

# Assessment of wasted myocardial work: a novel method to quantify energy loss due to uncoordinated left ventricular contractions

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**Russell K, Eriksen M, Aaberge L, Wilhelmsen N, Skulstad H, Gjesdal O, Edvardsen T, Smiseth OA.** Assessment of wasted myocardial work: a novel method to quantify energy loss due to uncoordinated left ventricular contractions. *Am J Physiol Heart Circ Physiol* 305: H996–H1003, 2013. First published July 26, 2013; doi:10.1152/ajpheart.00191.2013.—Left ventricular (LV) dyssynchrony reduces myocardial efficiency because work performed by one segment is wasted by stretching other segments. In the present study, we introduce a novel noninvasive clinical method that quantifies wasted energy as the ratio between work consumed during segmental lengthening (wasted work) divided by work during segmental shortening. The wasted work ratio (WWR) principle was studied in 6 anesthetized dogs with left bundle branch block (LBBB) and in 28 patients with cardiomyopathy, including 12 patients with LBBB and 10 patients with cardiac resynchronization therapy. Twenty healthy individuals served as controls. Myocardial strain was measured by speckle tracking echocardiography, and LV pressure (LVP) was measured by micromanometer and a previously validated noninvasive method. Segmental work was calculated by multiplying strain rate and LVP to get instantaneous power, which was integrated to give work as a function of time. A global WWR was also calculated. In dogs, WWR by estimated LVP and strain showed a strong correlation ( $r = 0.94$ ) and good agreement with WWR by the LV micromanometer and myocardial segment length by sonomicrometry. In patients, noninvasive WWR showed a strong correlation ( $r = 0.96$ ) and good agreement with WWR using the LV micromanometer. Global WWR was  $0.09 \pm 0.03$  in healthy control subjects,  $0.36 \pm 0.16$  in patients with LBBB, and  $0.21 \pm 0.09$  in cardiomyopathy patients without LBBB. Cardiac resynchronization therapy reduced global WWR from  $0.36 \pm 0.16$  to  $0.17 \pm 0.07$  ( $P < 0.001$ ). In conclusion, energy loss due to incoordinated contractions can be quantified noninvasively as the LV WWR. This method may be applied to evaluate the mechanical impact of dyssynchrony.

heart failure; myocardial function; dyssynchrony; cardiac resynchronization therapy

IN A NORMAL LEFT VENTRICLE (LV), all segments contract in a synchronized fashion, and myocardial energy is used effectively to eject blood out of the ventricle. In ventricles with regional differences in contractility, as in ischemia, or a delay in electrical conduction, as in left bundle branch block (LBBB), some segments are stretched in systole, whereas others contract, resulting in a dyssynchronous contraction pattern. The result of this dyssynchrony is that a substantial amount of LV work is “wasted” on stretching opposing segments and therefore does not contribute effectively to LV

ejection. There is currently no clinical method to quantify how much work is wasted due to dyssynchrony.

Recently, we (9) introduced a noninvasive clinical method to quantify regional LV work. This method measures regional work in terms of LV pressure (LVP)-strain loop areas, which are constructed from a noninvasive LVP curve in combination with strain by speckle tracking echocardiography (STE). Analogous to the principle that the area of the LVP-volume loop reflects stroke work and global myocardial O<sub>2</sub> consumption (11, 12), it has been shown by Delhaas et al. (1) and Russell et al. (9) that the pressure-strain loop area may serve as an index of regional myocardial work and metabolism when segments within a given ventricle are compared. In the present study, we propose to use segmental LVP-strain data acquired by a noninvasive approach to quantify how much work is wasted in ventricles with dyssynchronous contractions. This energy loss is expressed as work consumed during segmental lengthening (negative work) as the ratio of work during segmental shortening (positive work), and we named this the “wasted work ratio” (WWR).

The main objective of the present study was to validate the WWR and investigate changes in WWR with cardiac resynchronization therapy (CRT) in patients with heart failure and LBBB.

First, we studied whether WWR can be measured by LV pressure-strain analysis in a dog model using sonomicrometry as a reference method for speckle tracking strain and in patients using micromanometer as reference method for LV pressure. Second, we investigated whether LV WWR can be measured and quantified noninvasively. Finally, we investigated changes in WWR in response to CRT in patients with heart failure and LBBB.

## METHODS

### Experimental Study

**Animal preparation.** Six mongrel dogs (either sex, body weight:  $35 \pm 1$  kg) were anesthetized, ventilated, and surgically prepared as previously described (13), including the induction of LBBB ( $n = 6$ ) by radiofrequency ablation (2). This study was approved by the National Animal Experimentation Board. Laboratory animals were supplied by the Centre for Comparative Medicine (Oslo University Hospital, Rikshospitalet, Oslo, Norway).

**Sonomicrometry.** Segment lengths were measured by pairs of 2-mm-wide sonomicrometry crystals (Sonometrics, London, ON, Canada) implanted subendocardially. Four circumferential segments incorporating all LV walls were analyzed. Strain was calculated as the percent length deviation from the end-diastolic length. Data were sampled at 200 Hz.

**Hemodynamic measurements.** Aortic pressure, left atrial pressure, and LVP were measured by micromanometers (MPC-500, Millar

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Instruments, Houston, TX). A fluid-filled catheter placed in the left atrium served as an absolute pressure reference for the LV micromanometer.

