Effects of Left Bundle-Branch Block on Cardiac Structure, Function, Perfusion, and Perfusion Reserve

Implications for Myocardial Contrast Echocardiography Versus Radionuclide Perfusion Imaging for the Detection of Coronary Artery Disease

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Background—We aimed to investigate the cardiac effects of left bundle-branch block (LBBB) using myocardial contrast echocardiography (MCE) to ascertain the value of MCE for detecting coronary artery disease (CAD) and to uncover the mechanism that affects the accuracy of single-photon emission computed tomography (SPECT) in these patients.

Methods and Results—Sixty-three symptomatic LBBB patients (group A), 10 left ventricular ejection fraction–matched control subjects without LBBB and no CAD (group B), and 10 normal control subjects (group C) underwent resting echocardiography. Rest and vasodilator MCE and SPECT were undertaken in LBBB patients. Septal (SW) and posterior wall (PW) thickness, thickening, quantitative myocardial blood flow (MBF), and MBF reserve were measured. SW/PW thickness and percentage thickening ratios were lower (P<0.01 and P<0.05, respectively) in group A compared with both groups B and C, but resting SW/PW MBF and MBF reserve ratios were similar in all 3 groups. MBF reserve but not MBF was reduced in groups A and B (2.2±0.7 versus 2.2±0.2; P=0.98) compared with group C (3.1±0.5; P<0.01). SW thickness was an independent predictor (P=0.006) of SPECT perfusion defects in LBBB patients without CAD. MCE (92%) had a sensitivity similar to SPECT (92%); however, the specificity of MCE (95%) was superior (P<0.0001) to SPECT (47%) for the detection of CAD.

Conclusions—Despite asymmetrical reduction in SW thickness and function, MBF is preserved and MBF reserve is homogeneously reduced in LBBB patients with left ventricular systolic dysfunction. Because of partial volume effects, the accuracy of SPECT for detecting CAD was significantly compromised compared with MCE in this patient cohort. (Circulation. 2008;117:1832-1841.)

Key Words: bundle-branch block ■ coronary disease ■ echocardiography ■ nuclear medicine ■ perfusion

Complete left bundle-branch block (LBBB) is a common ECG disorder that often is associated with coronary artery disease (CAD).1 LBBB in the presence of CAD is associated with a 3- to 4-fold increase in cumulative cardiovascular mortality.2 The accuracy of commonly used noninvasive techniques such as single-photon emission computed tomography (SPECT) for the detection of CAD in these patients is confounded by the heterogeneous effects of LBBB on myocardial structure, function, and perfusion, resulting in a high incidence of anteroseptal and septal perfusion defects in the absence of CAD.3-6 Alternative approaches, including the use of coronary vasodilators as stress agents in place of exercise or dobutamine and the application of different image interpretation algorithms, have reduced but not eliminated the incidence of false-positive results.6,7 Several hypotheses have been postulated to explain the cause of such perfusion defects seen on SPECT, including early activation of the septum, leading to shortened diastole and hence reduced blood flow8; partial volume effects caused by septal thinning and impairment of thickening noted in experimental models of LBBB with right ventricle pacing9; and increased septal intramyocardial pressure during diastole, resulting in reduced flow reserve.10

Clinical Perspective p 1841

Quantitative myocardial contrast echocardiography (MCE), which uses contrast agents that are entirely intravascular, has been shown in experimental models and humans to be accurate in assessing myocardial perfusion both at rest and during stress.11-13 The aims of the study were to investigate
the effects of LBBB on myocardial structure, function, and perfusion with MCE; to ascertain the value of MCE for the detection of CAD in LBBB patients; and to test the hypothesis that the partial volume effects caused by septal thinning and impaired thickening rather than true hypoperfusion are responsible for SPECT perfusion defects in patients without CAD.

