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Timing of myocardial shortening determines left ventricular regional myocardial work and regional remodelling in hearts with conduction delays

Marta Cvijic[1,2†], Jürgen Duchenne[1†], Serkan Ünlü[1,3,4], Blazej Michalski[1,5], Marit Aarones[6], Stefan Winter[7], Svend Aakhus[6,8], Wolfgang Fehske[7], Ivan Stankovic[9], and Jens-Uwe Voigt[1]*

[1]Department of Cardiovascular Diseases, University Hospital Leuven, Herestraat 49, 3000 Leuven, Belgium; [2]Department of Cardiology, University Medical Centre Ljubljana, Ljubljana, Slovenia; [3]Department of Pharmacology, Gazi University Institute of Health Sciences, Ankara, Turkey; [4]Atatürk Chest Diseases and Chest Surgery Education and Research Hospital, Ankara, Turkey; [5]Department of Cardiology, Medical University of Łodz, Łodz, Poland; [6]Department of Cardiology, Oslo University Hospital, Oslo, Norway; [7]Klinik für Innere Medizin und Kardiologie, St. Vinzenz Hospital, Cologne, Germany; [8]Department of Circulation and Imaging, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway; and [9]Department of Cardiology, University Clinical Hospital Centre Zemun, University of Belgrade, Serbia

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Aims The interaction between asynchronous regional myocardial activation and left ventricular (LV) wall remodelling has not been well established. We investigated the relationship between time of onset of longitudinal shortening (T_{onset}), regional myocardial work, and segmental LV wall thickness (SWT) in patients treated with cardiac resynchronization therapy (CRT).

Methods and results We analysed 26 patients with sinus rhythm, non-ischaemic cardiomyopathy (63 ± 9 years, 69% male, QRS duration 174 ± 18 ms) and positive response to CRT (15% reduction in end-systolic volume). Longitudinal strain was obtained by 2D speckle-tracking echocardiography before and after [14.5 (7–29) months] CRT. T_{onset} and SWT were measured in 18 segments per LV. Segmental myocardial work was calculated from non-invasive segmental stress–strain loop area. Before CRT, T_{onset} was the shortest in septal and anteroseptal and the longest in lateral and posterior walls ($P < 0.001$) and not different after CRT ($P = 0.733$). Before CRT, septal and anteroseptal walls were significantly thinner than lateral and posterior. After CRT, reverse remodelling increased thickness in septal and anteroseptal and thinned lateral and posterior segments ($P < 0.001$). Before CRT, non-uniformity in work distribution with reduced work in septal and anteroseptal and increased work in lateral and posterior walls ($P < 0.001$) was observed. After CRT, distribution of myocardial work was uniform ($P = 0.215$).

Conclusion Dys-synchronous myocardial shortening is related to thinning of early and thickening of late activated segments in heart failure with conduction delay. Correction of dys-synchrony leads to regression of inhomogeneity towards more evenly distributed wall thickness. Regional differences in myocardial work load that are homogenized by successful CRT are considered as the underlying pathophysiological mechanism.

Keywords myocardial shortening • wall thickness • dys-synchrony • left ventricular stress–strain loop • myocardial work • cardiac resynchronization therapy

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* Corresponding author. Tel: +32 (16) 349016; Fax: +32 (16) 344240. E-mail: jens-uwe.voigt@uzleuven.be

† These authors shared first authorship.

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Introduction

Dys-synchronous left ventricular (LV) contraction is associated with the development of LV systolic dysfunction and LV volume increase.[1,2] Animal models have demonstrated that induced dys-synchronous contraction causes inhomogeneous regional LV remodelling, with thinning of the early and thickening of the late-activated wall. However, in heart failure patients with ventricular conduction abnormalities, data on relation between dys-synchronous myocardial activation and LV wall thickness are conflicting[3–5] and the potential pathophysiological mechanisms of these changes are not completely understood. As shown in animal experiments, dys-synchronous contraction caused redistribution of myocardial work with reduced work in the early and increased work in late activated regions.[6] Clinical data are limited as invasive measurement of myocardial work is technically challenging. A methodology for the non-invasive assessment of myocardial work was first proposed by Russel *et al.*[7] They found that LV pressure (LVP) curve can be estimated with sufficient accuracy by deforming a standard pressure curve pattern according to the cardiac time intervals of the heart to be investigated. Consequently, regional LV pressure–strain loops could be constructed from the non-invasively estimated LVP in combination with regional LV deformation assessed by speckle-tracking echocardiography. The authors showed that the segmental loop areas corresponded well with invasive and directly measured myocardial work.[7] In this study, we propose to use LV stress–strain loop areas as an index of myocardial work, taking also into account the segmental radius of curvature and wall thickness, as both may differ considerably among LV segments in dys-synchronous hearts.

Restoration of LV synchronicity by cardiac resynchronization therapy (CRT) has been shown to induce LV reverse remodelling and improvement of ejection fraction (EF), leading consequently to a better clinical outcome.[8,9] Data whether resynchronization also induces changes of wall thickness are limited. It can be assumed, however, that LV reverse remodelling comprises both volumetric and wall thickness changes as part of the same process[3] and that changes may be related to the segmental work distribution within the LV.