**Echocardiography.** A Vivid 7 ultrasound scanner (GE Vingmed Ultrasound AS, Horten, Norway) was used to record conventional two-dimensional grayscale images (frame rate:  $64 \pm 12$  frames/s) of the LV (at the level of the papillary muscle) with short-axis apical two- and four-chamber views for STE.

**Experimental protocol.** Measurements were performed before and after the induction of LBBB. Data were recorded with the ventilator temporarily switched off.

### Clinical Study

**Validation of noninvasive versus invasively measured WWR.** Eighteen patients (mean age:  $66 \pm 8$  yr, 25% women and 75% men) underwent LV catheterization, including eleven patients with ischemic cardiomyopathy and seven patients with nonischemic dilated cardiomyopathy. Twelve of these patients had LBBB (QRS:  $160 \pm 20$  ms). Two of the patients with LBBB had a CRT device allowing for measurements with CRT on and off.

**Response in WWR to cardiac resynchronization therapy.** Ten additional patients with heart failure and New York Heart Association II–IV and LBBB were included. Coronary artery stenosis was ruled out by angiography before the investigation. Echocardiography was performed before the implantation of the CRT device ( $n = 10$ ) and at followup  $8 \pm 3$  mo later ( $n = 9$ ). To assess changes in wasted work after CRT, we deliberately included only responders in the patient population ( $>10\%$  reduction in end-systolic volume) to demonstrate changes in work as a result of the resynchronization treatment.

**WWR in healthy controls.** Twenty age- and sex-matched healthy individuals were recruited from the hospital staff. All had normal clinical examination, ECG, and echocardiography. This study was approved by the Regional Committee for Medical Research Ethics. All subjects gave written informed consent.

**Hemodynamic and echocardiographic measurements.** In all patients, myocardial strain was measured by STE (Vivid 7) in apical long-axis two- and four-chamber views (frame rate:  $65 \pm 6$  frames/s). Narrow sector two-dimensional imaging over the valves (frame rate:  $87 \pm 22$  frames/s) was used to define the opening and closure of the aortic and mitral valves.

In the invasive LVP group, LVP was measured by a micromanometer-tipped catheter (Microtip, Millar Instruments), and a fluid-filled catheter connected to an external pressure transducer served as absolute pressure reference. Pressure and strain data were recorded in a synchronized fashion and stored for offline analysis. An average of  $16 \pm 2$  segments (from a total of 18 segments) were analyzed in each patient.

### Data Analysis

**Estimation of the LVP curve.** The method for calculating the noninvasive LVP analog has been previously described in detail (9). In brief, we used an empiric reference curve for the LVP profile. This curve was obtained by pooling LVP data from a number of patients with different pathologies, and for each patient, the durations of isovolumic contraction (IVC), LV ejection, and isovolumic relaxation (IVR), defined by echocardiography, were set to the same arbitrary value by stretching or compressing the curves along the time axis. From this series of individual curves, a common average waveform was constructed. The profile of the averaged LVP waveform was used for the prediction of LVP in each specific subject by measuring the actual valvular timing for the relevant cardiac cycle and adjusting the duration of time intervals of IVC, ejection, and IVR phases by stretching or compressing the time axis of the averaged LVP curve to match the measured time intervals. To scale the amplitude of the pressure curve, peak arterial pressure was used in dogs in the experimental study and arterial cuff pressure in patients and control subjects in the clinical study. Separate reference curves were used for dogs and patients.

**Calculation of segmental work.** Work for individual segments as a function of time throughout the cardiac cycle was calculated from the strain recordings and from measured or estimated LVP from a representative heartbeat. This was done by obtaining the rate of segmental shortening (strain rate) by differentiation of the strain curve and multiplying this with instantaneous LVP. This resulted in a measure of instantaneous power, which was integrated over time to give work as a function of time (Fig. 1). Performing this calculation for the IVC, ejection, and IVR phases is mathematically the same as calculation of the area between the  $x$ -axis and the corresponding segment of the strain-pressure loop, however, keeping in mind that areas under sections of the loop that represent elongation are counted as negative

