Myocardial Structural, Perfusion, and Metabolic Correlates of Left Bundle Branch Block Mechanical Derangement in Patients With Dilated Cardiomyopathy

A Tagged Cardiac Magnetic Resonance and Positron Emission Tomography Study

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Background—Left bundle branch block (LBBB) influences on regional left ventricular (LV) structure, perfusion, and metabolism have not yet been thoroughly investigated in dilated cardiomyopathy patients.

Methods and Results—Eleven dilated cardiomyopathy patients with LBBB (mean±SD age, 62±11 years; LV ejection fraction, 35±8%) and 7 dilated cardiomyopathy patients without LBBB (mean±SD age, 58±9 years; LV ejection fraction, 37±10%) were studied by cardiac magnetic resonance and positron emission tomography. The left ventricle was divided in 3 regions: septum, adjacent (anterior-inferior walls), and lateral. Regional midwall circumferential strain, maximum shortening, and strain rate were obtained from tagged cardiac magnetic resonance. The systolic stretch index was calculated as positive strain rate (stretching) divided by total strain rate. Myocardial metabolic rate of glucose and resting and hyperemic myocardial blood flow were quantified by 2-[18F]fluoro-2-deoxyglucose and [13N]ammonia positron emission tomography, respectively. Compared with non-LBBB patients, LBBB patients showed a highly inhomogeneous systolic deformation pattern that changed gradually, moving from a discoordinate [systolic stretch index, 0.485 (0.284)] and poorly contracting (maximum shortening, −1.14±0.96%) septum to a coordinate [systolic stretch index, 0.002 (0.168)] and strongly contracting (maximum shortening, −13.63±2.58%) lateral region (both P<0.0001). This pattern was closely matched to the myocardial metabolic rate of glucose, disclosing lowest, intermediate, and highest values in the septum, adjacent, and lateral regions, respectively (P<0.0001). Septal-to-lateral thickness ratio was lower in LBBB than in non-LBBB patients (P=0.03). In both groups, the LV distribution of resting and hyperemic myocardial blood flow and myocardial blood flow reserve did not differ significantly.

Conclusions—In dilated cardiomyopathy patients, the extensive LV contraction abnormalities induced by LBBB cause regional myocardial metabolic and structural remodeling, without consistent changes in blood flow. (Circ Cardiovasc Imaging. 2010;3:482-490.)

Key Words: left bundle branch block ■ dilated cardiomyopathy ■ cardiac magnetic resonance ■ positron emission tomography

In dilated cardiomyopathy (DCM) patients, left bundle branch block (LBBB) occurs frequently and is associated with high cardiac morbidity and mortality.1 LBBB induces inhomogeneous activation and deformation of the ventricles, leading to inefficient contraction. Experimental data suggest that the redistribution of local workload induced by LBBB provokes substantial changes in regional myocardial blood flow (MBF)2,3 and glucose metabolism,3 along with structural remodeling.4 Studies performed in DCM patients show a global reduction of resting MBF and coronary flow reserve4 as well as a shift from fatty acid oxidation to glucose utilization.5–8 However, in DCM patients with LBBB, data on regional myocardial perfusion are conflicting9–13, whereas 2-[18F]fluoro-2-deoxyglucose ([18F]FDG) positron emission tomography (PET) imaging shows a relative reduction of glucose uptake in the septum compared with the lateral wall10,11 but without conclusive quantitative data on regional myocardial glucose metabolism. Deeper insight into the pathophysiologic changes induced by LBBB is warranted to better understand the potential causes of the adverse struc-
tural, functional, and metabolic myocardial remodeling, as well as of successful or failing resynchronization therapy. Accordingly, we investigated the influence of a dysynchronous contraction pattern on regional myocardial structure, perfusion, and metabolism by comparing DCM patients with LBBB and without LBBB who showed a similar degree of left ventricular (LV) dysfunction. Regional and global LV contraction patterns were evaluated by high temporal resolution tagged cardiac magnetic resonance (CMR), whereas MBF and glucose metabolism were quantified by PET imaging with $^{13}$N ammonia and $^{18}$F FDG as flow and metabolic tracers, respectively.

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Methods

Study Population

Between February 2008 and June 2009, 11 patients with DCM and LBBB and 7 DCM patients without LBBB were prospectively studied by CMR and PET. Inclusion criteria were as follows: (1) LV ejection fraction <50% on transthoracic echocardiography in the absence of previous heart failure symptoms or recent history of mild to moderate heart failure symptoms (New York Heart Association class II or III) stable with oral medications and (2) absence of coronary artery stenosis on invasive angiography. Exclusion criteria were diabetes, atrial fibrillation, acute myocarditis, infiltrative or moderate to severe valvular heart disease (based on echocardiographic evaluation), renal failure, and contraindications to CMR. The protocol was approved by the institutional ethics committee, and all patients gave written, informed consent.