Methods

Patient Population
Symptomatic patients with LBBB referred for coronary arteriography by their treating physician were included in the study. Patients with known CAD, angina, history of prior myocardial infarction, history of revascularization, significant valvular disease, or hemodynamic instability were excluded. Furthermore, 10 age- and left ventricular (LV) ejection fraction (LVEF)–matched control subjects without LBBB and with no coronary arteriographic evidence of CAD (>50% luminal diameter stenosis of any major epicardial artery or major branch) also were recruited. This was to account for the confounding effects of LVEF on cardiac structure, function, and perfusion. Ten age- and sex-matched patients admitted with chest pain with nondiagnostic ECG changes, no cardiac enzyme rise, and normal regional and global LV function both at rest and during stress echocardiography acted as normal control subjects.

The study complied with the Declaration of Helsinki. All patients gave written informed consent to the study protocol, which was approved by the Institutional Review Board of Northwick Park Hospital.

Study Design
LBBB was established by a standard 12-lead ECG before study recruitment and was confirmed by repeat 12-lead ECG on the study day. All patients underwent transthoracic 2-dimensional echocardiography, MCE, SPECT, and coronary arteriography. Stress MCE and SPECT were performed on the same day.

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

Two-Dimensional Echocardiography
Two-dimensional echocardiography was performed in standard apical and parasternal views with tissue harmonic imaging (SONOS 7500, Philips Medical Systems, Best, the Netherlands). LVEF, LV end-diastolic volume, and LV end-systolic volume were measured with Simpson’s apical biplane rule.14 End diastole was identified by the onset of the QRS complex; end systole was defined as the smallest LV diameter. Tracing of the LV contour excluded the papillary muscles and trabeculations within the LV cavity as recommended by the American Society of Echocardiography.14 Regional wall thickness (WT) for the septal wall (SW) and posterior wall (PW) was measured at 3 points in the cardiac cycle (end diastole, mid systole [midpoint between the onset of QRS and end systole], and end systole) from the parasternal long-axis 2-dimensional view; maximum WT was assessed; and a mean value was obtained. A narrow sector was used to maximize frame rate (65 to 75 Hz). Percentage of SW and PW thickening were calculated using the following formula: [(maximal WT–end-diastolic WT)×100]/end-diastolic WT. Ratios of SWT to PW and percentage thickening also were calculated.

MCE Studies
MCE was performed with Sonovue (Bracco Research SA, Geneva, Switzerland) at rest in the 3 apical views (apical 4-chamber, 2-chamber, and 3-chamber views) using low-power MCE (power modulation technique) at a mechanical index of 0.1. Background gains were set so that minimal tissue signal was seen. The color gains were then adjusted so that no Doppler signal was seen except at the mitral valve and proximal to the apex. Sonovue was infused at 50 to 70 mL/h with Vueject (BR-INF 100, Bracco Research SA), an infusion syringe pump that rotates gently throughout infusion to maintain microbubble suspension. The infusion rate was adjusted to obtain the best possible myocardial opacification with minimal attenuation. Once optimized, the machine settings were kept constant throughout the study. The focus was set at the mitral valve level but moved toward the apex if there was concern about a near-field artifact. Nonstandard apical views (eg, bringing the lateral wall into the sector field) were used, if required, to attempt to overcome basal attenuation artifacts. Flash echocardiography at a high mechanical index (1.0) was performed to achieve myocardial microbubble destruction, after which 15 consecutive end-diastolic frames were digitally captured in each view (3 sequences in each) at a low mechanical index (0.1). Imaging was repeated at peak hyperemia after administration of 0.56 mg/kg dipyridamole.

Normal myocardial perfusion at rest was considered to be present when all segments (16-segment model) showed homogeneous contrast opacification within 5 seconds after destructive imaging. A reversible perfusion defect was considered present when a contrast defect was observed 1 second after destructive imaging after vasodilator stress with the presence of a transmural defect filling from the subendocardium to subepicardium during subsequent cardiac cycles.13 CAD was considered to be present when 2 contiguous segments demonstrated perfusion defects (rest or stress). Multivessel disease was considered present when perfusion defects were noted in ≥1 vascular territory. The analysis was performed by an investigator (R.S.) who was blinded to clinical, coronary arteriographic, and SPECT data.