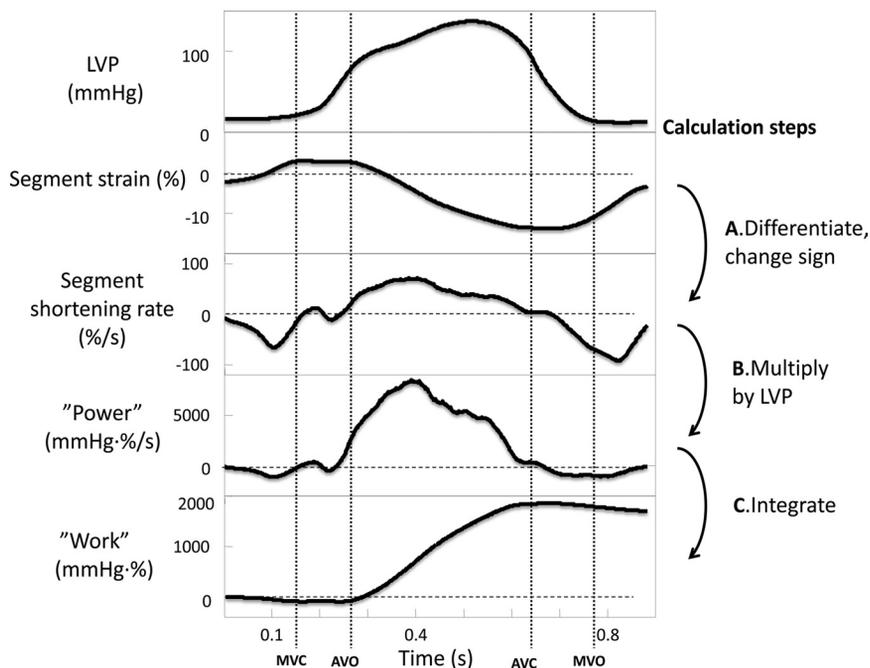


Fig. 1. Work of individual segments was calculated from strain recordings and left ventricular pressure (LVP). Work was calculated as a function of time throughout the cardiac cycle. This was done by obtaining the rate of segmental shortening (strain rate) by differentiation of the strain curve and multiplying this with instantaneous LVP. This resulted in a measure of instantaneous power, which was integrated over time to give work as a function of time. MVC, mitral valve closure; AVO, atrial valve opening; AVC, atrial valve closure; MVO, mitral valve opening.

(further details are presented in the APPENDIX). Work was calculated from mitral valve closure until mitral valve opening. The reason for this is that work losses can occur by stretching of segments in the isovolumic phases, especially in hearts with a dysynchronous contraction pattern.

**Analysis of segmental work.** Information was extracted from the segmental work curves over a time interval spanning from mitral valve closure to mitral valve opening. The following variables were calculated:  $W_{pos}$  and  $W_{neg}$ .  $W_{pos}$  is total positive work, the sum of all work performed during shortening of the segment. By definition,  $W_{pos}$  is a positive number.  $W_{neg}$  is total negative work, the sum of all work performed during elongation of the segment. Although a negative number by definition,  $W_{neg}$  is presented as a positive number to facilitate understanding of the relative differences between negative and positive work.

Global WWR was calculated as follows from the sum of work for all segments:

$$\text{Global WWR} = \frac{\sum W_{neg}}{\sum W_{pos}}$$

The net work contributing to systolic ejection for each segment was calculated as follows:

$$\text{Net work} = W_{pos} - W_{neg}$$

The WWR for each segment was also calculated as follows:

$$\text{Segmental WWR} = \frac{W_{neg}}{W_{pos}}$$

Figure 2 shows positive work (in black) and negative work (in red) during systole for a septal and lateral wall segment before and during CRT in a representative patient.

**Work analysis.** In the experimental study, the WWR calculated using strain by STE and estimated LVP was compared with the WWR calculated by strain by sonomicrometry and invasively measured LVP.

In the patients with invasive LVP, work was analyzed by two different methods: 1) STE strain and measured LVP and 2) STE strain and estimated LVP.

**Statistical analysis.** Values are expressed as means  $\pm$  SD. Results from different methods of measurement were compared using least-squares linear regression, Pearson correlation coefficients, and Bland-Altman plots with calculations of limits of agreement. For multiple comparisons, we used repeated-measures ANOVA with a least-significant-difference post test (SPSS 15.0, SPSS, Chicago, IL). All post hoc tests were compared with baseline.  $P$  values of  $<0.05$  were considered significant.

**RESULTS**

*Experimental Study*

**Validation of WWR calculated from estimated LVP and echocardiography versus measured LVP and sonomicrometry.** The analysis, which included measurements before and after the induction of LBBB, showed a strong correlation ( $r = 0.94$ ) and good agreement (SD = 0.07, mean difference = -0.03) between the global WWR calculated from estimated LVP and strain by STE versus WWR by LV micromanometer and segment length by sonomicrometry.

**Changes in WWR from baseline to LBBB.** The introduction of LBBB increased the global WWR measured by LVP and echocardiography from  $0.13 \pm 0.05$  to  $0.37 \pm 0.11$  ( $P < 0.001$ ). Peak strain for the septum and lateral wall were moderately reduced after the induction of LBBB, from  $-15 \pm 4\%$  to  $-10 \pm 4\%$  ( $P = 0.014$ ) and from  $-14 \pm 4\%$  to  $-11 \pm 7\%$  ( $P = \text{not significant}$ ), respectively. However, the work done by the septum decreased substantially, from  $951 \pm 320$  to  $349 \pm 346$  mmHg·% ( $P = 0.002$ ). In contrast, net work done by the lateral wall increased from  $756 \pm 266$  to  $1,059 \pm 516$  mmHg·% ( $P = 0.026$ ) despite the tendency of a decrease in peak strain (Table 1). Therefore,

