Cardiac Resynchronization Therapy Can Reverse Abnormal Myocardial Strain Distribution in Patients With Heart Failure and Left Bundle Branch Block

Ole-A. Breithardt, MD,*† Christoph Stellbrink, MD, FESC,* Lieven Herbots, MD,† Piet Claus, PtnD,† Anil M. Sinha, MD,* Bart Bijnens, PtnD,† Peter Hanrath, MD, FESC, FACC,* George R. Sutherland, MD, FESC†
Aachen, Germany; and Leuven, Belgium

OBJECTIVES
We studied the effects of cardiac resynchronization therapy (CRT) on regional myocardial strain distribution, as determined by echocardiographic strain rate (SR) imaging.

BACKGROUND
Dilated hearts with left bundle branch block (LBBB) have an abnormal redistribution of myocardial fiber strain. The effects of CRT on such abnormal strain patterns are unknown.

METHODS
We studied 18 patients (12 males and 6 females; mean age 65 ± 11 years [range 33 to 76 years]) with symptomatic systolic heart failure and LBBB. Doppler myocardial imaging studies were performed to acquire regional longitudinal systolic velocity (cm/s), systolic SR (s⁻¹), and systolic strain (%) data from the basal and mid-segments of the septum and lateral wall before and after CRT. By convention, negative SR and strain values indicate longitudinal shortening.

RESULTS
Before CRT, mid-septal peak SR and peak strain were lower than in the mid-lateral wall (peak SR: −0.79 ± 0.5 [septum] vs. −1.35 ± 0.8 [lateral wall], p < 0.05; peak strain: −7 ± 5 [septum] vs. −11 ± 5 [lateral wall], p < 0.05). This relationship was reversed during CRT (peak SR: −1.35 ± 0.8 [septum] vs. −0.53 ± 0.6 [lateral wall], p < 0.05; peak strain: −11 ± 6 [septum] vs. −7 ± 6 [lateral wall], p < 0.05). Cardiac resynchronization therapy reversed the septal–lateral difference in mid-segmental peak strain from −46 ± 94 ms (LBBB) to 17 ± 92 ms (CRT; p < 0.05).

CONCLUSIONS
Left bundle branch block can lead to a significant redistribution of abnormal myocardial fiber strains. These abnormal changes in the extent and timing of septal–lateral strain relationships can be reversed by CRT. The noninvasive identification of specific abnormal but reversible strain patterns should help to improve patient selection for CRT. (J Am Coll Cardiol 2003; 42:486–94) © 2003 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) is a new treatment option for patients with heart failure and left bundle branch block (LBBB). Several controlled clinical trials have demonstrated both the acute hemodynamic and long-term functional benefit of CRT in selected patients (1–3). Experimental studies based on tagged magnetic resonance imaging have suggested that asynchronous activation leads to a pronounced redistribution of regional fiber shortening (4,5). These phenomena might contribute to the reduction in ventricular function in patients with cardiomyopathies and LBBB. Thus, the identification of specific abnormal patterns in regional myocardial fiber strain redistribution might help to select those patients who are likely to benefit from CRT.

Myocardial deformation can be quantified by echocardiographic strain rate imaging (SRI), a technique based on processing of velocity data on color Doppler myocardial imaging (CDMI, or tissue Doppler imaging). The rate of regional myocardial deformation is measured by SRI. Integration of the regional strain rate (SR) curve enables the computation of myocardial shortening and lengthening (i.e., estimation of myocardial strain [디]) (6). In a healthy ventricle, regional peak SR values correlate well with invasive indexes of global systolic function, such as peak elastance and a peak positive rate of rise in left ventricular (LV) pressure (+dP/dt) (7,8). In diseased ventricles, SRI is able to identify regional changes associated with a range of pathologies and can allow the differentiation between healthy, ischemic and viable segments (9). Thus, we hypothesized that SRI might provide the optimal noninvasive approach to determine the nature of baseline regional contractile asynchrony and to assess the changes with pacing to define better patient selection criteria for CRT. For this purpose, we studied the regional deformation patterns in LBBB and evaluated the acute effects of CRT by echocardiographic SRI.