Quantitative MCE
Quantitative MCE was performed offline by a single observer (S.H.) unaware of the 2-dimensional echocardiographic or angiographic data. Standard commercial software (Q-Laboratory, Philips Medical Systems) was used to quantify myocardial replenishment for 15 frames after bubble destruction by placing the region of interest across the entire thickness of the myocardium, excluding the high-intensity endocardial and epicardial borders.2 The basal segments of the 16-segment LV model were not included in the quantitative analysis. QLab software automatically constructed background-subtracted plots of peak myocardial contrast intensity, representing myocardial blood volume (A), versus pulsing intervals, from which the slope of the replenishment curve depicting mean microbubble velocity (β) was derived. Frames showing wide variation in contrast intensity were discarded to minimize errors in the analysis. Myocardial blood volume was subsequently normalized for blood pool videointensity by placing the ventricular cavity region of interest adjacent to the myocardial region of interest using a previously validated equation: normalized A = 10^[(A/blood pool)/100]×100,13 SW and PW myocardial blood flow (MBF) and MBF reserve (MBFR) were calculated from these formulas: MBF=Å×β and MBFR=stress MBF/rest MBF. Ratios of SW to PW MBF and MBFR also were calculated.

Gated Technetium-99m Sestamibi SPECT
A separate-day stress-rest protocol was used. A rest study was performed on a separate day 60 to 90 minutes after injection of 600 MBq technetium-99m sestamibi. For stress imaging, 600 MBq technetium-99m sestamibi was injected at peak hyperemia after administration of dipyridamole (during stress MCE). Images were acquired 60 to 90 minutes after injection with a multihit camera with high-resolution collimators. The camera energy window (20%) was set on the 140-keV photopeak of technetium-99m sestamibi. Particular care was taken to avoid patient motion and overlap from extracardiac activity. A total of 32 projections (each lasting 40 seconds) were acquired over a 180° arc from the 45° right anterior oblique to the 45° left posterior positions. Both rest and stress...
tomographs were reconstructed in the vertical and horizontal long-
and short-axis planes and were simultaneously analyzed with a
standard 16-segment LV model. SPECT perfusion was graded with
a well-validated scoring system: 0 = normal tracer uptake, 1 = mildly
reduced tracer uptake, 2 = moderately reduced tracer uptake, 3 =
severely reduced tracer uptake, and 4 = absent tracer uptake.16

A rest defect was defined as a score of $\geq 2$ in at least 1 segment
(matching 16-segment LV model). A fixed defect was any resting
defect that remained unchanged during stress with an accompanying
wall thickening abnormality on gated SPECT. A reversible defect
was defined as a reduction in tracer uptake by at least 1 grade except
when the resting score was 0 when the change in score should be $> 2$.
CAD was considered present when a resting defect and/or a
reversible defect were detected in $\geq 2$ contiguous segments. SPECT
myocardial quantification was performed with MyoQuan software.17 The software calculates and quantifies perfusion and perfu-
sion deficits in myocardial SPECT data through the analysis of polar
maps generated from the radial slices. Normalized perfusion values
were displayed in the 16-segment grid model. The qualitative and
quantitative assessments of SPECT data were performed by 2
independent observers (A.J. and C.K.) who were blinded to clinical,
MCE, and coronary arteriographic data.

Coronary Arteriography

Selective coronary arteriography was performed, and patients with
CAD were defined as those demonstrating $\geq 50\%$ luminal diameter
stenosis of any major epicardial artery or major branch. Multivessel
disease was defined as CAD in the left anterior descending artery and
right coronary artery or left circumflex artery.

Statistical Analysis

Results from normally distributed continuous data are expressed as
mean $\pm$ SD. Categorical variables are presented as percentages. The
paired t test was used to compare the differences within groups, and
the independent t test was used to compare continuous variables
between groups. One-way ANOVA was used with post hoc Tukey
adjustment in the multiple comparisons between different groups of
continuous variables to minimize the type I error. We used $\chi^2$
tests to compare categorical variables between groups. A receiver-
operating characteristics curve was plotted to determine the best
MBF reserve cutoff value for predicting significant CAD. One-way
ANOVA was used to compare the MCE variables among various
grades of stenosis. The presence of abnormality in either of the
coronary territories was considered to be positive for the detection of
CAD on a per-patient basis.