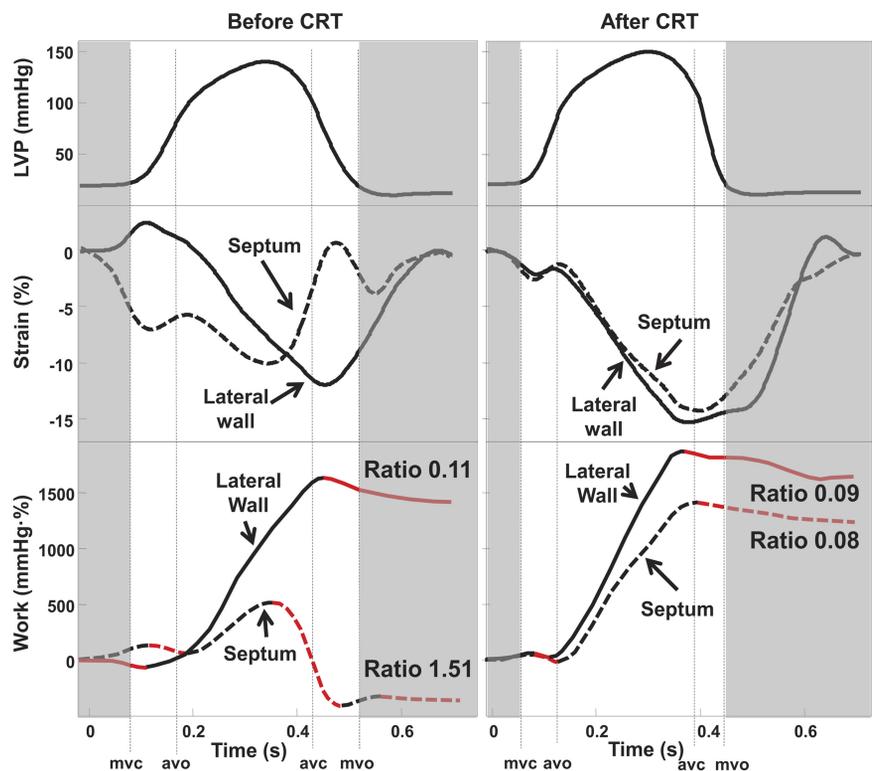


Fig. 2. Estimated LV pressure (top), strain (middle), and calculation of wasted work for the septum and lateral wall (bottom) in a representative patient with left bundle branch block (LBBB; left) and after treatment with cardiac resynchronization therapy (CRT; right). Vertical lines indicate valvular events measured by echocardiography. Negative and positive work during systole is marked as red and black, respectively. Wasted work ratios (WWRs) were calculated using cumulated work from MVC to MVO.

Table 1. Hemodynamic variables and work calculations for the experimental study

	Baseline		LBBB	
Global measures: hemodynamic variables and WWR				
Heart rate, beats/min		121 ± 17		122 ± 13
QRS width, ms		68 ± 5		116 ± 7*
LV dP/dt <sub>max</sub> , mmHg/s		1284 ± 198		1098 ± 189*
LV end-diastolic pressure, mmHg		10 ± 3		10 ± 4
Peak LVP, mmHg		96 ± 12		94 ± 9
WWR		0.13 ± 0.05		0.37 ± 0.11*
Regional measures: strain and work				
	Septum	Lateral Wall	Septum	Lateral wall
Peak strain, %	-15 ± 4	-14 ± 4	-10 ± 4*	-11 ± 7
Positive work, mmHg·%	1,106 ± 368	917 ± 256	669 ± 275	1,295 ± 615†
Negative work, mmHg·%	155 ± 134	164 ± 102	320 ± 288	236 ± 170
Net work, mmHg·%	951 ± 320	756 ± 266	349 ± 346*	1,059 ± 516*†
Segmental WWR	0.14 ± 0.11	0.19 ± 0.15	0.52 ± 0.49*	0.18 ± 0.09†

Values are means ± SD;  $n = 6$  subjects/group. Work analyses were calculated from longitudinal strain by speckle tracking echocardiography and invasively measured left ventricular (LV) pressure (LVP). LBBB, left bundle branch block; WWR, wasted work ratio; septum, midseptal and anterioseptal segments; lateral wall, midlateral and posteriolateral segments. \* $P < 0.05$  vs. baseline; † $P < 0.05$ , septum vs. lateral wall.

changes in peak strain after the induction of LBBB did not reflect changes in regional work.

### Clinical Study

**Validation of the WWR using estimated versus measured LVP.** There was a strong correlation ( $r = 0.96$ ) and good agreement (SD = 0.03, mean difference = -0.01) between the global WWR calculated by STE and invasive versus noninvasive LVP (Figs. 3 and 4).

**WWRs in healthy normal individuals.** Figure 5 shows a bull's-eye plot with segmental WWRs from a representative healthy individual. The WWR was  $< 0.14$  in every segment, which implies that LV work was dominated by positive work (i.e., shortening work) and there was very little negative work (i.e., work wasted during systolic lengthening). The global WWR for healthy normal individuals was  $0.09 \pm 0.03$ .

**WWRs in patients with cardiomyopathy.** In patients with LBBB, peak strain values for the septum were, on average, half of the value of the lateral wall. For the septum, the segmental WWR was  $1.57 \pm 0.97$ . Since  $WWR > 1$  implies more negative than positive work, this implies that, on average, net septal work was negative. In some patients with LBBB, net

septal work was positive, although it was markedly reduced. The lateral wall, however, showed increased positive work compared with the control group and the segmental WWR was increased, but to a moderate degree compared with the septum ( $0.18 \pm 0.11$ ; Fig. 5A).

In patients with cardiomyopathy and narrow QRS ( $96 \pm 18$  ms) without LBBB, the segmental WWR was moderately increased to  $0.17 \pm 0.08$  for the septum and  $0.27 \pm 0.26$  for the LV lateral wall, and global WWR was  $0.21 \pm 0.09$ .