Electrocardiography

LBBB was defined as a QRS duration ≥120 ms, presence of notched R waves in lateral precordial leads (V5 and V6) and I and aVL, small or absent initial r waves in right precordial leads (V1 and V2) followed by deep S waves, absent septal q waves in left-sided leads, and a prolonged intrinsiod deflection (>60 ms) in V5 and V6.

Cardiac Magnetic Resonance

All patients were examined with a 1.5-T scanner (CVi, GE Healthcare), and ECG-vectorcardiogram triggering. LV function was assessed by breath-hold, steady-state free-precession cine CMR in the cardiac short-axis and 2-chamber and 4-chamber long-axis views. In the cardiac short-axis view, the left ventricle was completely encompassed by contiguous 8-mm-thick slices. To determine the timing of mitral and aortic valves, high temporal resolution cine CMR in a 3-chamber long-axis view was obtained by setting the number of cardiac phases to achieve a temporal resolution of 12 ms. To investigate wall thickness abnormalities, 3 base-to-apex short-axis cine CMR slices (basal-middle-apical) were also acquired. Sequence parameters were as follows: field-of-view=380 mm, repetition time/echo time=3.2 ms/1.6 ms, α=60°, matrix=224×192, and number of phases=30 (except for high temporal resolution 3-chamber cine CMR). Tagged CMR was acquired with a segmented gradient-echo pulse sequence, and a nonselective radiofrequency pulse separated by spatial modulation of magnetization-encoding gradients was used to achieve a tag separation of 7 mm. Three base-to-apex short-axis slices were planned by using the same geometry as the 3 short-axis cine CMR (basal-middle-apical), and 2 sets of identical tag lines were acquired for each short-axis slice (the second set was rotated by 90°). The number of cardiac phases was set to obtain a temporal resolution of 12 ms and was identical for both tag line sets. Other sequence parameters were as follows: field-of-view=380 mm, slice thickness=8 mm, repetition time/echo time=6.5 ms/2.3 ms, α=15°, and matrix=256×160. After administration of 0.2 mmol/kg gadodiamide, a segmented inversion-recovery gradient-echo pulse sequence was used to identify and quantify myocardial late gadolinium enhancement. In the short-axis orientation, the left ventricle was completely encompassed by contiguous 8-mm-thick slices. Images were also acquired in 2-chamber and 4-chamber long-axis views. Late gadolinium enhancement imaging was started 10 minutes after contrast administration, and inversion time was individually adapted to suppress the signal of normal remote myocardium (typical range, 250 to 300 ms). Sequences parameters were as follows: field of view=380 mm, slice thickness=8 mm, repetition time/echo time=4.6 ms/1.3 ms, α=20°, and matrix=256×192.

Positron Emission Tomography

$^{13}$N ammonia and $^{18}$F FDG PET studies were performed (mean±SD) 4±1 and 10±3 days after CMR examination, respectively. All patients were studied after an overnight fast. β-Blocking agents were discontinued 48 hours before imaging, whereas caffeine and theophylline were withdrawn 24 hours before. Patients were positioned on the bed of the PET-computed tomography scanner (Discovery VCT, GE Healthcare). Heart rate, blood pressure, and 9-lead ECG were continuously monitored. After scout acquisition (120 KVP, 10 mA), a transmission scan (140 KVP, 20 to 30 mA, pitch=1.35) was performed. Thereafter, 7.4 MBq/kg body weight (0.2 mCi/kg) of $^{13}$N ammonia was injected intravenously (20 to 30 seconds). Dynamic acquisition in 2D mode was started simultaneously with the tracer injection (20 frames×6 seconds, 6 frames×30 seconds, and 3 frames×300 seconds), followed by static acquisition in 3D mode (1 frame×300 seconds). After completion of the baseline study and an additional 15 minutes, patients underwent dipyridamole (0.56 mg/kg IV in 4 minutes) stress testing and $^{13}$N ammonia PET imaging as previously described. On a separate day, an $^{18}$F FDG PET study was performed. Patient preparation, monitoring, positioning, and transmission scans were similar to those of the perfusion study. Under fasting condition, $^{18}$F FDG (260 to 300 MBq IV) was injected (20 to 30 seconds), and dynamic acquisition in 2D mode was started simultaneously (18 frames×5 seconds, 3 frames×10 seconds, 4 frames×30 seconds, 3 frames×120 seconds, 2 frames×150 seconds, and 7 frames×300 seconds), followed by static acquisition in 3D mode (1 frame×600 seconds). Venous blood samples were obtained before and 30 and 60 minutes after tracer injection for monitoring plasma glucose concentration.

LV Segmentation for Myocardial Tagging and PET Measurements

For both imaging modalities, the left ventricle was divided into 17 segments according to the American Heart Association classification by using right ventricular-LV insertions and papillary muscles as landmarks. The apex (segment 17) was not included in the analysis, and the 16 segments were grouped into 3 cardiac regions: (1) septum, including segments 2, 3, 8, 9, and 14; (2) adjacent region, including segments 1, 4, 7, 10, 13, and 15; and (3) lateral region, including segments 5, 6, 11, 12, and 16 (Figure 1). Unless stated otherwise, PET and CMR regional data were obtained by averaging the corresponding segmental values.