The effect of various parameters for the prediction of SPECT
perfusion defect was obtained by logistic regression analysis. Sub-
sequently, the joint effects of the explanatory factors on the SPECT
perfusion defect were examined together in a multivariate analysis.
Only factors with values of $P < 0.1$ in the univariable analysis were
included in the multivariable analysis. A backwards selection pro-
cedure was used to determine the final model. McNemar’s test was
used to compare the sensitivity and specificity of MCE and SPECT.
A value of $P < 0.05$ (2 sided) was considered significant. Statistical
analysis was performed with Analyze-it software for Microsoft Excel
(version 1.62, Analyze-it Software Ltd, Leeds, UK) and SPSS
version 14.0 (SPSS Inc, Chicago, Ill).

The authors had full access to and take full responsibility for the
integrity of the data. All authors have read and agree to the
manuscript as written.

Results

Patient Demographics

The demographics of the LBBB patient population are summarized in Table 1. Table 2 showed no significant differences in age and Framingham risk score between the 3
groups.

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CAD</td>
</tr>
<tr>
<td>Patient demographics, n (%)</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Men, n (%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
</tr>
<tr>
<td>Family history of CAD, n (%)</td>
</tr>
<tr>
<td>Framingham risk score, %</td>
</tr>
<tr>
<td>Presenting symptoms, n (%)</td>
</tr>
<tr>
<td>Chest pain</td>
</tr>
<tr>
<td>Shortness of breath</td>
</tr>
<tr>
<td>Coronary arteriography, n (%)</td>
</tr>
<tr>
<td>1-Vessel disease</td>
</tr>
<tr>
<td>2-Vessel disease</td>
</tr>
<tr>
<td>3-Vessel disease</td>
</tr>
<tr>
<td>LAD disease</td>
</tr>
<tr>
<td>RCA/LCx disease</td>
</tr>
<tr>
<td>Multivessel disease (LAD + RCA/LCx)</td>
</tr>
<tr>
<td>LVEF, %</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending coronary artery; RCA, right coronary
artery; and LCx, left circumflex artery. n = 63.

Correlates of Myocardial Structure in LBBB

The ratio of SWT to PWT was significantly lower in group A
(LBBB and no CAD) compared with groups B (LVEF-
matched control subjects without LBBB and no CAD) and C
(normal control subjects), whereas no differences were noted
between groups B and C (Table 3). This was because SWT in
group A was significantly lower than in both groups B and C.

Correlates of Myocardial Function in LBBB

The ratio of percentage of SW to PW thickening was significantly lower in patients with LBBB (group A) com-
pared with groups B and C, whereas no differences were
noted between groups B and C (Table 3). The primary reason
for the reduced ratio of SW to PW thickening in group A was
that SW thickening was lower compared with group B despite
similar reductions in LVEF and comparable LV volumes.
Both groups A and B showed significant reductions in
percentage SW and PW thickening compared with normal control subjects (Group C).

Correlates of Myocardial Perfusion in LBBB

Although LBBB patients demonstrated smaller SWT and
percentage wall thickening compared with groups B and C,
there were no significant differences in indexes of MBF
(Table 3). Resting A, B, and MBF were similar across all 3
groups, as were the ratios of SW to PW MBF (1.01 $\pm$ 0.14,
0.99 $\pm$ 0.15, and 1.02 $\pm$ 0.15, respectively). Similarly, no sig-
nificant differences were noted in patients with LBBB with...
Table 2. Comparison Between Patients With LBBB Without CAD, No LBBB Without CAD (LVEF Matched), and Normal Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Group A; No CAD, LBBB</th>
<th>Group B; No CAD, No LBBB</th>
<th>Group C; Normal Control Subjects</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>38</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Mean age, y</td>
<td>67±9</td>
<td>64±9</td>
<td>64±6</td>
<td>NS</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>19 (50)</td>
<td>3 (30)</td>
<td>6 (60)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>18 (47)</td>
<td>6 (60)</td>
<td>5 (50)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>10 (26)</td>
<td>3 (30)</td>
<td>3 (30)</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>12 (32)</td>
<td>4 (40)</td>
<td>2 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td>6 (16)</td>
<td>2 (20)</td>
<td>2 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>Family history of CAD, n (%)</td>
<td>5 (14)</td>
<td>4 (40)</td>
<td>3 (30)</td>
<td>NS</td>
</tr>
<tr>
<td>Framingham risk score, %</td>
<td>15±7</td>
<td>14±9</td>
<td>16±5</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>37±14*</td>
<td>35±8*</td>
<td>62±5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVESV, m/s</td>
<td>96±69†</td>
<td>90±30‡</td>
<td>39±11</td>
<td>0.03</td>
</tr>
<tr>
<td>LVEDV, m/s</td>
<td>141±65§</td>
<td>131±39‡</td>
<td>103±24</td>
<td>NS</td>
</tr>
</tbody>
</table>