The purpose of this study was to investigate the relation between timing of myocardial shortening, regional myocardial work, and LV wall thickness in heart failure patients with ventricular conduction delay and to determine the effect of CRT on LV wall reverse remodelling.

Methods

Study population

The study population was selected from our database of heart failure patients, who underwent CRT device implantation according to the guidelines criteria [LVEF of ≤35%, QRS duration of ≥120 ms, New York Heart Association (NYHA) functional class II–IV, optimal pharmacotherapy at least 3 months before implantation]. This study had been approved by the ethical committee of our university which had also waived the need for an informed consent due to its retrospective nature. We meticulously selected 26 patients who were in sinus rhythm, with non-ischaemic cardiomyopathy and a positive response to CRT [defined as 15% reduction in LV end-systolic volume (ESV) at follow-up] and which had a baseline and follow-up echocardiography with excellent echogenicity, suitable for speckle tracking and detailed regional morphological analysis of the entire myocardium.

Echocardiographic data acquisition and analysis

Echocardiographic data were acquired using commercially available scanners (Vivid 5, 7, and E9, GE Vingmed Ultrasound, Norway). Digitally stored data were retrospectively analysed offline using EchoPac workstation (EchoPAC BT13, GE Healthcare). The 2D speckle tracking was performed using images acquired in apical four-chamber, two-chamber, and long-axis views [frame rate 58 (50–63) frames/s]. We used minimal temporal and spatial smoothing settings. Eighteen local (mid-segmental) longitudinal strain curves were analysed per LV. Time to onset of shortening (T_{onset}) was defined as the time from the first deflection of the QRS complex (the ECG onset of Q- or R-wave) to the beginning of the down slope in the strain curve (*Figure 1*). We additionally calculated for each segment time delays in the onset of shortening vs. the first shortening segment of the ventricle (T_{delay}). Opening and closing of LV valves was used to determine time intervals.

LV volumes and EF were calculated using the modified biplane Simpson method. Segmental LV wall thickness (SWT) was measured at end diastole (defined by mitral valve closure) at exactly the same position where local strain curves were derived from. Papillary muscles were not included in thickness measurements. As successful reverse remodelling was a prerequisite for inclusion, the follow-up SWT was considered as the more normal state and baseline SWT was therefore normalized to the follow-up SWT (relative SWT, in percent of follow-up SWT).

Calculation of segmental myocardial work

Our non-invasive estimate of LVP was based on the methodology of Russell *et al.*[7] A standard pressure curve was deformed according to the time intervals of the heart to be investigated and the non-invasively determined systolic blood pressure. Then, this estimated LVP curve was used to calculate the segmental wall stress curves according to the Laplace formula,[10] taking into account the segmental curvature and the wall thickness. The segmental curvature was approximated by fitting a circle[11] to the midwall contour line derived from the speckle-tracking software ('Full Trace' export function). SWT was measured as described above. Finally, segmental stress–strain loops were constructed and the area of the loop was used as measure of segmental myocardial work. All post-processing was performed using a dedicated, MATLAB-based (version 2013a, The MathWorks, Inc., Natick, MA, USA) research software (TVA version 21.02, JU Voigt, Leuven, Belgium). A schematic diagram of the calculation of LV stress–strain loop areas is presented in *Figure 2*.

To allow a comparison among patients, the segment with the largest loop area was used as a reference (100%), and all other segmental values were reported as a percentages of this value. This calculation was done separately for every patient before and after CRT.

Cardiac resynchronization therapy

All patients had undergone CRT implantation prior to inclusion. LV pacing leads were positioned, guided by coronary venography, preferably in the lateral and the posterolateral venous branches. Device settings were optimized within a week of CRT device implantation based on surface electrocardiography and Doppler echocardiography, as deemed clinically appropriate.[12]

Statistical analysis

Normality was assessed with the use of the Shapiro–Wilk test. Continuous variables were expressed as mean and standard deviation, if

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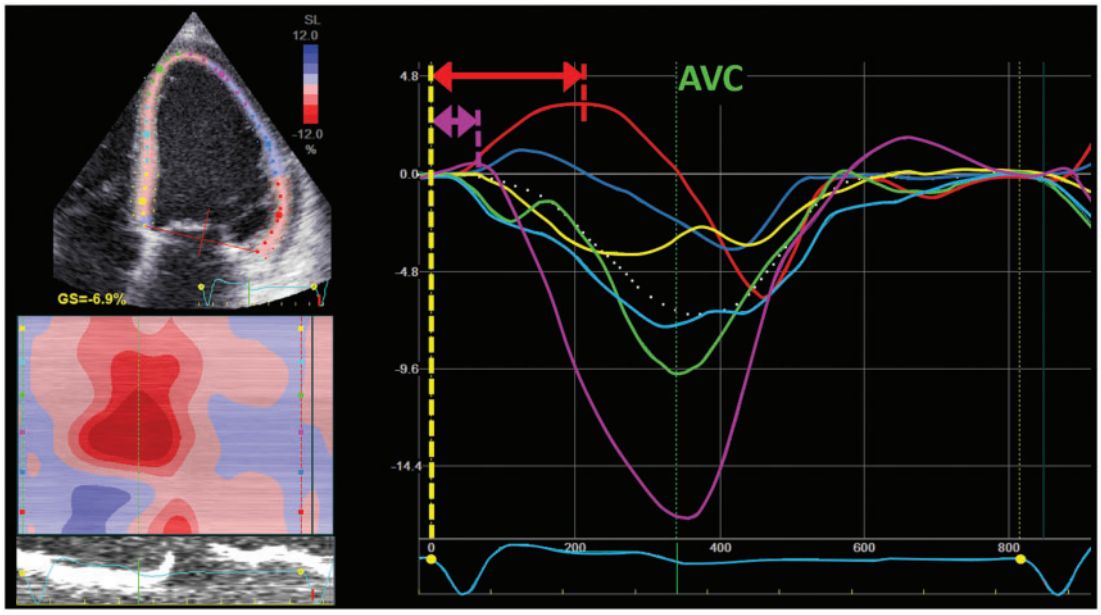