**Changes in the WWR with CRT.** When CRT was introduced in patients with LBBB, the septum showed a dramatic increase in positive work and a reduction in negative work, and the septal WWR decreased to  $0.18 \pm 0.09$  (Fig. 5B). The lateral wall showed only minor changes with CRT (Figs. 2 and 4 and Table 2). These changes in segmental work with CRT were reflected in a reduction in the global WWR from  $0.36 \pm 0.16$  to  $0.17 \pm 0.07$ .

### DISCUSSION

In the present report, we introduce a novel, noninvasive method that quantifies how much work is wasted in ventricles with dyssynchronous contraction patterns. The method gives segmental information about positive work (systolic shorten-

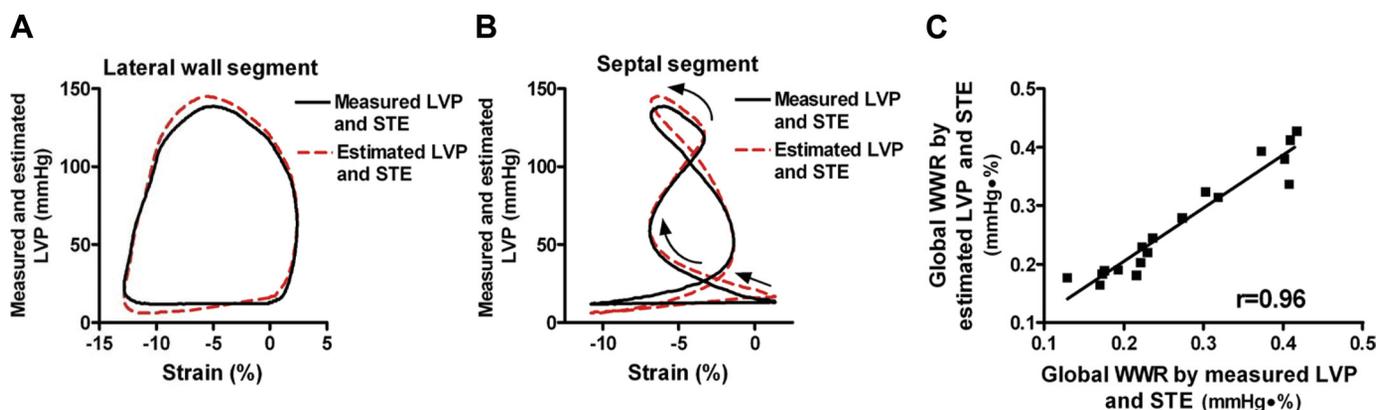


Fig. 3. Representative traces from a patient with LBBB showing pressure-strain loops by LVP and speckle tracking echocardiography (STE; black line) versus estimated LVP and STE (red dotted line) for a lateral wall segment (A) and a septal segment (B). C: correlation between WWRs by estimated LVP and STE versus measured LVP and STE.

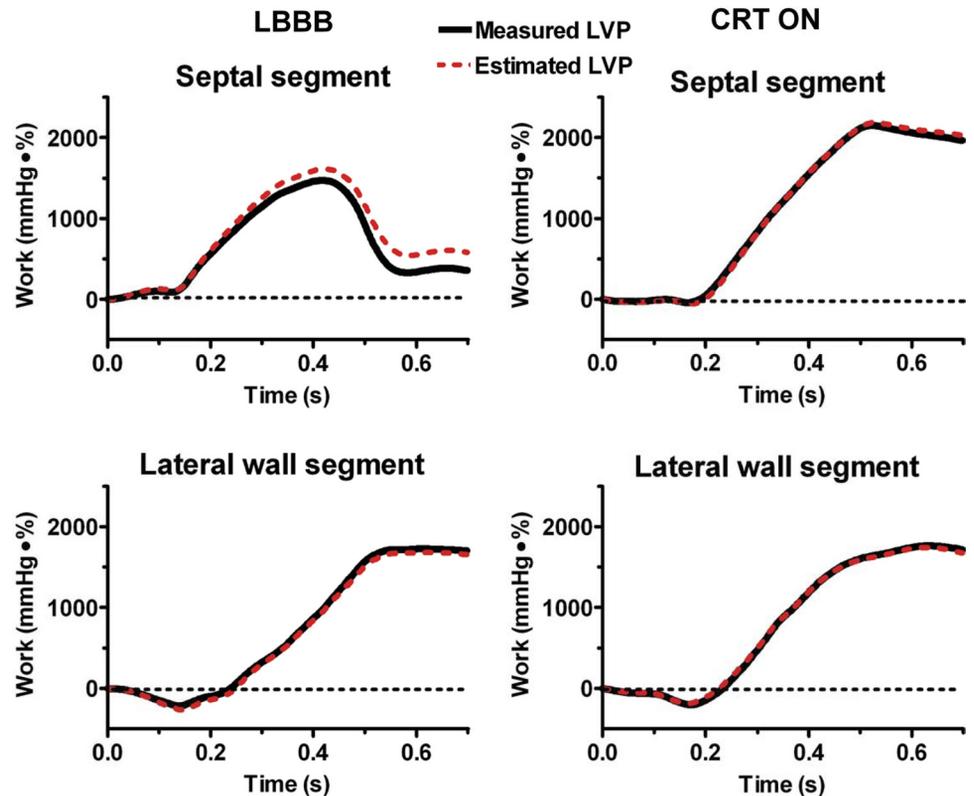


Fig. 4. Work analysis by LVP and STE (solid line) versus the noninvasive method by estimated LVP and STE (dashed line) for a septal segment and a lateral wall segment in a patient with the CRT device turned on and off.