LVESV indicates LV end-systolic volume; LVEDV, LV end-diastolic volume; and NS, not significant between the 3 groups. The χ² test was used for categorical variables; 1-way ANOVA was used for continuous variables.

*P<0.001, †P<0.02, ‡P=NS vs group C.

Comparison of LBBB Patients With and Without CAD

No significant differences were noted in LBBB patients with and without CAD for SWT (P=0.60), PWT (P=0.51), and ratio of SWT to PWT (P=0.37). Similarly, there were no significant differences for percentage of SW thickening (P=0.56), percentage of PW thickening (P=0.17), and ratio of SW to PW thickening (P=0.49). However, in the LBBB group with CAD, MBFR (0.78±0.46) was significantly lower than in the group without CAD (0.53±0.49); and with both CAD and LBBB (0.49±0.99), but β tended to be lower in the CAD group (P=0.07). Resting MBFR was not reduced in patients with LBBB (group A) compared with LVEF-matched control subjects without LBBB (group B) and normal control subjects (group C). Similarly, the ratios of SW to PW MBFR were similar in all 3 groups. However, MBFR was reduced equally in groups A and B (2.2±0.7 versus 2.2±0.2; P=0.98) compared with normal control subjects (3.1±0.5; P<0.0005; Figure 1).

Table 3. Comparison of Myocardial Structure, Function, and Perfusion in LBBB Patients (No CAD) With No LBBB, LVEF-Matched Control Subjects, and Normal Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Group A; LBBB, No CAD (n=38)</th>
<th>Group B; No LBBB, Age and LVEF Matched (n=10)</th>
<th>Group C; Normal Control Subjects, Age Matched (n=10)</th>
<th>P (1-Way ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameters of myocardial structure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SW thickness, cm</td>
<td>1.22±0.17††</td>
<td>1.35±0.10</td>
<td>1.38±0.11</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean PW thickness, cm</td>
<td>1.32±0.15</td>
<td>1.33±0.08</td>
<td>1.38±0.07</td>
<td>NS</td>
</tr>
<tr>
<td>Mean SWT/PWT ratio</td>
<td>0.93±0.07§§</td>
<td>1.02±0.07</td>
<td>1.00±0.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Parameters of myocardial function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SW thickening, %</td>
<td>23.8±5.4¶‡**</td>
<td>28.0±4.5††</td>
<td>35.8±4.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PW thickening, %</td>
<td>27.4±5.0</td>
<td>27.5±4.7</td>
<td>34.9±5.4†‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SW/PW thickening ratio</td>
<td>0.88±0.17§§§</td>
<td>1.03±0.14</td>
<td>1.03±0.07</td>
<td>0.004</td>
</tr>
<tr>
<td>Parameters of myocardial perfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SW resting A</td>
<td>7.9±2.8</td>
<td>7.8±2.1</td>
<td>7.9±3.3</td>
<td>NS</td>
</tr>
<tr>
<td>SW resting β</td>
<td>0.73±0.13</td>
<td>0.70±0.14</td>
<td>0.69±0.10</td>
<td>NS</td>
</tr>
<tr>
<td>SW resting MBF</td>
<td>5.5±2.0</td>
<td>5.4±1.6</td>
<td>5.5±2.6</td>
<td>NS</td>
</tr>
<tr>
<td>SW MBFR</td>
<td>2.2±0.7¶¶</td>
<td>2.2±0.2‡‡</td>
<td>3.1±0.5</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>SW/PW resting MBF ratio</td>
<td>1.01±0.14</td>
<td>0.99±0.15</td>
<td>1.02±0.15</td>
<td>NS</td>
</tr>
<tr>
<td>SW/PW MBFR ratio</td>
<td>1.07±0.43</td>
<td>1.05±0.15</td>
<td>1.06±0.16</td>
<td>NS</td>
</tr>
</tbody>
</table>

The probability values in each subsection are for pairwise comparisons using post hoc Tukey adjustment to account for multiple comparisons.