Figure 1 Calculation of the time to onset of longitudinal shortening. Speckle-tracking longitudinal strain curves from a CRT candidate patient with LBBB, derived from the apical four-chamber view. Time to the onset of longitudinal shortening (horizontal arrows) was measured as the time from the first deflection of the QRS complex in the ECG (yellow dot) to the beginning of the myocardial shortening from each strain curve. For the sake of clarity, the figure shows the measurement from only two strain curves. AVC, aortic valve closure.

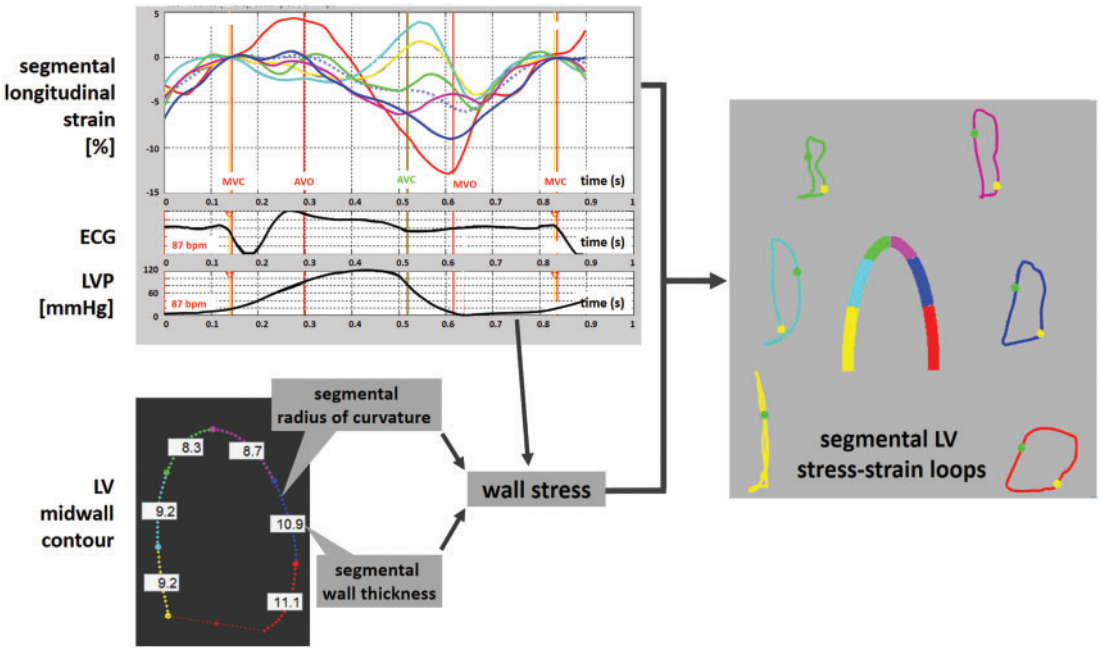


Figure 2 Schematic diagram with the steps involved in the calculation of segmental left ventricular stress-strain loop area. Calculation of the segmental LV stress–strain loop area using a MATLAB-based research software, exemplified for the apical four-chamber view. Segmental strain curves were imported from speckle-tracking software (EchoPac), valve timing was measured in Doppler traces of the mitral and aortic valve. Then, an LVP profile is estimated using an empiric reference curve,[7] the timing information from the valves and the systolic blood pressure of the patient. The LV midwall contour was also imported from the speckle tracking software ('Full Trace' export of EchoPac) to calculate the local curvature. Segmental wall stress (SWT) was measured in the 2D image. LVP, SWT, and curvature were used to calculate SWT according to the Laplace formula. Finally, segmental stress strain loops were constructed and the loop area was used as measure of regional work load. All loop displays are equally scaled.