ing) and negative work (systolic lengthening), allowing for the assessment of local and global energetic efficacy as the ratio between negative and positive work. The validity of this method was confirmed in the experimental part of the study. Furthermore, in the clinical study, we showed that the WWR based on a noninvasive LVP estimate corresponded well with calculations using invasive LVP. We showed that significant work was wasted in patients with LBBB and was subsequently recruited when CRT was introduced, suggesting that the work analysis may represent a means to explore the hemodynamic impact of electrical dyssynchrony.

#### Work Analysis

As shown by Hisano and Cooper (4), the area of the myocardial force-dimension loop represents the work performed during a cardiac cycle. However, due to the complexities of measuring force, LVP has been used as a surrogate to force. The use of pressure as a substitute for force may be viewed as a limitation. However, a previous study (10) from our group has shown that pressure-length loops reflect regional changes in myocardial work compared with force-segment length loops. Furthermore, we have shown that the stress-strain loop area, calculated using curvature and area strain, showed quantitatively similar information compared with stress-segment length loop area when regional differences within the same heart were compared. Another argument that supports that pressure-strain loops reflect regional work is our previous demonstration that pressure-strain loop area reflects regional glucose metabolism as assessed by [ $^{18}\text{F}$ ]flurodeoxyglucose positron emission tomography (9).

Since invasive LVP is often not available, we introduced a noninvasive estimate of the LVP curve, which was constructed

by adjusting an empiric average waveform according to the duration of the isovolumic and ejection phases as defined by echocardiography, and peak pressure is set equal to arterial cuff pressure. The validity of calculating regional myocardial work from noninvasive LVP and strain by STE has been confirmed both in an animal model and in patients (9).

Using segment length for the assessment of regional work may be viewed as a limitation as it depends on the relation of the crystal implantation site to myofiber orientation, which varies through the ventricular wall. A previous study (3) assessed regional work using wall thickness measurement as it does not depend on fiber direction. Ideally, regional work should be calculated using area strain; however, in a clinical setting strain analyses are commonly performed for longitudinal and circumferential segments, and we therefore used these measurements for work analysis in the present study. Furthermore, we (9) have previously shown that work analysis using segmental strain reflects work using area strain.

#### Wasted Work

In a normal heart, all segments contract almost simultaneously, and they therefore contract against similar LVP. However, in a ventricle with regional differences in the timing of contraction, segmental contractions occur against different pressures. Therefore, information about both the degree of shortening and LVP during shortening is needed to compare work between the segments.

The same is true for the calculation of wasted energy during elongation of the segments, since the energy loss depends on both the elongation distance and LVP during elongation. In ventricles with nonuniformity in the timing of relaxation, some segments will start relaxing and elongate in late systole, at high