METHODS
Patients. Twenty consecutive heart failure patients were studied. Two patients were subsequently excluded from analysis because of poor transthoracic image quality. Thus, data on 18 patients (12 males and 6 females; mean age 65 ± 11 years [range 33 to 76 years]) with New York Heart Association functional class III/IV heart failure were ana-
analyzed. Echocardiography was performed after implantation of the CRT device and before initiation of active CRT. All patients received a biventricular pacing system with a right ventricular (RV) apical lead and LV pacing electrodes implanted through the coronary sinus and positioned in a LV epicardial vein. This coronary sinus lead was placed in a lateral position in 11 (61%) of 18 patients, in a posterior position in 6 patients (33%), and in an anterior position in 1 patient (6%).

Nine patients had presented with nonischemic cardiomyopathy (NICM), and nine had evidence of underlying coronary artery disease by coronary angiography and were classified as having ischemic cardiomyopathy (ICM). None of them had any evidence of myocardial ischemia at rest or an indication for revascularization. Six of nine patients with ICM had a previous transmural myocardial infarction (two anterior and four inferior).

All patients had LBBB with a mean QRS width of 167 ± 22 ms (range 120 to 196 ms) and a mean PR interval of 200 ± 38 ms (range 140 to 260 ms). Echocardiography documented LV dilation in all patients with a mean LV end-diastolic diameter of 75 ± 10 mm (range 61 to 95 mm) and a mean biplane ejection fraction of 23 ± 9% (range 9% to 37%). Exercise capacity was reduced, with a mean peak oxygen consumption (VO2max) of 11.9 ml/kg/min (range 9.9 to 15.5 ml/kg/min).

Protocol. All patients underwent a standard echocardiographic examination at rest both during “pacing off” and during CRT with the permanent programmed atrioventricular delay (mean 117 ± 18 ms). Reprogramming of the pacemakers to “no pacing” and CRT were performed during the same echocardiographic examination.

Image acquisition and machine settings. Ultrasound data were acquired either on a Vivid V or Vivid VII echocardiographic scanner (GE-Vingmed Ultrasound, Horten, Norway) with 2.5- to 3.5-MHz transducers and were recorded both in gray scale and CDMI. The CDMI data were recorded from the basal and mid-septal and lateral wall segments in the apical four-chamber view. For the apical two-chamber view, SR analysis was not feasible in the majority of patients due to either a poor signal-to-noise ratio or poor alignment of the Doppler beam with the longitudinal motion of the wall. The image sector width was set as narrow as possible to achieve the highest possible acquisition frame rates (>140 fps−1), and the pulse repetition frequency was set to avoid aliasing. For each myocardial wall, CDMI cine loops containing three consecutive cardiac cycles were stored digitally for post-processing.

Image analysis. A detailed description of the SR acquisition procedure has previously been presented by our group, with a reproducibility for regional longitudinal SR and strain measurements ranging from 11% to 14% (10). In brief, we analyzed CDMI data clips offline on a PC workstation using customized software (SPEQLE, Katholic University Leuven, Belgium) to derive regional velocity profiles from the basal and mid-segments of each wall. A semi-automatic tracking algorithm was applied to maintain the sample volume in the region of interest throughout the cardiac cycle.

Regional SR was estimated from the spatial gradient of the myocardial velocity profile over a user-defined sample volume with a computational area of 10 mm. By convention, SR is expressed as a positive parameter when the segment thins/shortens and as a negative parameter when the segment thins/shortens. In normal myocardium, longitudinal directional changes from the apical views are characterized by systolic shortening (negative SR) and diastolic lengthening (positive SR). An increase in the rate of longitudinal systolic shortening will result in a more negative SR value and is expressed as an increased/higher peak SR, and vice versa.