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Table 1 Characteristics of study population

Clinical characteristics	
Age (years)	63 ± 9
Male (%)	18 (69.2)
NYHA class (II/III/IV)	5/18/1
β-blocker (%)	22 (85)
ACEi/ARB (%)	22 (85)
Spironolactone (%)	14 (54)
Electrocardiographic parameters	
LBBB (%)	26 (100)
QRS duration (ms)	174 ± 18
Baseline echocardiographic parameters	
LVESV (ml)	159 (126–189)
LVEDV (ml)	208 (176–236)
EF (%)	24 ± 8
Follow-up echocardiographic parameters	
LVESV (ml)	62 (46–86)
LVEDV (ml)	124 (91–156)
EF (%)	46 ± 10

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; EF, ejection fraction; LBBB, left bundle branch block; LVEDV, left ventricular diastolic volume; LVESV, left ventricular systolic volume; NYHA, New York Heart Association.

normally distributed, or otherwise by median and 25th and 75th percentiles (inter-quartile range). Categorical data were summarized as frequencies and percentages. The paired *t*-test was used for comparison between the baseline and the follow-up. Comparisons between groups were performed using one-way analysis of variance (ANOVA) and two-way repeated-measures ANOVA was used to analyse within-groups data. Bonferroni correction was applied due to multiple comparisons. Correlations between variables were described by Pearson correlation coefficients. Intraclass correlation coefficient (ICC) was used to test the reproducibility of the analysed methods, and the inter-observer agreement between two readers (M.C. and J.D.). Readers were blinded for the timing of the echocardiographic recording. A two-tailed *P*-value of ≤0.05 was considered statistically significant. Data were analysed using SPSS version 20 (IBM, Chicago, IL, USA).

Results

Study population

The characteristics of the study population are summarized in *Table 1*. After CRT implantation, echocardiography was performed at a median follow-up time of 14.5 (7–29) months. Median relative decrease of ESV during follow-up period was 61% (38–70).

Time to onset of longitudinal shortening

Before CRT, a dys-synchronous onset of shortening among the 18 LV segments was observed (*Figure 3A*). The earliest activated segment was most often the apical septal and mid-septal segment and the latest activated was most often the basal posterior or basal lateral segment. The time delay between the earliest and the latest activated segments was on average 199 ± 33 ms. After CRT, the intraventricular mechanical dy-ssynchrony decreased significantly (114 ± 22 ms; $P < 0.001$ vs. baseline). Segmental timing and significant changes of T_{onset} after CRT are presented in *Figure 3A*.

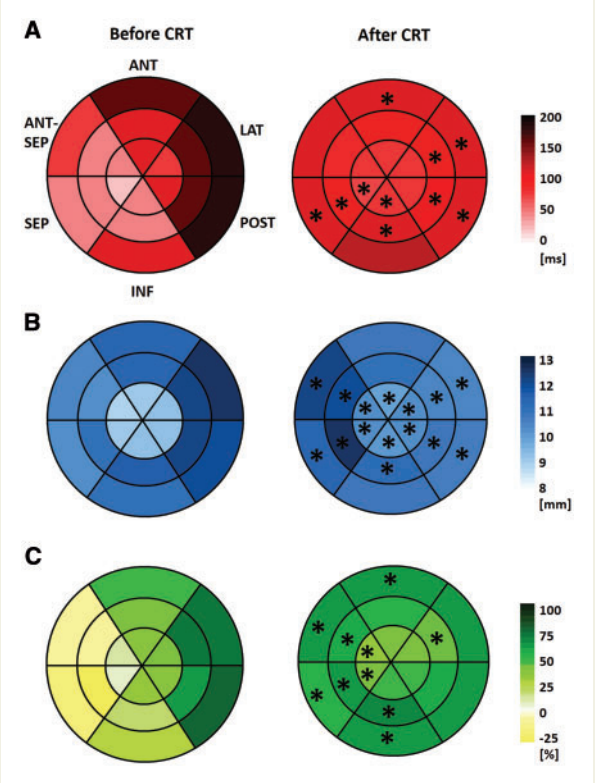


Figure 3 Distribution of time to onset of shortening, wall thickness and myocardial work. Colour coded bull's eye maps for (*A*) average segmental time to onset of longitudinal shortening (T_{onset}), (*B*) average segmental LV wall thickness (SWT) and (*C*) average segmental relative stress–strain loop area before and after CRT using an 18-segment model. Segments with significant (P <0.05) change after CRT are noted with an asterisk. ANT, anterior; ANT SEP, anterior septum; SEP, septum; INF, inferior; POST, posterior; LAT, lateral.

If analysed per wall, typical patterns of T_{onset} distribution were observed before CRT (ANOVA $P < 0.001$ between walls, *Figure 4A*), with the earliest shortening in septal and anteroseptal walls (53 ± 25 ms and 74 ± 39 ms, respectively) and the latest in lateral and posterior walls (140 ± 41 ms and 149± 43 ms, respectively, $P < 0.001$). This difference disappeared after CRT (ANOVA $P = 0.733$ between walls, *Figure 4A*).

Left ventricular wall thickness

Before CRT, an inhomogeneous distribution of SWT was observed within the LV while after CRT, LV wall thickness became more uniform. Segments with significant changes of SWT after CRT are presented in *Figure 3B*.