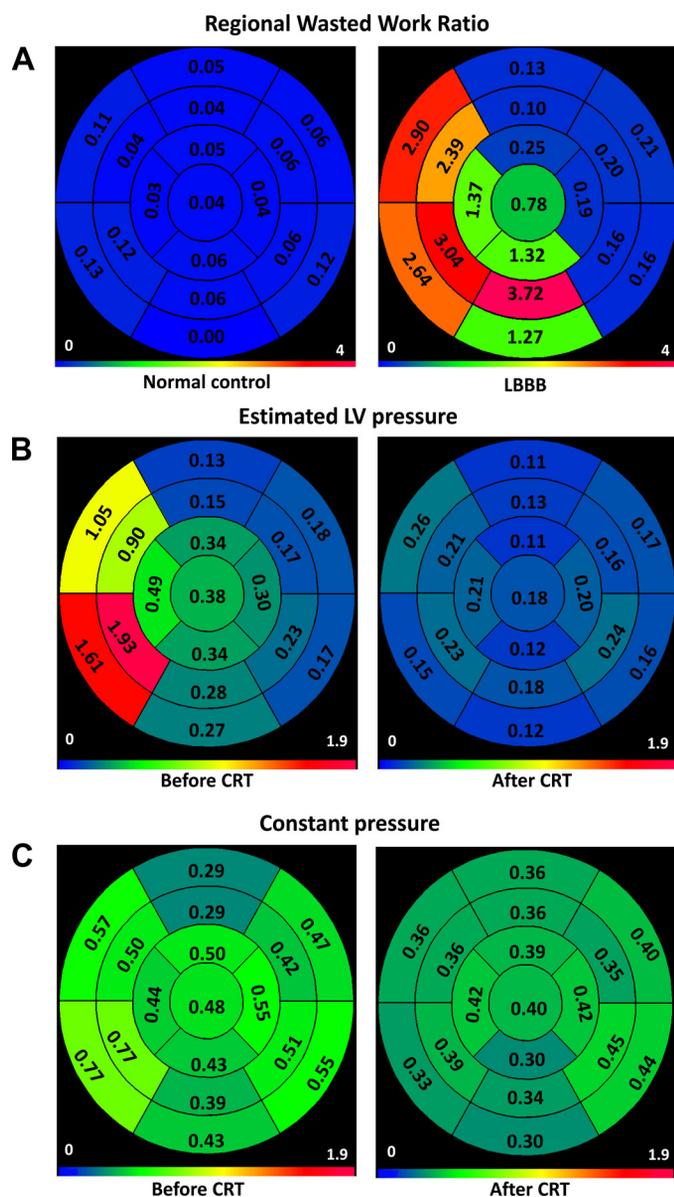


Fig. 5. Bull's-eye plots showing segmental WWRs. *A*: plots from a normal control subject and a patient with LBBB. *B*: regional mean values for all patients before and after CRT. WWR values of  $>1$  imply more negative work than positive work. *C*: regional mean values for all patients before and after CRT when constant pressure was assumed and changes in strain only were considered.

LVP, while other segments are still contracting. This means that a substantial amount work done by the contracting segments is wasted on stretching other segments. Typically, during LBBB, much of septal contraction occurs during the preejection phase at a time when the LVP is low, and, therefore, the septum performs little work (8). As seen in the present study, peak septal strain during LBBB in the animal model was only marginally reduced compared with the lateral wall, but net work done by the septum was approximately one-third relative to the lateral wall (Table 1). In patients with LBBB, peak strain for the septum was, on average, half of that for the lateral wall, which is in keeping with a previous study (5). The average segmental WWR, however, was above 1.5, indicating that negative (wasted) work exceeded positive work. Therefore,

instead of the septum contributing to the hemodynamic performance of the LV, external work was done on the septum, which thereby “absorbed” work done by other segments.

Measuring wasted work is therefore a method for quantifying work that is being done by the ventricle but does not contribute to LV ejection and, provided the myocardium is viable, should represent a measure of contractile reserve. This was supported by our findings in patients with LBBB who showed a decrease in the WWR and an increase in ejection fraction when CRT was introduced (Table 2).

In a previous study (1), wasted work was estimated as the difference between strain at end systole and peak strain during or after systole. The main limitation of this method is that it does not take into account pressure, which is higher during lengthening in late systole than during postsystolic shortening. Therefore, stretching of a segment before arterial valve closure represents a greater degree of wasted work compared with shortening after arterial valve closure when pressure is rapidly declining. Although this is an interesting index of mechanical dyssynchrony, it does not provide a measure of work since it does not incorporate load. Our method incorporates a measure of regional load (LVP), thereby taking into account the energetic effects of deformation at different pressures. The importance of taking into account pressure was illustrated by an additional data analysis in which we considered strain only as a marker of wasted work. In this analysis, which is detailed in the APPENDIX, we calculated work by assuming constant LVP, set to an arbitrary value of 1 mmHg. The result from this analysis was that the wasted work and WWR differed substantially from results when cyclic LV pressure was used, as shown in Fig. 5. The septum, which had WWR  $>1$  in most segments during LBBB, and therefore performed more negative than positive work, appeared to do predominantly positive work when looking at strain only. Similarly, the effect of CRT as reflected in the difference in WWR between the septum and lateral wall became far less pronounced when pressure was ignored (Fig. 5, *B* and *C*). We therefore propose that our method, which incorporates a LVP estimate, gives important additional information about regional myocardial function.

Since myocytes are unable to recycle chemical energy when the segments are stretched, this energy will instead be converted to heat in the tissue. Measurements of WWR will, for this reason, indicate the overall efficacy of the LV myocardium in converting metabolic substrates into cardiac work. Quantification of regional work in ventricles with uncoordinated contractions may provide important insights into mechanisms of remodeling and progressive LV dysfunction (1, 6, 7, 14).

#### Limitations

When estimating the LVP curve by the noninvasive method, we used an empiric standardized reference curve based on several invasively recorded pressure traces. One may argue that a mathematically derived curve profile determined by regression analysis may be used instead of a tabulated reference curve. A principal limitation of both concepts is that the waveform might be inaccurate for some pathologies. The waveform found by regression analysis will, in addition, contain errors caused by limitations in the number of degrees of freedom used in the regression function. Using an empiric standardized reference curve based on averaging of invasive measurements is, for this reason, expected to give a

Table 2. Hemodynamic variables and noninvasive work calculation for CRT and the control group for the clinical study

	Normal Subjects		Patients With LBBB		Patients With LBBB and CRT	
Global measurements: hemodynamic variables and WWR						
Heart rate, beats/min	63 ± 9		67 ± 18		59 ± 5	
Age, yr	63 ± 8		65 ± 7		65 ± 6	
Ejection fraction, %	60 ± 4		29 ± 6		42 ± 14*	
QRS width, ms	90 ± 8		171 ± 16		145 ± 13	
Global WWR	0.09 ± 0.03		0.36 ± 0.16		0.17 ± 0.07*	
	Septum	Lateral wall	Septum	Lateral wall	Septum	Lateral wall
Regional measurements: Strain and work						
Peak strain, %	-20 ± 4	-19 ± 3	-6 ± 3	-12 ± 5	-12 ± 5*	-12 ± 5
Positive work, mmHg·%	2,168 ± 465	2,084 ± 327	434 ± 202	1,572 ± 451†	1,328 ± 489*	1,225 ± 498
Negative work, mmHg·%	191 ± 104	170 ± 101	591 ± 350	263 ± 162†	212 ± 120*	242 ± 136
Net work, mmHg·%	1,978 ± 483	1,913 ± 307	-158 ± 384	1,308 ± 460†	1,116 ± 489*	983 ± 505
Segmental WWR	0.09 ± 0.06	0.08 ± 0.05	1.57 ± 0.97	0.18 ± 0.11	0.18 ± 0.09*	0.23 ± 0.14