CMR Analysis

All CMR studies were analyzed off-line on a workstation (Advantage AW 4.4, GE Healthcare) with dedicated cardiac software (MASS version 6, Leiden, The Netherlands) by a single experienced operator. LV volumes, mass, and global function were determined from the stack of short-axis cine images. LV volumes and mass were normalized to body surface area. The ratio of LV end-diastolic volume to LV mass was calculated and used as a measure of global end-diastolic wall stress. End-diastolic images of the 3 short-axis cine CMR slices (basal-middle-apical) were used to determine segmental wall thickness by dividing the myocardium into 6 equal (for basal and middle slices) and 4 (for apical slice) sectors by selecting the inferior right ventricular-LV insertion as a landmark.

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The presence of late gadolinium enhancement was determined on postcontrast images, and its extent was automatically calculated on short-axis images as a hyperenhanced region with signal intensity $>6$ SD above the mean signal intensity of the remote myocardium, as previously reported for nonischemic cardiomyopathy, and expressed as LV percentage.

**Myocardial Tagging Analysis**

Three base-to-apex (basal-middle-apical) short-axis tagged CMR images were analyzed off-line with harmonic-phase imaging. Midwall circumferential strain was obtained for all 16 segments during the whole cardiac cycle. During systole, for each patient, global ($E_{peak}$) and regional ($e_{peak}$) maximum circumferential shortening and systolic stretch index (SSI) were calculated with an automated custom-made method developed in MATLAB 7.0 (see online-only Data Supplement).

**PET Analysis**

PET scans were evaluated by a single, experienced operator for measurement of absolute MBF and myocardial metabolic rate of glucose (MMRG). Resting and hyperemic MBF quantifications were successfully achieved in all patients. Measurement of MBF at rest and after intravenous dipyridamole with $[13N]$ammonia has been described in detail elsewhere.

In brief, the left ventricle was divided into 17 segments (segment 17 was not included in further analysis), and the $[13N]$ammonia data were used to compute absolute regional MBF (mL $\cdot$ min$^{-1} \cdot$ g$^{-1}$) with dedicated software (Munich-Heart/NM Software) in combination with a previously validated method. Mean LV MBF was obtained for each study condition by averaging regional MBF in 16 segments. MBF reserve was calculated as the ratio between hyperemic and resting MBF. $[18F]$FDG uptake quantification was successfully achieved in all but 2 patients (1 in each group) who showed almost no uptake as long as 60 minutes after tracer injection. For determination of MMRG ($\mu$mol $\cdot$ min$^{-1} \cdot$ g$^{-1}$), myocardial and blood-pool time-activity curves were used to perform a Patlak analysis. Data obtained 8 to 10 minutes after $[18F]$FDG administration (starting from the myocardial and blood-pool time-activity curves intersection) were used to calculate the slope of the Patlak plot and to determine segmental MMRG from a lumped constant value of 1.0 and average blood glucose concentrations measured throughout the FDG study. Mean LV MMRG was computed by averaging the values obtained in 16 segments (segment 17 was excluded). To assess the homogeneity of blood flows and MMRG distribution in the left ventricle, a coefficient of variation was calculated for resting and hyperemic MBF, and after intravenous dipyridamole with $[13N]$ammonia has been divided into 17 segments (segment 17 was not included in further analysis), and the $[13N]$ammonia data were used to compute absolute MBF and myocardial metabolic rate of glucose (MMRG). Resting and hyperemic MBF quantifications were successfully achieved in all patients. Measurement of MBF at rest and after intravenous dipyridamole with $[13N]$ammonia has been described in detail elsewhere. In brief, the left ventricle was divided into 17 segments (segment 17 was not included in further analysis), and the $[13N]$ammonia data were used to compute absolute regional MBF (mL $\cdot$ min$^{-1} \cdot$ g$^{-1}$) with dedicated software (Munich-Heart/NM Software) in combination with a previously validated method. Mean LV MBF was obtained for each study condition by averaging regional MBF in 16 segments. MBF reserve was calculated as the ratio between hyperemic and resting MBF. $[18F]$FDG uptake quantification was successfully achieved in all but 2 patients (1 in each group) who showed almost no uptake as long as 60 minutes after tracer injection. For determination of MMRG ($\mu$mol $\cdot$ min$^{-1} \cdot$ g$^{-1}$), myocardial and blood-pool time-activity curves were used to perform a Patlak analysis. 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Table 2. Global LV CMR and PET Measurements