*P<0.05 vs group B; †P<0.01 vs group C; ‡P<0.0001 vs PW; §P=0.005 vs group B; ||P<0.002 vs group C; ¶P=0.05 vs group B; #P<0.001 vs group C; **P=0.0003 vs PW; ††P=0.002 vs group C; ‡‡P<0.005 vs groups A and B; §§P=0.03 vs group C; ||||P=0.02 vs group C; ‡‡‡P<0.001 vs group C; #‡‡‡P<0.0001 vs group C.
reduced compared with LBBB patients without CAD ($P<0.0001$).

Distribution of Perfusion Defects
Of the 38 patients without CAD, 20 (53%) demonstrated perfusion abnormalities on SPECT, 18 of which (90%) were septal. The majority of perfusion defects were fixed. MCE demonstrated normal perfusion in all these patients; however, MCE demonstrated perfusion abnormalities in 2 patients (5%) with normal SPECT perfusion. The distribution of perfusion abnormalities by the 2 techniques is illustrated in Figure 2.

Relation Between Regional WT, Function, and Indexes of MBF in Patients With and Without SPECT Perfusion Defects
Quantitative SPECT analysis revealed that the ratio of SW to PW count was significantly reduced ($P=0.01$) in patients with visual SPECT perfusion defects ($0.79\pm0.06$) compared with those without SPECT defects ($0.85\pm0.07$). Furthermore, perfusion defects were significantly ($P=0.009$) larger in the septum in patients with visual perfusion defects ($26\pm8\%$) compared with those without ($18\pm11\%$). The qualitative tracer uptake score in patients with perfusion defects was $2.5\pm0.27$, with 97% of the defects classified as moderate to severe. Mean SWT, end-diastolic SWT, SW thickening, and LVEF were significantly lower in patients with septal SPECT perfusion defects compared with those without such defects (Table 4). Mean SWT was significantly lower than mean PWT ($1.15\pm0.12$ and $1.28\pm0.13$ cm, respectively; $P<0.0001$) in patients with SPECT perfusion defects. However, there was no difference between mean SWT and mean PWT in patients with normal SPECT perfusion ($1.35\pm0.20$ and $1.35\pm0.21$ cm, respectively; $P=0.92$). On multivariable analysis, mean SWT emerged as the only independent predictor ($P=0.006$) of false SPECT perfusion defects. The

Table 4. Univariable Predictors of Septal SPECT Perfusion Defect in Patients With LBBB and No CAD

<table>
<thead>
<tr>
<th>Normal Perfusion (n=18)</th>
<th>Perfusion Defect (n=20)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting HR, bpm</td>
<td>70±11</td>
<td>70±14</td>
</tr>
<tr>
<td>Stress HR, bpm</td>
<td>83±11</td>
<td>84±14</td>
</tr>
<tr>
<td>Mean PWT, cm</td>
<td>1.35±0.21</td>
<td>1.28±0.13</td>
</tr>
<tr>
<td>Mean SWT, cm</td>
<td>1.35±0.20</td>
<td>1.15±0.12</td>
</tr>
<tr>
<td>Diastolic PWT, cm</td>
<td>1.18±0.17</td>
<td>1.11±0.11</td>
</tr>
<tr>
<td>Diastolic SWT, cm</td>
<td>1.12±0.16</td>
<td>0.99±0.10</td>
</tr>
<tr>
<td>PW thickening, %</td>
<td>27.6±5.9</td>
<td>26.9±4.2</td>
</tr>
<tr>
<td>SW thickening, %</td>
<td>26.4±5.9</td>
<td>21.4±4.1</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>42±13</td>
<td>32±15</td>
</tr>
<tr>
<td>LVESV, mL</td>
<td>82±54</td>
<td>116±73</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>130±60</td>
<td>159±70</td>
</tr>
<tr>
<td>Posterior resting MBV, dB</td>
<td>8.01±2.93</td>
<td>7.15±2.30</td>
</tr>
<tr>
<td>Posterior resting MBF, dB/s</td>
<td>5.6±1.95</td>
<td>5.3±1.68</td>
</tr>
<tr>
<td>Posterior MBFR</td>
<td>2.16±0.55</td>
<td>2.03±0.85</td>
</tr>
<tr>
<td>Septal resting MBV, dB</td>
<td>8.37±3.37</td>
<td>7.49±2.51</td>
</tr>
<tr>
<td>Septal resting MBF, dB/s</td>
<td>5.7±2.32</td>
<td>5.5±2.21</td>
</tr>
<tr>
<td>Septal MBFR</td>
<td>2.15±0.72</td>
<td>2.30±0.88</td>
</tr>
</tbody>
</table>