Analysis per wall revealed an asymmetry in wall thickness before CRT (ANOVA $P < 0.001$ between walls) (*Figure 4B*). Septal and anteroseptal walls (10.3 ± 1.4 mm and 10.1 ± 1.1 mm, respectively) were significantly thinner than lateral and posterior walls (11.3 ± 0.9 mm and 11.5 ± 0.9 mm, respectively, $P < 0.05$). After CRT, reverse

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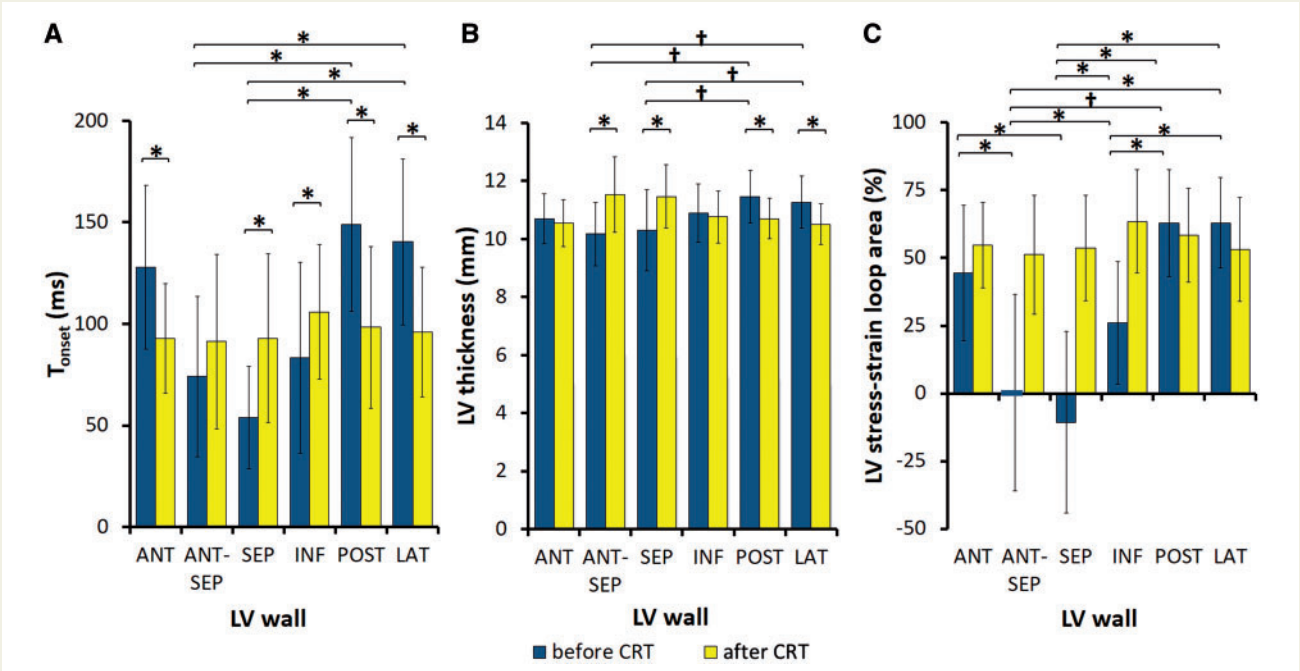


Figure 4 Time to onset of shortening, wall thickness and myocardial work. Segmental time to onset of longitudinal shortening (T_{onset}, *A*), SWT (*B*) and segmental work, expressed as relative stress–strain loop area (*C*), averaged per LV wall, before and after CRT. *P<0.001, †P<0.05. Annotation of walls as in *Figure 3*.

remodelling with significant increase of thickness was observed in septal and anteroseptal walls and with significant decrease of thickness in lateral and posterior walls (*Figure 4B*). No significant change of wall thickness was observed in anterior and inferior walls.

Myocardial work

Before CRT, relative segmental LV stress–strain loop area showed segmental differences of myocardial work with highest in the base lateral and base posterior segments and lowest or even negative relative work in the base and mid-septal segments (*Figure 3C*). After CRT, a uniform distribution of myocardial work was observed. *Figure 5* shows an example of strain curves and stress–strain loops of a representative patient before and 12 months after CRT.

If analysed per wall, a typical pattern of regional work distribution was detected before CRT (ANOVA $P < 0.001$ between walls, *Figure 4C*), with the lowest relative LV stress–strain loop areas in septal and anteroseptal walls (-10.7 ± 33.6% and 0.2 ± 33.3%, respectively) and the highest in lateral and posterior walls (63.0 ± 16.7% and 62.9 ± 19.8%, respectively, $P < 0.001$). This difference disappeared after CRT implantation (ANOVA $P = 0.215$ between walls, *Figure 4C*).

Relation between time of longitudinal shortening, wall thickness, and myocardial work

Significant positive correlations were observed between timing of shortening, wall thickness, and myocardial work before CRT. Baseline T_{onset} correlated with baseline absolute SWT ($r = 0.375$; $P < 0.001$), but a stronger correlation was found when the delay between segments was compared with the relative wall thickness (T_{delay} vs. relative SWT: $r = 0.510$; $P < 0.001$) (*Figure 6A*). The baseline relative segmental LV stress–strain loop area correlated both with relative SWT ($r = 0.353$; $P < 0.001$) and with the time of longitudinal shortening (T_{onset}: $r = 0.470$; T_{delay}: $r = 0.479$; $P < 0.001$, for all).

When three-chamber and four-chamber views were analysed separately stronger correlations were found. The strongest correlation between T_{delay} and relative SWT was observed in the three-chamber view ($r = 0.628$; $P < 0.001$) (*Figure 6B*). The strongest correlation between myocardial work and wall thickness was found in the three-chamber view ($r = 0.472$; $P < 0.001$) (*Figure 6C*) and the strongest correlation between myocardial work and timing of shortening in the four-chamber view ($r = 0.630$; $P < 0.001$) (*Figure 6D*).