<table>
<thead>
<tr>
<th>Measurements</th>
<th>DCM With LBBB (n=11)</th>
<th>DCM Without LBBB (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CMR data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV EDV index, mL/m²</td>
<td>128.4±44</td>
<td>132±29</td>
</tr>
<tr>
<td>LV ESV index, mL²/m²</td>
<td>84.4±40</td>
<td>85±28</td>
</tr>
<tr>
<td>LV SV index, mL²/m²</td>
<td>42±12</td>
<td>47±11</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>92±24</td>
<td>77±22</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>35±8</td>
<td>37±10</td>
</tr>
<tr>
<td>LGE, n (%)</td>
<td>6(54)</td>
<td>3(43)</td>
</tr>
<tr>
<td>LGE extent, % of LV</td>
<td>6.4</td>
<td>8.7</td>
</tr>
<tr>
<td>LV EDV/LV mass, mL/g</td>
<td>1.39±0.33</td>
<td>1.85±0.68</td>
</tr>
<tr>
<td>LV Epeak, %</td>
<td>−7.3±2.1</td>
<td>−7.7±2.8</td>
</tr>
<tr>
<td>LV SSI median (IQR)</td>
<td>0.23(0.19)</td>
<td>0.04(0.13)*</td>
</tr>
<tr>
<td><strong>PET data</strong></td>
<td></td>
<td></td>
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<tr>
<td>Resting MBF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPP, (beats/min)× mm Hg</td>
<td>7530±1716</td>
<td>7382±1283</td>
</tr>
<tr>
<td>MBF, mL·min⁻¹·g⁻¹</td>
<td>0.50±0.07</td>
<td>0.54±0.12</td>
</tr>
<tr>
<td>CV MBF</td>
<td>0.13±0.05</td>
<td>0.14±0.07</td>
</tr>
<tr>
<td>Hyperemic MBF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPP, (beats/min)× mm Hg</td>
<td>8896±1963</td>
<td>9342±2333</td>
</tr>
<tr>
<td>MBF, mL·min⁻¹·g⁻¹</td>
<td>0.94±0.20</td>
<td>0.87±0.26</td>
</tr>
<tr>
<td>CV MBF</td>
<td>0.15±0.07</td>
<td>0.19±0.08</td>
</tr>
<tr>
<td>MBB reserve</td>
<td>1.83±0.50</td>
<td>1.80±0.63</td>
</tr>
<tr>
<td>CV MBB reserve</td>
<td>0.10±0.04</td>
<td>0.15±0.12</td>
</tr>
<tr>
<td>Myocardial glucose utilization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMRG, μmol·min⁻¹·g⁻¹</td>
<td>0.30±0.12</td>
<td>0.24±0.11</td>
</tr>
<tr>
<td>CV MMRG</td>
<td>0.37±0.15</td>
<td>0.14±0.03*</td>
</tr>
</tbody>
</table>

EDV indicates end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; LGE, late gadolinium enhancement; LGE, late gadolinium enhancement; IQR, interquartile range; RPP, rate-pressure product; CV, coefficient of variation. Plus/minus values are mean±SD.

*P<0.05.

considered statistically significant. Analyses were performed with SPSS version 13 (SPSS, Chicago, Ill).

Results

Global LV Measurements

Patients with and without LBBB did not differ with respect to clinical characteristics (Table 1), common CMR variables, and PET-measured blood flow and MBF reserve (Table 2). Epeak was normally distributed (Kolmogorov-Smirnov test=0.66, P=0.78), whereas LV SSI did not show a normal distribution (Kolmogorov-Smirnov test=1.67, P=0.008). Patients with and without LBBB had similar values of Epeak whereas LBBB patients showed greater LV SSI than did non-LBBB patients, denoting a more pronounced inhomogeneity of systolic deformation (Table 2). Resting and hyperemic MBF and MBF reserve did not differ between patients with and without LBBB. Although LV MMRG was similar in the 2 groups, patients with LBBB had a higher MMRG variation coefficient than did patients without LBBB, demonstrating greater regional inhomogeneity in glucose utilization (Table 2). LV SSI was correlated positively with the