Velocity and SR profiles were averaged over three consecutive cycles (spatial processing: 5 radial pixels, 3 lateral pixels [median averages]). The regional SR profiles were integrated over time to obtain the natural systolic strain profiles. This curve was then used to define the extent of systolic shortening (negative strain) or lengthening (positive strain). An increase in the extent of systolic shortening (i.e., more negative strain) is expressed as increased/higher strain, and vice versa.

We incorporated data from anatomic M-mode recordings on aortic and mitral valvular opening and closure to identify the duration of LV isovolumic contraction time (IVCT), ejection, and isovolumic relaxation time (IVRT). These data were obtained from parasternal CDMI cine loops from cycles with identical R-R intervals. For each myocardial segment analyzed, regional peak positive velocity (Vmax cm/s), peak negative SR (SRmax, s−1), and the extent of longitudinal shortening (negative strain, %) were assessed during LV systole (i.e., during IVCT and the ejection period) (Fig. 1). The isovolumic peak in Vmax was excluded from the analysis. Time to peak systolic velocity (t-Vmax) and strain rate (t-SRmax) were measured from the onset of the QRS complex as the reference point. The temporal differences in regional peak systolic velocity (ΔSL[Vmax],

Abbreviations and Acronyms

CDMI = color Doppler myocardial imaging
CRT = cardiac resynchronization therapy
ε = strain
ICM = ischemic cardiomyopathy
IVCT = isovolumic contraction time
IVRT = isovolumic relaxation time
LBBB = left bundle branch block
LV = left ventricle/ventricular
NICM = nonischemic dilated cardiomyopathy
RV = right ventricle/ventricular
SR = strain rate
SRI = strain rate imaging
Vmax = peak positive velocity
ms) and regional peak systolic strain (ΔSL[SR_{max}], ms) between the septal and lateral wall segments were calculated to quantify the acute effects of CRT on contractile synchrony during ejection.

We performed an additional visual qualitative comparison of the mid-septal and mid-lateral strain relationships during LV systole. For each wall, we separately assessed the presence of regional shortening or lengthening during LV systole (IVCT, ejection) and compared the regional timing to the onset of shortening.

The effectiveness of CRT was verified by a comparison of two-dimensional and Doppler echocardiographic parameters before and after CRT (2,11). We measured the response in LV ejection fraction (%), mitral diastolic filling time, and the interval between the RV and LV pre-ejection delay (ΔPEP [ms]; onset of QRS complex to onset of RV/LV ejection by pulsed-wave Doppler).

**Statistical analysis.** Continuous data are expressed as mean values ± SD. The Wilcoxon signed-rank test was applied for paired comparisons between pacing modes and between walls. Unpaired data were compared by the Mann-Whitney U test. A p value <0.05 was considered significant for all comparisons. The analysis was performed using StatsDirect version 1.605 (CamCode, Ashwell, U.K.).
Table 1. Longitudinal Systolic Left Ventricular Function Estimated by Regional Velocities and Deformation Parameters in the Apical Four-Chamber View

<table>
<thead>
<tr>
<th>Myocardial Wall</th>
<th>Segment</th>
<th>$V_{max}$ (cm/s)</th>
<th>$SR_{max}$ (s$^{-1}$)</th>
<th>$e_{eject}$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBBB Septum</td>
<td>Basal</td>
<td>2.4 ± 1.1</td>
<td>−1.3 ± 1.0</td>
<td>−11 ± 10</td>
</tr>
<tr>
<td></td>
<td>Mid</td>
<td>2.1 ± 1.2</td>
<td>−1.4 ± 0.7</td>
<td>−15 ± 7</td>
</tr>
<tr>
<td>Lateral</td>
<td>Basal</td>
<td>2.0 ± 1.3</td>
<td>−0.71 ± 0.4*</td>
<td>−8 ± 8</td>
</tr>
<tr>
<td></td>
<td>Mid</td>
<td>1.6 ± 1.5</td>
<td>−1.3 ± 0.7</td>
<td>−12 ± 5</td>
</tr>
<tr>
<td>CRT Septum</td>
<td>Basal</td>
<td>2.5 ± 1.1</td>
<td>−1.5 ± 1.1</td>
<td>−9 ± 10</td>
</tr>
<tr>
<td></td>
<td>Mid</td>
<td>2.0 ± 0.9</td>
<td>−1.5 ± 0.8</td>
<td>−14 ± 9</td>
</tr>
<tr>
<td>Lateral</td>
<td>Basal</td>
<td>1.7 ± 0.9*</td>
<td>−0.9 ± 0.6*</td>
<td>−8 ± 6</td>
</tr>
<tr>
<td></td>
<td>Mid</td>
<td>1.5 ± 1.2</td>
<td>−1.5 ± 1.0</td>
<td>−12 ± 6</td>
</tr>
</tbody>
</table>