Feasibility and reproducibility

A total of 936 segments was analysed and adequate measurements were achievable in 881 (94%) segments. Intra- and inter-observer agreement was strong for both T_{onset} [ICC 0.962 (0.945–0.974) and ICC 0.930 (0.894–0.954), respectively] and T_{delay} [ICC 0.961 (0.943–0.973) and ICC 0.942 (0.905–0.963), respectively] and good for SWT [ICC 0.918 (0.881–0.944) and ICC 0.825 (0.730–0.886), respectively] as well as for relative LV stress–strain loops area [ICC 0.930 (0.893–0.954) and ICC 0.874 (0.809–0.918, respectively].

Discussion

In this proof of concept study, we could demonstrate that dys-synchronous myocardial shortening is related to a reduction of myocardial

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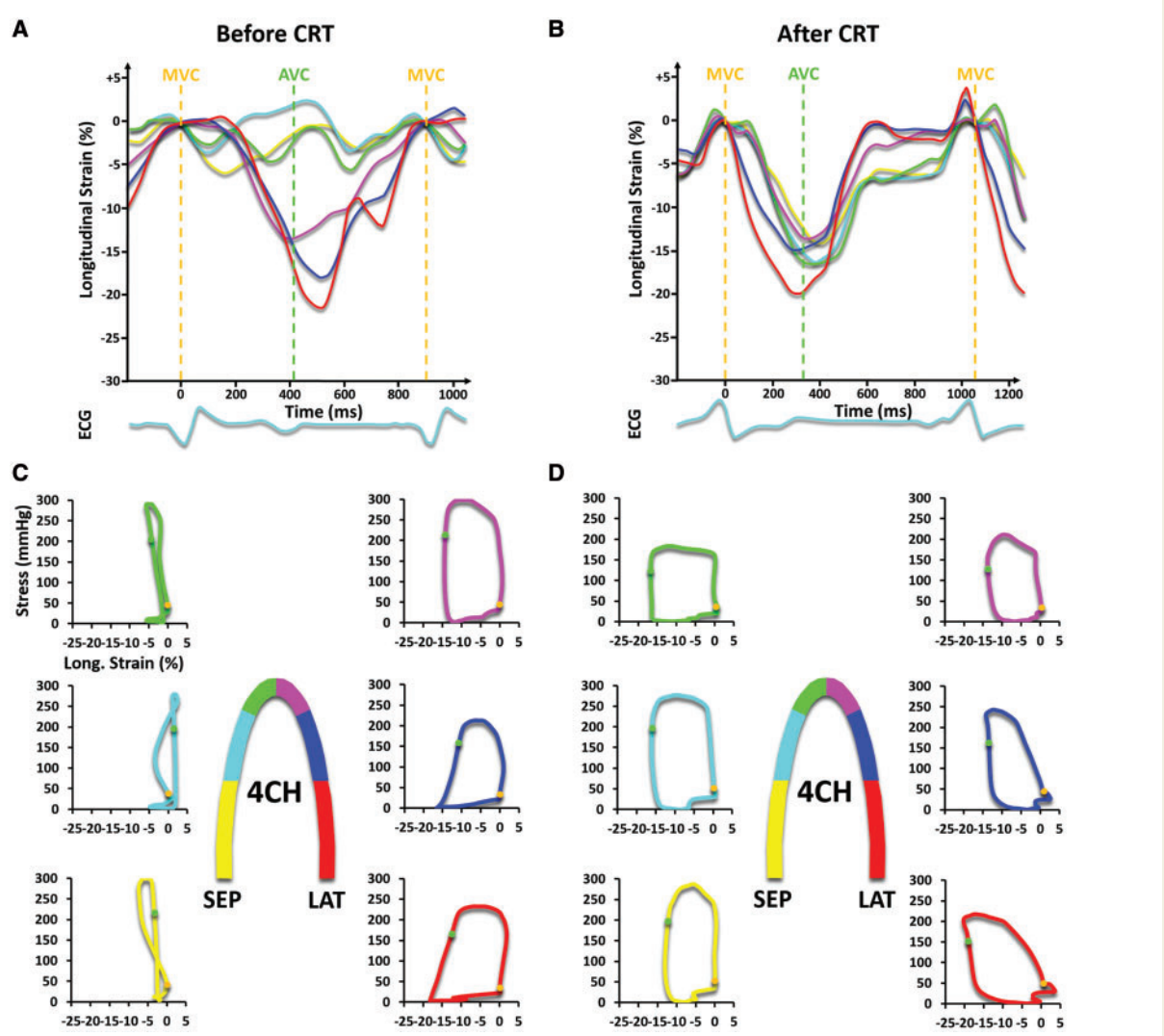


Figure 5 Representative example of LV segmental strain curves and stress-strain loops before and after CRT. Speckle-tracking longitudinal strain curves derived from the apical four-chamber view before (*A*) and 12 months after CRT (*B*) in a representative patient from our study population (Patient GDT). LV segmental stress–strain loops before (*C*) and 12 months after CRT (*D*) in the same patient. Dys-synchronous contraction pattern with earliest shortening in septal segments and latest shortening in lateral segments are found before CRT (*A*), whereas after CRT an almost completely synchronized contraction can be observed. Before CRT, segmental LV stress–strain loops show a figure-of-eight configuration and lowest or even negative work while lateral work is highest (*C*). After CRT, a uniform distribution of myocardial work was observed (*D*). The segmental color coding is the same for strain curves and for stress-strain loops. The vertical yellow and green lines in Panels A, B and dots in Panels C, D indicate mitral and aortic valve closure (AVC, MVC), respectively. 4CV, four-chamber view; LAT, lateral; SEP, septal.

work and thinning of the early and to an increasing of myocardial work and thickening of the late activated regions. We further found that correction of dys-synchrony with CRT homogenizes myocardial work distribution and, consequently, segmental LV wall thickness.