Table 3. Regional CMR and PET Measurements

<table>
<thead>
<tr>
<th>Measurements</th>
<th>DCM With LBBB (n=11)</th>
<th>DCM Without LBBB (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Septum</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wall thickness, mm</td>
<td>8.0±1.6</td>
<td>9.5±1.5</td>
</tr>
<tr>
<td>Epeak, %</td>
<td>−1.14±0.96</td>
<td>−4.86±2.37*</td>
</tr>
<tr>
<td>SSI, median (IQR)</td>
<td>0.485(0.284)</td>
<td>0.089(0.111)*</td>
</tr>
<tr>
<td>Resting MBF, mL·min⁻¹·g⁻¹</td>
<td>0.48±0.10</td>
<td>0.51±0.07</td>
</tr>
<tr>
<td>Hyperemic MBF, mL·min⁻¹·g⁻¹</td>
<td>0.85±0.21</td>
<td>0.81±0.18</td>
</tr>
<tr>
<td>MBF reserve</td>
<td>1.81±0.47</td>
<td>1.70±0.48*</td>
</tr>
<tr>
<td>MMRG, μmol·min⁻¹·g⁻¹</td>
<td>0.19±0.09</td>
<td>0.25±0.08*</td>
</tr>
<tr>
<td><strong>Adjacent region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wall thickness, mm</td>
<td>9.0±1.3</td>
<td>9.0±1.1</td>
</tr>
<tr>
<td>Epeak, %</td>
<td>−7.16±3.70</td>
<td>−8.12±3.05</td>
</tr>
<tr>
<td>SSI, median (IQR)</td>
<td>0.106(0.176)</td>
<td>0.012(0.019)*</td>
</tr>
<tr>
<td>Resting MBF, mL·min⁻¹·g⁻¹</td>
<td>0.48±0.11</td>
<td>0.48±0.08</td>
</tr>
<tr>
<td>Hyperemic MBF, mL·min⁻¹·g⁻¹</td>
<td>0.87±0.24</td>
<td>0.80±0.23</td>
</tr>
<tr>
<td>MBF reserve</td>
<td>1.82±0.47</td>
<td>1.72±0.58</td>
</tr>
<tr>
<td>MMRG, μmol·min⁻¹·g⁻¹</td>
<td>0.26±0.10</td>
<td>0.24±0.09</td>
</tr>
<tr>
<td><strong>Lateral region</strong></td>
<td></td>
<td></td>
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<tr>
<td>Wall thickness, mm</td>
<td>10.8±0.9</td>
<td>9.6±1.6</td>
</tr>
<tr>
<td>Epeak, %</td>
<td>−13.63±2.58</td>
<td>−10.8±3.78*</td>
</tr>
<tr>
<td>SSI, median (IQR)</td>
<td>0.002(0.168)</td>
<td>0.003(0.004)</td>
</tr>
<tr>
<td>Resting MBF, mL·min⁻¹·g⁻¹</td>
<td>0.44±0.10</td>
<td>0.47±0.08</td>
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<tr>
<td>Hyperemic MBF, mL·min⁻¹·g⁻¹</td>
<td>0.78±0.24</td>
<td>0.75±0.22</td>
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<tr>
<td>MBF reserve</td>
<td>1.80±0.46</td>
<td>1.78±0.67</td>
</tr>
<tr>
<td>MMRG, μmol·min⁻¹·g⁻¹</td>
<td>0.34±0.15</td>
<td>0.24±0.09*</td>
</tr>
</tbody>
</table>

See the footnote to Table 2 for explanation of abbreviations. Plus/minus values are mean±SD.

*P<0.05.

MMRG variation coefficient (Spearman’s rho=0.51, P=0.046), whereas no association was observed with variation coefficients for resting MBF (P=0.84), hyperemic MBF (P=0.67), and MBF reserve (P=0.80).

Regional LV Measurements

Regional CMR and PET measurements in the 2 groups are summarized in Table 3. In LBBB patients, the septum and lateral region tended to be thinner and thicker, respectively, compared with the wall thickness of the corresponding regions in non-LBBB patients, resulting in a lower septo-lateral wall thickness ratio in LBBB patients than in non-LBBB patients (0.74±0.14 vs 1.00±0.08, P=0.03). Epeak was normally distributed (Kolmogorov-Smirnov test=0.82, P=0.51), whereas regional SSI did not show a normal distribution (Kolmogorov-Smirnov test=1.49, P=0.024). In LBBB patients compared with non-LBBB patients, Epeak was reduced in the septum and increased in the lateral region, whereas SSI was higher in the septum and adjacent region. Regional myocardial deformation in 2 representative patients with and without LBBB is shown in Figure 2. Resting and hyperemic MBF did not differ between the 2 groups, whereas MBF reserve in the septum was higher in LBBB patients than in non-LBBB patients (P=0.046). In
LBBB patients, MMRG was lower in the septum and higher in the lateral region compared with patients without LBBB (Table 3).

The semiquantitative analysis of the regional flow–metabolism relation showed that, compared with non-LBBB patients, those with LBBB had more LV "mismatch" segments (n=16 vs n=52, P=0.005) and "reverse mismatch” patterns (n=0 vs n=48, P<0.0001). In LBBB patients 5 (10%), 5 (10%), and 42 (80%) of 52 segments with flow metabolism “mismatch” and 29 (60%), 14 (29%) and 5 (10%) of 48 segments with flow metabolism “reverse mismatch” were located in the septum, adjacent, and lateral regions, respectively (both P<0.0001). In non-LBBB patients, 1 (6%), 8 (50%), and 7 (44%) of 16 segments with a flow metabolism

Figure 2. Midwall circumferential strain and strain rate curves corresponding to septal (A), adjacent (B), and lateral (C) regions in a representative patient with LBBB (Figure 2A) and without LBBB (Figure 2B). In the first case, the septum undergoes prominent, early passive stretching and nearly absent late shortening, resulting in a high SSI (0.875) and null \( \varepsilon_{\text{peak}} \) value. The adjacent region shows a certain degree of early passive stretching preceding late shortening, whereas the lateral region displays no early passive stretching, resulting in effective (SSI=0) and vigorous \( \varepsilon_{\text{peak}} = -14.6\% \) systolic shortening. In a patient without LBBB, septal, adjacent, and lateral regions shorten effectively during systole, as denoted by no early systolic stretching and negative \( \varepsilon_{\text{peak}} \) values.
Regional Gradients of Systolic Deformation, Myocardial Perfusion, and Glucose Metabolism in Patients With and Without LBBB

In LBBB patients, regional SSI gradually decreased and $\varepsilon_{\text{peak}}$ became progressively more negative from the septum to adjacent and lateral regions. These trends were closely matched to the MMRG distribution, showing lowest, intermediate, and highest values in the septum, adjacent, and lateral regions, respectively ($P=0.06$). Regional distribution of $[^{13}\text{N}]$ammonia, $[^{18}\text{F}]$FDG uptake, and flow metabolism relation in 2 representative patients with and without LBBB are shown in Figure 3.