*p < 0.05 vs. septum. Data are presented as the mean value ± SD.
CRT = cardiac resynchronization therapy; $e_{eject}$ = strain during ejection; LBBB = left bundle branch block; SR = strain rate; $V_{max}$ = peak positive velocity.

RESULTS

Longitudinal LV function during LBBB and CRT. The results for the systolic parameters of regional longitudinal velocity and deformation are summarized in Table 1. We found no significant difference between basal and mid-septal and lateral wall $V_{max}$ although there was a tendency toward slightly higher mean values in the basal and mid-septum. During CRT, $V_{max}$ decreased significantly in the basal lateral wall, but was not affected in the other segments.

In both walls, we found nearly normal peak systolic SR before CRT (normal septal systolic $SR_{max}$ of approximately −1.5 ± 0.35 [10]), but severely reduced overall shortening, expressed by the low systolic strain values (Table 1). Cardiac resynchronization therapy had no significant effect on either systolic $SR_{max}$ or systolic peak negative strain.

However, the separate analysis of longitudinal deformation in IVCT and in the ejection period revealed significant differences (Table 2). Before CRT, almost half of systolic septal shortening occurred during IVCT. In contrast, we observed only minimal lateral wall shortening during IVCT. Lateral wall shortening was delayed to the ejection period and significantly exceeded septal shortening. These relationships were reversed with CRT: during CRT, the septum shortened mainly during the ejection period, and the extent of septal shortening exceeded lateral wall shortening, which was partly transferred to the IVCT interval and occurred earlier.

Septal-lateral strain relationships during LBBB and CRT. Before CRT, the average peak systolic myocardial velocities in the mid-wall segments occurred almost simultaneously in the septum and lateral wall, as indicated by the low $\Delta SL(V_{max})$. In contrast, the quantitative and qualitative comparisons of the septal-lateral strain relationships revealed characteristic patterns associated with LBBB (Table 3, Fig. 2). Septal shortening clearly started before lateral shortening in 15 (83%) of 18 patients (8 with NICM, 7 with ICM). The septum reached its absolute peak shortening before the end of ejection in 16 (89%) of 18 patients, resulting in a negative $\Delta SL(e_{eject})$.

Lateral wall post-systolic shortening was observed in 13 (72%) of 18 patients (4 with NICM, 9 with ICM). Septal shortening during IVCT was identified in 16 (89%) of 18 patients and was accompanied by early systolic lateral wall lengthening in eight patients (44%; 6 with NICM, 2 with ICM). Patients with lateral wall lengthening during IVCT presented with a significantly higher lateral $SR_{max}$ compared with patients without lengthening during IVCT (1.6 ± 0.8 vs. 0.95 ± 0.4 s$^{-1}$, p < 0.05). Lateral wall post-systolic shortening during IVRT was accompanied by septal lengthening in 11 patients (61%).

During CRT, the temporal asynchrony in $e_{max}$ was reduced, but the timing of peak systolic velocities was not significantly affected. There was only a nonsignificant trend toward an earlier septal $V_{max}$ and delayed lateral $V_{max}$ during CRT (p = 0.06). Simultaneous septal-lateral shortening was observed in 7 (39%) of 18 patients (3 with NICM, 4 with ICM), and earlier onset of lateral wall shortening was identified in five patients (28%). However, in six patients (33%), septal shortening still began before lateral wall shortening. For both walls, peak shortening frequently ended before the end of the ejection period (lateral: 12 [67%] of 18 patients; septal: 13 [72%] of 18).

