Panel 4). Histopathological examination confirmed the diagnosis of a papillary fibro-elastoma. The severe stenosis on the proximal LAD was bypassed by implanting the left internal mammary artery on the mid-LAD. Postoperative course was uneventful, with no residual chest pain at follow-up.



Supplementary data are available at *European Heart Journal – Cardiovascular Imaging* online.