“mismatch” pattern were located in the septum, adjacent, and lateral regions, respectively ($P=0.06$). Regional distribution of $[^{13}\text{N}]$ammonia, $[^{18}\text{F}]$FDG uptake, and flow metabolism relation in 2 representative patients with and without LBBB are shown in Figure 3.

**Discussion**

In this study, we have demonstrated that LBBB induces relevant abnormalities in systolic deformation of the LV regions, leading to extensive redistribution of myocardial glucose metabolism and asymmetric LV hypertrophy. Conversely, blood flows and MBF reserve were not influenced by contraction abnormalities and thereby, were uniformly distributed across LV regions in patients with and without LBBB.

**Influence of Regional Systolic Deformation Pattern on Myocardial Metabolism and Structural Remodeling**

DCM patients with LBBB showed a high septal SSI, indicating that nearly 50% of the entire systolic deformation consisted of early passive stretching. This pattern was associated with low septal $\varepsilon_{\text{peak}}$, denoting a very modest contribution of the septum to global LV contraction. The systolic deformation pattern changed progressively from the septum to adjacent and lateral regions, showing a gradual decrease in SSI (ie, systolic stretching) along with more negative $\varepsilon_{\text{peak}}$ values (ie, increase in circumferential shortening). Interestingly, the regional workload redistribution was associated with important changes in glucose utilization, which was lowest in the septum and highest in the lateral region. Notably, an inhomogeneous distribution of $\varepsilon_{\text{peak}}$ was also observed in the ventricles without LBBB. This change was qualitatively similar but quantitatively less compared with ventricles of LBBB patients and was not associated with regional changes in MMRG distribution. This finding suggests the presence of a threshold in systolic deformation abnormality above which metabolic derangements occur. In an animal model of LV dysfunction with high-frequency LV free-wall pacing, we observed a diffuse increase in LV glucose utilization compared with baseline but without consistent regional differences. This was likely due to the inability of LV free-wall pacing to cause a sufficient degree of ventricular discoordination, as suggested by a similar magnitude of wall stress in the pacing and opposite site.

We also found that fasting global LV glucose utilization was increased in DCM patients to an extent similar to that observed in DCM patients in previous studies. This metabolic shift is likely the expression of impaired myocardial efficiency and may be detrimental in the long run through 2 main mechanisms: (1) increased oxidative stress, linked to high reliance on glucose as a substrate, and (2) reduced myocardial metabolic reserve.

Regionally, we found that LBBB patients showed lower MMRG in the septum and adjacent region compared with the lateral region, but these values were consistently greater than global LV glucose utilization measured in normal subjects under fasting conditions or after a glucose load. On the other hand, the glucose metabolism of the lateral region was prominently enhanced, being even higher than that measured in LV myocardium of normal subjects during exercise, and comparable to MMRG assessed by PET in dysfunctional ventricles after a glucose load. These findings support the
concept that the relative reduction of septal \([^{18}\text{F}]\text{FDG}\) uptake in LBBB ventricles, reported mainly in nonquantitative PET studies,\textsuperscript{10,11} was actually due to a huge increase in absolute glucose utilization of the lateral region rather than a real reduction of septal glucose metabolism.

Interestingly, along with metabolic remodeling, we also observed that the unbalanced distribution of mechanical workload was associated with structural LV remodeling, as denoted by a lower septal-to-lateral wall-thickness ratio in DCM patients with LBBB compared with patients without LBBB. In concordance with previous experimental\textsuperscript{4} and clinical\textsuperscript{9} data, this finding suggests that in LBBB patients, the redistribution of local workload induced an asymmetric LV hypertrophy.\textsuperscript{29}

**Influence of Regional Systolic Deformation Pattern on Regional Flow and Flow Metabolism Relation**

Resting and hyperemic MBF and MBF reserve were globally reduced, as has already been found in DCM populations,\textsuperscript{5} but were not influenced by the regional pattern of systolic deformation. These findings are concordant with those reported by Nowak et al.,\textsuperscript{13} describing a uniform distribution of resting MBF studied by PET in DCM patients with LBBB, but diverge from those of Knaapen et al.,\textsuperscript{12} who presented decreased resting \([^{15}\text{O}]\text{water}\) uptake in the septum compared with the lateral wall in dysfunctional left ventricles of patients with LBBB and homogenization after resynchronization therapy. This discrepancy can be explained by (1) differences in the study populations, because in the latter study, 7 of 16