<table>
<thead>
<tr>
<th>Myocardial Wall</th>
<th>$SR_{max}$-IVCT ($s^{-1}$)</th>
<th>$SR_{max}$-Eject ($s^{-1}$)</th>
<th>$\epsilon_{IVCT}$ (%)</th>
<th>$\epsilon_{eject}$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBBB Septum</td>
<td>−1.4 ± 0.7</td>
<td>−0.8 ± 0.5</td>
<td>−6 ± 5</td>
<td>−7 ± 5</td>
</tr>
<tr>
<td></td>
<td>Lateral</td>
<td>−0.7 ± 0.7*</td>
<td>−1.2 ± 0.6*</td>
<td>−0.1 ± 1*</td>
</tr>
<tr>
<td>CRT Septum</td>
<td>1.1 ± 0.8</td>
<td>−1.4 ± 0.8†‡</td>
<td>−2 ± 4†‡</td>
<td>−11 ± 6†‡</td>
</tr>
<tr>
<td></td>
<td>Lateral</td>
<td>1.3 ± 1.1</td>
<td>−0.9 ± 0.6*‡</td>
<td>−3 ± 4</td>
</tr>
</tbody>
</table>

*p < 0.05 vs. septum. †p < 0.01 vs. LBBB. ‡p < 0.05 vs. LBBB. Data are presented as the mean value ± SD.
IVCT = isovolumic contraction time; other abbreviations as in Table 1.
during IVRT, continued lateral wall shortening with concomitant septal wall lengthening coincided in only four patients (22%). The response of ICM and NICM patients to CRT was comparable. We found no significant relationship between the QRS width and ΔSL($V_{\text{max}}$) or ΔSL($\varepsilon_{\text{max}}$) before and after CRT.

**Motion versus deformation.** Septal $V_{\text{max}}$ was observed 89 ± 108 ms before maximal septal negative strain ($\varepsilon_{\text{max}}$). This dissociation between motion and deformation was significantly larger in the lateral wall, where $V_{\text{max}}$ occurred 165 ± 86 ms before $\varepsilon_{\text{max}}$ (p < 0.05 vs. septum). In 4 of 18 patients, the maximal mid-septal strain development was observed before, or was simultaneous with, mid-septal $V_{\text{max}}$ (Fig. 3), and in 12 of 18 patients, we found a negative ΔSL($\varepsilon_{\text{max}}$), indicating delayed systolic shortening in the lateral wall.

Cardiac resynchronization therapy led to significant but divergent effects on the septal-lateral differences in motion and deformation. Mean ΔSL($V_{\text{max}}$) decreased, but mean ΔSL($\varepsilon_{\text{max}}$) increased, indicating that peak lateral wall shortening now occurred before peak septal shortening (Table 3, Figs. 2 and 4). In the septum, the mean delay between $V_{\text{max}}$ and $\varepsilon_{\text{max}}$ was prolonged to 151 ± 15 ms (p < 0.05 vs. LBBB), and the corresponding delay in the lateral wall was reduced to 110 ± 83 ms (p < 0.05 vs. LBBB).

Patients with ICM showed a larger delay between motion and deformation, as compared with patients with NICM. Before CRT, mid-septal $V_{\text{max}}$ preceded $\varepsilon_{\text{max}}$ by 142 ± 104 ms in patients with ICM, but only by 36 ± 89 ms in NICM patients (p < 0.05). Similar differences were observed in the mid-lateral wall (ICM: 215 ± 54 ms vs. NICM: 116 ± 88 ms, p < 0.05). During CRT, this motion–deformation delay was reduced (mid-septum: 162 ± 43 ms [ICM] vs. 140 ± 80 ms [NICM] p = NS; mid-lateral wall: 141 ± 72 ms [ICM] vs. 80 ± 87 ms [NICM], p = NS).