Values are means ± SD;  $n = 20$  normal subjects, 10 patients with LBBB, and 9 patients with LBBB and cardiac resynchronization therapy (CRT). Work analyses were calculated from longitudinal strain by speckle tracking echocardiography and the estimated LVP curve. \* $P < 0.05$ , patients with LBBB vs. patients with LBBB and CRT; † $P < 0.05$ , septum versus lateral wall.

more accurate profile, supporting its use over pressure traces defined as mathematical functions. Furthermore, the method has been thoroughly validated, and it performs well under a wide range of different hemodynamic conditions (9). However, for minor changes in regional work, the lack of a true LVP value represents a limitation. The accuracy of the estimated LVP curve may be improved by including data from arterial tonometry and by using specific reference curves for different patient populations.

The LVP-strain analysis does not provide a direct measure of work since the radius of curvature and wall thickness were not incorporated in the calculations. Therefore, comparison of absolute positive or negative work estimates between different ventricles may not be valid. Comparison of WWR between different hearts, however, should be a valid measure since it is a relative measure that compensates for limited information about local geometry. The reproducibility for the WWR was not assessed in the present report; however, interobserver variability for both strain and noninvasive pressure estimate (9) has previously been evaluated.

The experimental data set and the data set from patients with simultaneous LVP measurements and strain analysis have also been used in a previous publication from our group (9).

The assessment of regional work proposed in the present report relies on strain rate based on STE, and relatively low time resolution may therefore represent a limitation. In the present report, we had a frame rate of  $64 \pm 12$  frames/s in the experimental study and found this to be sufficient compared with the results using sonomicrometry.

### Conclusions

The present study introduces a noninvasive clinical method to quantify the negative impact of dyssynchrony on myocardial work and energy utilization. Studies should be done to determine if this new method will be useful in risk stratification and in the selection of therapy for patients with dyssynchrony.

### APPENDIX

#### Calculation of Segmental Work

Work of individual segments was calculated from strain recordings and LVP. Instead of calculating only one value of work in a completed

cardiac cycle for each segment, equal to the area of the strain-pressure loop, work was calculated as a function of time throughout the cardiac cycle. This was done by obtaining the rate of segmental shortening (strain rate) by differentiation of the strain curve (Fig. 1, third trace) and multiplying this with instantaneous LVP (Fig. 1, fourth trace). This resulted in a measure of instantaneous power, which was integrated over time by the trapezoidal method to give work as a function of time (Fig. 1, bottom trace). Performing this calculation for a complete cycle is mathematically the same as calculation of the strain-pressure loop area according to Green's theorem.

*In detail.* Let  $P_{LV}(t)$  be the recorded or estimated pressure in the LV as a function of time ( $t$ ) and let  $\epsilon(t)$  be the strain of a myocardial segment as a function of time.

Thus, the segment shortening rate [ $v(t)$ ; strain velocity] is as follows:

$$v(t) = -\frac{d\epsilon}{dt}(t) \quad (1)$$

and the power developed by the segment [ $P(t)$ ] is as follows:

$$P(t) = v(t)P_{LV}(t) = -\frac{d\epsilon}{dt}(t)P_{LV}(t) \quad (2)$$

The work performed by the segment as a function of time [ $W(t)$ ] is the integral of power from  $t' = 0$  to  $t' = t$ , as follows:

$$W(t) = \int_0^t P(t')dt' = \int_0^t -\frac{d\epsilon}{dt}(t')P_{LV}(t')dt' \quad (3)$$

where  $t'$  is an integration variable.

#### Calculation of WWR Using Constant Pressure

To highlight the importance of changes in regional load when assessing work, we performed calculations using the nonweighted sum of segment shortening as a surrogate for positive work and the sum of elongation as negative work. This is equivalent to using our calculation method as described in the present report but assuming a constant pressure of 1 instead of a time-varying pressure. The calculations were performed for IVC, ejection, and IVR phases using raw data from the same patients before and after CRT. The bull's-eye plots shown in Fig. 5 demonstrate that when the WWR was calculated using a constant pressure, the difference in the WWR between the septum and lateral wall was significantly reduced and the effect of CRT became far less pronounced.

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## DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

## AUTHOR CONTRIBUTIONS

Author contributions: K.R., M.E., N.W., H.S., O.G., T.E., and O.A.S. conception and design of research; K.R., L.A., N.W., H.S., and O.G. performed experiments; K.R., M.E., L.A., H.S., and O.G. analyzed data; K.R., M.E., L.A., N.W., H.S., T.E., and O.A.S. interpreted results of experiments; K.R., M.E., and O.A.S. prepared figures; K.R., M.E., O.G., T.E., and O.A.S. drafted manuscript; K.R., M.E., H.S., O.G., T.E., and O.A.S. edited and revised manuscript; K.R., M.E., L.A., N.W., T.E., and O.A.S. approved final version of manuscript.

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