![Figure 4. Median, quartiles, extreme values, and outliers (×) of \(ε_{\text{peak}}\), SSI, and MMRG across LV regions in DCM patients with (left) and without (right) LBBB. \(◊P=0.001, †P<0.0001, ‡P=0.020; §P=0.003; #P=0.040, \Delta P=\text{NS.}\)
patients had ischemic LV dysfunction; and (2) differences in the kinetic properties of flow tracers. In fact, [15O]water and [13N]ammonia are not equivalent, because the former is directly dependent on MBF, whereas [13N]ammonia uptake depends on both blood flow and active transport across the cardiomyocyte membrane. In our study, it is conceivable that the metabolic component of [13N]ammonia extraction could have partially masked the differences in regional blood flows in DCM patients with LBBB.

We also analyzed PET data by the classic semiquantitative approach commonly used to assess the presence of a regional flow metabolism “mismatch” pattern in ischemic heart disease. In the present study, LBBB patients showed a predominance of “mismatch” in the lateral region and “reverse mismatch” in the septum, compared with patients without LBBB. These findings are in line with previous semiquantitative PET studies that describe “mismatch” and “reverse mismatch” patterns in DCM patients. In earlier studies, however, these patterns were interpreted as hallmarks of myocardial ischemia and reduced septal glucose metabolism, respectively. Our results, obtained by quantitative analysis of PET and CMR data, suggest a somewhat different explanation. In LBBB patients, the septal “reverse mismatch” pattern was associated with a relative but not absolute reduction in glucose metabolism. On the other hand, the lateral region “mismatch” pattern was associated with a marked increase in glucose utilization rather than a reduced resting MBF.

**Study Limitations**

The study was mainly exploratory, enrolling a small number of patients without a preliminary sample size calculation. Patients underwent CMR and [13N]ammonia and [18F]FDG PET imaging in 3 different sessions but with a short time delay (clinical status, hemodynamic conditions, and medications remained unchanged). In the absence of dedicated software for coregistration of CMR and PET images, LV segmentation was achieved according to standards and the same protocol for each imaging modality. We assessed myocardial glucose metabolism by [18F]FDG PET imaging without glucose loading to better emphasize regional differences in glucose utilization under more physiologic conditions. We did not measure plasma free fatty acid concentrations, which could have influenced myocardial glucose utilization. However, the 2 groups showed comparable global LV glucose metabolism, and they differed only in regional MMRG, which should not be affected by circulating free fatty acid levels. We intentionally enrolled patients without advanced disease to better study the consequences of LBBB on myocardial perfusion, structure, and metabolism. Accordingly, we could not evaluate the potential benefit of resynchronization therapy on those abnormalities. Finally, study findings should be extrapolated with caution to patients with different clinical characteristics.

**Conclusions**

In DCM patients with LBBB, the marked regional changes in systolic deformation induce asymmetric LV hypertrophy and redistribution of glucose metabolism without consistent variation in myocardial perfusion. In particular, the highly coordinated and vigorously contracting lateral region tends to become thicker, and its metabolism shifts to near-maximal glucose utilization, becoming strongly dependent on this substrate. The uncoordinated and poorly contracting septum tends to become thinner but preserves its metabolic reserve. These regional changes may further promote adverse LV remodeling, leading to such extensive alterations that ultimately cannot be attenuated or eventually reversed by resynchronization therapy. Accordingly, larger studies are warranted to identify CMR/PET patterns that may predict the response to resynchronization therapy in DCM patients with LBBB.

**Acknowledgments**

We thank Daniele De Marchi, Petra Keilberg, Chiara Cinzia Marzuolo, Oreste Sorace, Silvia Pardini, and Danilo Bonora for invaluable technical help in performing CMR and PET studies.

**Disclosures**

None.

**References**


**CLINICAL PERSPECTIVE**

In patients with dilated cardiomyopathy, the occurrence of left bundle branch block leads to inhomogeneous left ventricular (LV) activation and deformation. The potentially deleterious consequences on myocardial perfusion, structure, and metabolism have not been well defined; understanding these abnormalities would shed light on the processes by which left bundle branch block leads to progressive LV dilatation and dysfunction. By means of high temporal resolution tagged cardiac magnetic resonance and positron emission tomography imaging, we demonstrated that the asynchronous LV deformation caused by left bundle branch block is associated with asymmetric LV hypertrophy and extensive redistribution of glucose utilization without consistent changes in myocardial blood flow. In particular, the highly coordinate and vigorously contracting lateral region shows hypertrophy and shifts its metabolism to high glucose utilization, nearly exhausting its metabolic reserve. Conversely, the uncoordinated and poorly contracting septum tends to become thinner but with preserved metabolic reserve. The novel pathophysiologic implications of these results pose the basis for future studies of this multi-imaging approach in select dilated cardiomyopathy patients for optimal cardiac resynchronization therapy.
Myocardial Structural, Perfusion, and Metabolic Correlates of Left Bundle Branch Block Mechanical Derangement in Patients With Dilated Cardiomyopathy: A Tagged Cardiac Magnetic Resonance and Positron Emission Tomography Study

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Circ Cardiovasc Imaging. 2010;3:482-490; originally published online May 12, 2010; doi: 10.1161/CIRCIMAGING.109.934638

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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SUPPLEMENTAL MATERIAL
Supplemental Methods

The aim of this supplemental document is to describe the automatic algorithm used to calculate the parameters of global and regional LV deformation.