**Effects of CRT on two-dimensional and Doppler-derived variables.** Cardiac resynchronization therapy increased the LV ejection fraction, reduced the intraventricular delay between RV and LV ejection (ΔPEP), and improved the mitral diastolic filling time and LV peak +dP/dt by continuous-wave Doppler (Table 4). A reduction in ΔSL($\varepsilon_{\text{max}}$) of at least 50 ms was associated with a higher decrease in ΔPEP (−62 ± 41 vs. −26 ± 14 ms, p < 0.05), but with no significant differences in LV ejection fraction increase (28 ± 30% vs. 25 ± 22%, p = NS) and mitral filling time increase (29 ± 11% vs. 25 ± 23%, p = NS).

**DISCUSSION**

Contractile function is depressed in heart failure patients with dilated cardiomyopathy, due to various cellular and extracellular biochemical abnormalities. The presence of LBBB often causes asynchronous LV contraction, and this contributes independently to further impairment in global systolic function (12). In such hearts, the redistribution of myocardial fiber strain induced by asynchronous activation has been quantified in animal experiments and was associated with changes in both regional blood flow and metabolism (13). This impaired synchrony reduces overall cardiac efficiency and increases myocardial energy demands (14). Furthermore, it can lead to abnormal segments in which myocardial stretching might occur during ejection, and these may have a pro-arrhythmic effect (15).

**Myocardial deformation in LBBB.** Our SRI results confirm the previously reported experimental magnetic resonance imaging findings on the effects of asynchronous activation on myocardial deformation (4). In most patients, lateral wall contraction was delayed in comparison with the septum, and this relationship was, in contrast to a recently published study (16), independent of the underlying etiology (ICM or NICM).

The comparative analysis of septal and lateral wall longitudinal deformation in LBBB demonstrated an earlier onset of mid-septal shortening during IVCT, with a consecutively lower peak SR during ejection. The early-developed septal force is dissipated in generating sufficient energy to open the aortic valve and in stretching the late-activated posterolateral wall. The latter event represents wasted energy during early ejection (14).

In almost half of the study population (44%), we identified simultaneous early systolic septal shortening and lateral wall lengthening, indicating that the septum generated an active force on the lateral wall, thereby stretching it. Passive stretch might influence regional myocardial contractility by means of a local Frank-Starling mechanism, caused by the regional difference in effective preload. This would explain the observed higher peak negative SR in late-activated lateral walls with early systolic lengthening (stretch). The passive pre-stretch would enable the late-activated segments to shorten faster and to a greater extent in order to compensate for the increased loading conditions in late-activated regions. Similar conclusions have been drawn previously based on magnetic resonance imaging data (4). In accordance with our results, this trial also demonstrated that

---

Table 3. Septal and Lateral Timing of Left Ventricular Motion and Deformation During Left Bundle Branch Block and Cardiac Resynchronization Therapy in Mid-Wall Segments

<table>
<thead>
<tr>
<th></th>
<th>$t_{V_{\text{max}}}$−S (ms)</th>
<th>$t_{V_{\text{max}}}$−L (ms)</th>
<th>ΔSL($V_{\text{max}}$) (ms)</th>
<th>$t_{\varepsilon_{\text{max}}}$−S (ms)</th>
<th>$t_{\varepsilon_{\text{max}}}$−L (ms)</th>
<th>ΔSL($\varepsilon_{\text{max}}$) (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBBB</td>
<td>247 ± 92</td>
<td>222 ± 74</td>
<td>25 ± 85</td>
<td>336 ± 110</td>
<td>388 ± 58∗</td>
<td>−52 ± 103</td>
</tr>
<tr>
<td>CRT</td>
<td>220 ± 56</td>
<td>242 ± 81</td>
<td>−22 ± 75</td>
<td>371 ± 61</td>
<td>352 ± 88†</td>
<td>19 ± 96†</td>
</tr>
</tbody>
</table>