Timing of myocardial shortening, wall thickness, and myocardial work before CRT

In our group of heart failure patients with conduction delays, inhomogeneous onset of longitudinal myocardial shortening and asymmetric LV wall thickness were found. The earlier activated septal region was thinner than the late activated lateral and posterior walls. Our results are in line with previously study which described that the propagation of T_{onset} was consistently from septum to lateral wall in patients with left bundle branch block (LBBB).[13] However, data regarding LV wall thickness in CRT candidates are scarce and inconsistent.[3–5] Soliman *et al.*[4] found that the lateral wall was thicker than the septal wall before CRT in patients who responded to resynchronization therapy, whereas other authors reported no difference in thickness between walls.[3,5] Of note, different conduction abnormalities and aetiology were presented in these studies, whereas our group was very

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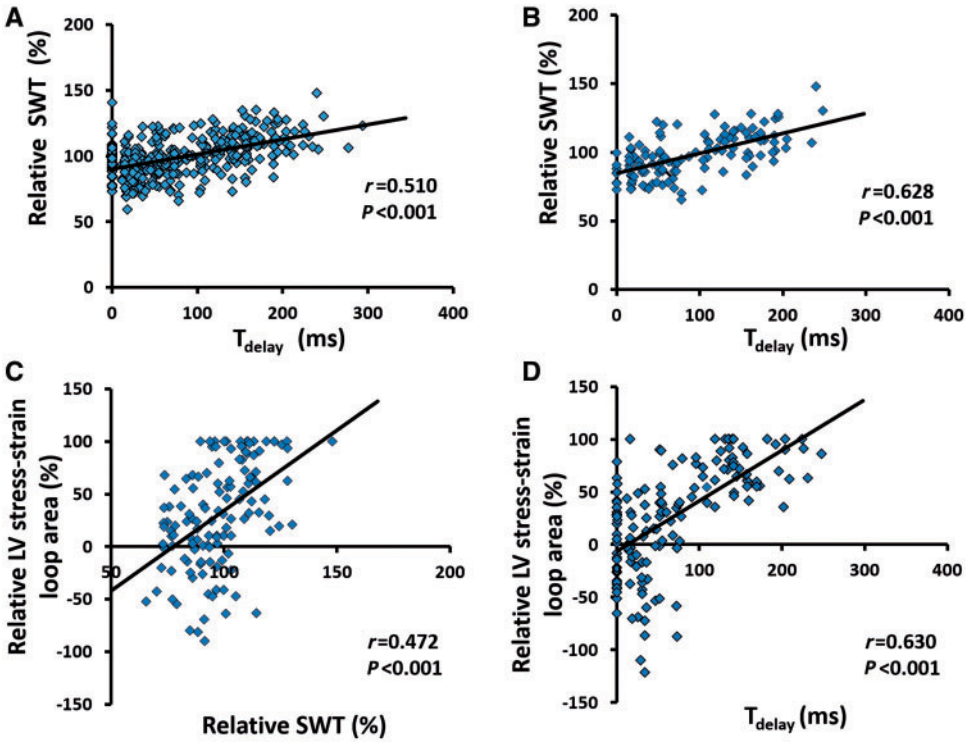


Figure 6 Timing of shortening, myocardial work and relative segmental wall thickness. Correlations between the time delay of segmental shortening (T_{delay}), relative segmental LV stress–strain loop area and the relative SWT. (*A*) All segments, (*B* and *C*) three-chamber view only, and (*D*) four-chamber view only. See text for details.

uniform, consisted only of LBBB patients with non-ischaemic cardiomyopathy who revealed reverse remodelling following CRT. Discrepancy of methodology should also be taken into consideration.[3–5] Recent studies measured wall thickness from parasternal long axis or only from mid-ventricular short-axis view while we aimed at a comprehensive evaluation of wall thickness in 18 segments within the LV. Our findings are in line with the results from animal studies, where the late activated region was thicker than the early activated region in a model with asynchronous activation due to ventricular pacing or ablation-induced LBBB.[1,2,14]