1. Algorithm Inputs

The algorithm used two principal inputs. The first input was given by all 16 segmental circumferential strain signals ($\varepsilon_{cc}(t)$) obtained at midwall by HARP$^{1,2}$ method, and processed by a moving average filter of 3 sample widths to reduce the noise sensitivity. Moreover, the segmental strain rate signals ($e(t)$) were calculated by a temporal differentiation of the circumferential strain curves. The $e(t)$ signals were split into positive ($e_p(t)$) and negative ($e_n(t)$) signals according to the following expressions$^3$:

$$e_p(t) = \max(0,e(t)) \quad e_n(t) = \min(0,e(t))$$

The second input contained the information regarding the time of aortic valve opening ($T_{avo}$), the time of aortic valve closure ($T_{avc}$) and the time of mitral valve opening ($T_{mvo}$), determined by means of high-temporal resolution 3-chamber cine CMR. The *systolic time window* was defined as the time between the aortic valve opening and closure.

2. Definition of global and regional LV deformation parameters

The global strain ($E_{cc}(t)$) and strain rate signals ($e_g(t)$) were computed by averaging the filtered $\varepsilon_{cc}(t)$ and $e(t)$ over all 16 segments, respectively. In the *systolic time window*, maximum shortening value ($E_{peak}$) and the corresponding time ($T_{peak}$) of $E_{cc}(t)$ curve were calculated (Figure 1A).
The regional (septum – adjacent – lateral) circumferential strain and strain rate signals were computed by averaging respectively the filtered $\varepsilon_{cc}(t)$ and $e(t)$ over those LV segments assigned to a determined region, according to the previously described protocol (see the manuscript). The corresponding regional maximum shortening values ($\varepsilon_{\text{peak}}$) were also calculated in the systolic time window (Figure 1B).

3. Definition of the ejection phase

The onset time ($T_{\text{onset}}$) of deformation in the global $E_{cc}(t)$ curve was calculated using the following steps (Figure 2):

1) the definition of the time points $t_k$ corresponding to the global $e(t_k) = 0$;
2) the estimation of the first $t_k$ time point that satisfies $|E_{cc}(t_k)| \geq 5\%$ of $|E_{\text{peak}}|$;
3) the calculation between $S_1 (= t_{k-1})$ and $S_2 (= t_k)$ of the strain rate ($e_{12}(t)$) and the maximum strain rate ($e_{\text{max}}$) signals corresponding to the $E_{cc}(t)$ curve;
4) the estimation of the onset time ($T_{\text{onset}}$) as the first time point where $e_{12}(t) \geq 10\%$ of $e_{\text{max}}$.

The ejection phase was assumed to start from the $T_{\text{onset}}$ value and to end at the $T_{\text{peak}}$ value, and the regional and global systolic stretch index (SSI) was calculated within this time interval (see next section).

4. Definition of regional and global systolic stretch index

Global and regional systolic stretch indexes (SSI) were determined by using the following expression:
where $\bar{e}_p(t)$ and $\bar{e}_n(t)$ represent the average positive and negative strain rate curves. The time $t_1$ was the starting point ($T_{onset}$) and $t_2$ the ending point ($T_{peak}$) of the ejection phase (Figure 3).

Considering that the area below the positive and negative strain rate curves measured respectively the amount of stretching and shortening (Equation 2), the calculated global and regional SSI ranged from 0 (normally shortening) to 1 (completely stretching).
Figure 1.
Figure 2.
Figure 3.
Supplemental Figure Legends

**Figure 1.** A) Global circumferential strain curve obtained by averaging the $\varepsilon_{cc}(t)$ over 16 segments. $E_{peak}$ and $T_{peak}$ represent the maximum value of circumferential shortening and the corresponding time point in the systolic time window, respectively. B) Example of regional circumferential strain curve obtained by averaging the $\varepsilon_{cc}(t)$ over the segments assigned to a certain LV region (in the example, the adjacent region in a patient with LBBB). In the systolic time window, the regional maximum value of shortening ($\varepsilon_{peak}$) is also calculated.

**Figure 2.** Method used to calculate the onset time ($T_{onset}$) of deformation in the global $E_{cc}(t)$ curve.

**Figure 3.** A) Positive and negative global strain rate curves obtained by averaging the strain rate signals over 16 segments. B) Positive and negative regional strain rate curves obtained by averaging the positive and negative strain rate signals of the segments assigned to a certain LV region (in the example, the adjacent region in a patient with LBBB).
Supplemental References