*p < 0.05 vs. septum, †p < 0.01 vs. LBBB. Data are presented as the mean value ± SD. L = lateral wall; S = septum; ΔSL($V_{\text{max}}$) = temporal difference in regional peak systolic velocity; $t_{V_{\text{max}}}$ = time to peak systolic velocity, other abbreviations as in Table 1.
Figure 2. Velocity and strain curves before (LBBB) and after cardiac resynchronization therapy (CRT) from the septal and lateral wall mid-segments in a 73-year-old patient. The derived strain curves from the mid-segments clearly show the regional asynchrony in deformation. Maximal septal contraction occurs before aortic valve opening (top left panel, arrow) and is accompanied by lateral wall lengthening. The septum lengthens after aortic valve opening and does not contribute to ejection. Peak lateral wall contraction is observed very late in systole and persists into the post-systolic period (bottom left panel, arrowhead). During CRT, systolic contraction occurs simultaneously in both walls, contributing equally to ejection (right panels). Note also the shorter isovolumic contraction (IVC) time with CRT. IVRT = isovolumic relaxation time.
early-activated segments contract against a low afterload and show reduced longitudinal strain and work load, but they waste energy by pre-stretching later activated segments. The inhomogeneous distribution of myocardial load and deformation may ultimately lead to adaptive changes on the cellular level with evolution of regional hypertrophy and biochemical abnormalities in the late-activated segments (17). Thus, the presence of a late-activated region with increased wall stress and work load, as identified noninva-

Figure 3. Curved color M-mode echocardiogram acquired by post-processing color Doppler myocardial imaging data displaying regional velocity (left panels) and strain rate (right panels) in the mid-septum (top panels) and mid-lateral wall (bottom panels) of a study patient. The vertical line indicates the onset of the QRS complex. The septal wall shows early systolic shortening (arrow), coded yellow-red in the strain rate image, despite negative velocities in early systole (coded blue in the velocity image). In contrast, the lateral wall moves apical toward the transducer, as indicated by the red color in the velocity image, but shortens significantly later, as compared with the septum (arrowhead). Early systolic lengthening (coded blue in the strain rate image) precedes systolic shortening.

Figure 4. Same patient as in Figure 3 after cardiac resynchronization therapy (CRT). Compared with left bundle branch block (Fig. 3), CRT had no significant effect on the velocity profiles. In contrast, systolic shortening occurred simultaneously in both walls (arrows).
Table 4. Effects of CRT on Echocardiographic Parameters

<table>
<thead>
<tr>
<th></th>
<th>No CRT</th>
<th>CRT</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>73 ± 14</td>
<td>72 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>24 ± 11</td>
<td>28 ± 9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ΔPEP (ms)</td>
<td>64 ± 31</td>
<td>12 ± 19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral FT (ms)</td>
<td>363 ± 93</td>
<td>445 ± 111</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>+dP/dt&lt;sub&gt;max&lt;/sub&gt; (mm Hg/s)</td>
<td>423 ± 167</td>
<td>561 ± 180</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data are presented as the mean value ± SD.

CRT = cardiac resynchronization therapy; +dP/dt<sub>max</sub> = peak positive rate of rise in left ventricular pressure; FT = filling time; ΔPEP = interval between right and left ventricular pre-ejection delay.

sively by early systolic lengthening (stretch) and a delay to peak deformation, might have a significant impact on the progression of the underlying disease and therefore patient prognosis.

**Effects of CRT on myocardial deformation.** Reprogramming to active CRT allowed us to study the acute effects of the altered activation sequence on longitudinal deformation and the exclusion of any potential long-term effects related to reverse remodeling. The results demonstrate that short-term CRT leads to a significant redistribution of longitudinal myocardial deformation and that the majority of patients were well resynchronized or even “oversynchronized” (i.e., delayed septal shortening) by CRT. In a large proportion of patients (39%), we observed a simultaneous onset of systolic shortening. The frequently observed phenomenon of early systolic lateral wall lengthening in LBBB was virtually eliminated by CRT, indicating more energy-efficient contraction, less energy wasting, and more homogeneous wall stress distribution. Late systolic lengthening of the septum was observed less frequently. Cardiac resynchronization therapy improved mid–septal shortening while lateral wall shortening normalized (i.e., decreased). The reversal of the septal–lateral strain relationship implies that the motion-activated septum by almost 100 ms, on average. However, the mid–septum is generating a higher ejection force, most probably as the result of an optimized local preload. This unloading of the intrinsically late-activated region and the reduction of abnormal myocardial stretch may favorably affect the recovery of regional myocardial function, promote LV reverse remodeling, and reduce pro–arrhythmia (15,18).