HR indicates heart rate; LVESV, LV end-systolic volume; LVEDV, LV end-diastolic volume; and MBV, myocardial blood volume.
end-diastolic WT cutoff of 1.02 cm provided a sensitivity of 80% and specificity of 83% (area under the curve, 0.88; Figure 3). Figure 4 shows an example of a patient with normal coronary arteriography who had a normal MCE study but whose SPECT revealed significant fixed perfusion defects in the septum and apex.

Diagnostic Accuracy of Quantitative MCE for the Detection of CAD

Sensitivity and specificity for the detection of CAD (≥50% luminal diameter stenosis) for 63 anterior and 62 posterior (failure to intubate right coronary artery in 1 patient) coronary territories by quantitative MCE were determined by plotting a receiver-operating characteristics curve (Figure 5). The area under the curve was higher for the detection of CAD in the anterior circulation (0.95) compared with posterior circulation (0.88). An MBFR cutoff of 0.85 provided a sensitivity of 89%, specificity of 91%, positive predictive value of 80%, and negative predictive value of 95% for anterior circulation; those values for posterior circulation were 79%, 84%, 68%, and 90% and on a per-patient basis were 80%, 79%, 71% and 86%, respectively. MBFR was significantly higher in patients with coronary artery stenosis ≥50% stenosis compared with patients with >50% stenosis (2.00±0.77 versus 0.78±0.46; \( P<0.0001 \); Figure 6). Among patients with CAD, MBFR also was able to differentiate between differing grades of coronary artery stenosis (Figure 7).

Diagnostic Accuracy of Qualitative MCE for the Detection of CAD: Comparison With Qualitative SPECT

Of the 25 patients with CAD, both qualitative MCE and qualitative SPECT detected CAD in 23 patients (92%). However, of the 38 patients with no CAD, MCE correctly predicted the absence of CAD in 36 patients (95%) and SPECT in 18 patients (47%; \( P<0.0001 \)). The positive predictive values of MCE and SPECT were 92% and 54% and the negative predictive values were 95% and 90%, respectively, for the prediction of CAD. MCE was more accurate than SPECT for the detection of CAD (94% versus 65%; \( P=0.0003 \)). At the vascular territory level, MCE correctly localized left anterior descending artery disease in 16 of 18 (89%) compared with SPECT, which detected 13 of 18 (72%) (\( P=0.001 \)). The specificities of MCE and SPECT in this territory were 90% and 45% (\( P<0.001 \)). Localization of right coronary artery/left circumflex artery disease was similar between MCE and SPECT (sensitivity, 72% versus 68%, \( P=NS \); specificity, 80% versus 75%, \( P=NS \)). MCE was abnormal in all 12 patients (100%) with multivessel disease and correctly detected 11 of 12 patients (92%) with multivessel disease. The corresponding numbers for SPECT were 83% and 58%. The number of segments demonstrating reversible defects in patients with CAD was significantly lower than in patients with no CAD.