We observed that dys-synchronous activation of LV caused inhomogeneous distribution of myocardial work, with reduced or even negative work in the septal and increased work in the lateral and posterior regions. This is in line with an experimental study where a three-fold difference in total work among LV walls was found in animal model with induced dys-synchrony.[6] Similar results were found in CRT candidates who had a marked misbalance in regional myocardial work with wasted work in septum and increased work in lateral wall.[15–17] As observed in patients with LBBB, the onset of shortening of the septal regions is during early systolic phase, when the afterload is still very low, and stretching during the late ejection, with a small net effect of shortening during ejection, whereas the lateral and posterior walls shorten during the ejection phase, when the workload is higher. Our data suggest that the differences in regional loading due to dys-synchronous shortening cause non-uninform LV wall thickness, with thickening of late activated and more loaded lateral walls and thinning of the early activated and less loaded septal regions. This is supported also by results of animal experiments, where induced redistribution of regional workload caused asymmetric hypertrophy of LV and histological proven increase of myocyte volume in hypertrophic region.[1,2] Additionally, there are few data showing that dys-synchrony might also generate alterations in genes and protein expression that regulate contractile function and pathological hypertrophy.[18,19]

To the best of our knowledge, this is the first study that demonstrated direct relationship between the segmental onset of shortening, myocardial work, and wall thickness in CRT candidates. These correlations were most pronounced in segments of the four- and three-chamber views, which show the highest dys-synchrony. In our study, relative SWT correlated stronger with time of shortening and myocardial work than absolute baseline SWT. This can be explained by the fact that relative SWT reflects regional abnormalities better than absolute SWT as it is normalized to the varying normal thickness of the different regions of the LV. Comparing both measurements of time of shortening, T_{delay} correlated better with SWT and myocardial work than T_{onset}. As T_{delay} was calculated as time delays in onset shortening between early activated segment and each other segments in every patient, it better represent differences of onset of shortening within LV segments than T_{onset}, where also variations of the segmental electromechanical delay between patients can blur the results.

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In this study, we introduce a modification of previous published pressure–strain loop area for LV work analysis[7] by implementing a local wall stress calculation considering in addition segmental wall thickness and curvature. Given the observed segmental differences in SWT and the varying local curvature of the LV wall, we expect that such LV stress–strain loop areas more appropriately reflect regional myocardial work as pressure–strain loop areas based on a single LVP curve which is uniformly used for all segments.

Timing of myocardial shortening, wall thickness, and myocardial work after CRT

Our results demonstrate that a successful CRT results not only in a resynchronization of myocardial shortening but also in more balanced myocardial work distribution, which would explain the differential LV reverse remodelling with thinning of lateral and posterior and thickening of septal regions. However, previous studies reported the regression of LV thickness in both lateral and septal region in CRT responders.[4,5] In these studies, LV thickness was measured only in one level of LV (mid-ventricle) and it is likely that results might not reflect the differential changes in thickness in other parts of the LV wall. Additionally, the time course of LV wall reverse remodelling after CRT is varying. As the process of wall remodelling might not be completed at the follow-up echocardiography, the extent of changes of SWT could be underestimated.

Similar to our findings, Vecera *et al.*[15] reported more balanced distribution of work over the LV after CRT. They also found, that in responders, the global as well as the septal wasted work approached normal values with CRT. Our findings suggested that changes in load distribution after successful CRT might lead to regional adaptation of myocardial wall thickness. Increased work in the previously unloaded septum will then cause thickening of this region, whereas decrease of work in the previously overloaded lateral and posterior walls will induce thinning. In our study, some minor non-uniformity in LV thickness was also found after CRT, with a trend towards thicker septal regions. As there was no significant difference in T_{onset} and also regional myocardial work among LV walls after CRT, this discrepancy cannot be attributed to dys-synchronous shortening.

Timing of myocardial shortening and infarct scar

Our data showed that early activation of a myocardial region results in its unloading which might lead to the idea to pace partially scarred regions to prevent LV remodelling. Although this strategy might theoretically appear appealing, it may also increase the dys-synchrony of the LV, which could have deleterious effects on its own. In addition, lead placement in a scar region might result in bad capture or insufficient early contraction, which could reduce the intended effect. Furthermore, it has been shown to increase the risk for ventricular arrhythmias.[20] Therefore, as computer simulations suggest, the optimal LV lead position should be a compromise between a position distant from the scar and from the septum,[21] while the concept of early activation for potential scar unloading remains to be demonstrated *in vivo*.

Limitations

This study has limitations inherent to its retrospective nature and the study population. Also using 2D echocardiography for measuring SWT has technical limitations and is dependent on adequate acoustic windows. Cardiac magnetic resonance provides higher spatial resolution and has the potential to detect SWT more accurate but unfortunately cannot be used after CRT implantation. The onset of local shortening was derived from speckle tracking-based strain curves that depend on the initially drawn region of interest and are subject to temporal and spatial smoothing settings of the post-processing software. To obtain strictly local and time resolved information, we have minimized all smoothing and used regional strain curves instead of the standard segmental averages. As we used an estimated LVP curve, which is based on the correct timing of opening and closing of valves, errors in timing events might influence estimated LVP, and thereafter LV stress–strain loop area. In our study, however, the reproducibility of local thickness and timing measurements were more than sufficient to support our findings. Furthermore, myocardial curvature was measured only within the image plane. The consideration of the actual 3D shape of the LV might further improve estimates.[22]

Conclusion

In heart failure patients with ventricular conduction delay, inhomogeneous LV wall thickness is related to asynchronous myocardial shortening. Correction of dys-synchrony leads to a regression of this inhomogeneity. We suggest regional differences in myocardial work load that are homogenized by successful CRT as the underlying pathophysiological mechanism.

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