**Myocardial motion versus deformation.** We found a strong dissociation between regional myocardial motion and deformation. During LBBB, peak myocardial ejection velocities preceded peak ejection shortening in the early-activated septum by almost 100 ms, on average. However, some patients showed opposite relationships (Fig. 1). The average motion–deformation delay was greater in the late-activated lateral wall and in ICM patients. During CRT, this sequence was reversed. This suggests that the motion–deformation delay is dependent on the degree of asynchrony and on the underlying disease.

Thus, the timing of myocardial motion (V<sub>max</sub>) does not reliably display myocardial deformation and tends to underestimate the degree of asynchrony, in particular, in the presence of ischemic heart strain. Velocity parameters have been shown to be useful in identifying patients with ventricular asynchrony (19), but SR deformation imaging should be the preferred modality for correct identification of the regional contraction delay.

**Study limitations.** Our analysis was limited to data collection from the apical four-chamber view, as this was the only image plane that provided reliable information on longitudinal deformation in two opposing walls in a sufficient number of patients. Yet, it would be desirable to obtain information on LV deformation from the complete ventricular cavity. However, adequate longitudinal alignment of the Doppler beam is crucial in CDMI, in particular, for SRI, but in most heart failure patients, it is complicated by ventricular dilation. Therefore, a complete echocardiographic longitudinal SR evaluation covering all myocardial walls seems to be not feasible currently.

Ultrasonic SRI provides important information on regional deformation, but the identification of shortening and lengthening does not differentiate between active (internal) and passive (external, elastic) force development. Passive pre–stretch of a myocardial segment by an externally applied active force may increase the stored elastic energy in this segment. This stored elastic energy may then lead to passive shortening, depending on the regional loading conditions. In such a case, the presence of late systolic shortening, as identified by a negative SR, does not necessarily indicate active contraction but may also be due to passive elastic recoil.

The quantitative analysis focused on peak myocardial motion and deformation during global (and not local) LV systole. This limits the comparison of our findings with those of other studies and might explain why we found no significant effect of CRT on the peak systolic septal velocities, as reported previously (19,20). A larger patient population is required to obtain reliable information on the full spectrum of asynchrony in LBBB patients and to correlate the findings to the acute effects on mitral regurgitation (21), long-term clinical improvement (3), and possible reverse remodeling (11).

Myocardial motion velocities and deformation parameters by CDMI are low in patients with advanced systolic heart failure, which complicates the identification of peak systolic motion and deformation and makes the results susceptible to artifacts and errors. A time-consuming offline analysis protocol with careful tracking of the region of interest, identification of global ventricular timing, and averaging of several beats were applied to enable data analysis. Technical improvements are required to make SRI data analysis easier and applicable for routine clinical use.

**Conclusions.** The presence of LBBB in failing hearts leads to a significant redistribution of regional wall stress, which may in turn contribute to the progression of the underlying disease, independent of biochemical and cellular alterations. These deleterious effects of asynchronous activation can be assessed noninvasively by ultrasonic SRI and provide infor-
mation on the impact of asynchrony in the individual patient. This may help to improve patient selection for CRT and to identify better long-term responders. In particular, the noninvasive identification of an excessively preloaded, late-activated region should stimulate the use of CRT to relieve the overloaded myocytes by early activation. Strain rate imaging can be used for monitoring the efficacy of this approach and helps us to understand the responsible mechanisms for reverse remodeling.

Reprint requests and correspondence: Dr. Ole-A. Breithardt, Medizinische Klinik I, Univ.-Klinikum Aachen, Pauwelsstr. 30, D-52075, Aachen, Germany. E-mail: olebreithardt@gmx.de.

REFERENCES