Figure 4. MCE shows normal perfusion at rest (top left) and at stress (top right). SPECT (bottom) demonstrated a fixed perfusion defect effecting the septum and apex in a patient with no CAD.
Discussion

This is the first study that simultaneously assessed cardiac structure, function, perfusion, and MBFR with quantitative MCE in patients with symptomatic LBBB who also underwent coronary arteriography. The study demonstrated that 40% of such patients had CAD. Coronary risk factors and modes of presentation were similar in patients with and without CAD. LVEF is reduced in these patients, but there was no significant difference between LVEF in patients with and without CAD. In patients with LBBB, regardless of CAD, there were asymmetrical reductions in SWT and function compared with the PW. However, patients with similarly reduced LVEF without LBBB and no CAD did not demonstrate asymmetrical reductions in SWT and function compared with the PW. SWT and function in patients with LBBB but not in those without LBBB also were asymmetri-

cally reduced compared with normal control subjects. Despite asymmetrical reductions in SWT and function in patients with LBBB, resting myocardial blood volume and MBF were homogeneously preserved, but MBFR was reduced, albeit homogeneously, compared with normal controls. The present study further showed that SPECT perfusion defects were common and located predominantly within the septum in patients with LBBB without CAD. They were largely fixed and due to partial volume effects secondary to septal thinning and reduced septal thickening. Preservation of resting myocardial blood volume, MBF, and homogeneous MBFR suggests that true hypoperfusion was not the cause of the perfusion defects seen on SPECT.

Partial volume effects are of particular relevance in myocardial SPECT studies because of the limited spatial resolution of gamma cameras (10 to 12 mm). Our study showed that an end-diastolic SWT of 10 mm produced a perfusion defect in 80% of patients. Furthermore, during SPECT image acquisition, systolic thickening and diastolic relaxation of the myocardium result in continuous changes in the recovery coefficient because the myocardial counts actually measured depend considerably on systolic thickening. Myocardial thickening leads to a higher recovery coefficient and subsequently to greater myocardial counts. In our study, mean

Figure 5. Receiver-operating characteristics curve demonstrating diagnostic accuracy of quantitative MCE for the detection of CAD in patients with LBBB. A, Anterior circulation. B, Posterior circulation. AUC indicates area under the curve; Sens., sensitivity; Spec., specificity; PPV, positive predictive value; and NPV, negative predictive value.

(P=0.008) greater with MCE (6.8±3.0) compared with SPECT (4.4±3.7). If only reversible defects were considered to represent CAD, then the sensitivity of MCE on a vascular territory basis was 84%, but the sensitivity of SPECT dropped to 57% (P=0.03).

Figure 6. Relationship between quantitative MCE-derived MBFR and detection of significant CAD.

Figure 7. Relationship between quantitative MCE-derived MBFR and detection of differing grades of coronary stenosis.
systolic SWT was the only independent factor accounting for perfusion defects in the septum among other confounding variables.

Experimental models in which right ventricular pacing was used to mimic LBBB demonstrated similar asymmetrical reduction in SWT and function. Several investigators found that during right ventricular pacing, regional shortening of the septum, which is activated early, is reduced compared with the PW, which is activated late.9,18 It is likely that as a result of this asynchronous activation of the left ventricle, redistribution of mechanical load occurs in the left ventricle, so mechanical load is least in the early activated SW.18 This probably results in an adaptive reduction in wall thickness and function of the septum. However, resting myocardial blood volume and perfusion are preserved despite a reduction in WT and function. Preservation of septal myocardial perfusion in patients with LBBB also was shown in recent positron emission tomography studies using 150O water and 13N-NH3, which are robust markers of MBF, as blood flow tracers.19,20 In addition, our study demonstrated that MBFR is reduced, although homogeneously, throughout the LV. These findings support the hypothesis that asymmetrical reductions in SWT and function with preserved myocardial perfusion occur as a physiological response to a regional decrease in myocardial load. Symmetrical reduction in MBFR probably resulted from underlying cardiomyopathy in the absence of CAD.

Clinical Implications
Cardiac resynchronization therapy is now a recognized management strategy in heart failure and LBBB. One of the underlying mechanisms of the success of cardiac resynchronization therapy is that it likely restores synchronous activation, allowing more homogeneous distribution of mechanical load throughout the LV and thus reversing septal dysfunction. In our study, in which no patients had prior acute myocardial infarction, myocardial viability was maintained as predicted by preserved myocardial blood volume and MBF. However, myocardial blood velocity, which reflects MBF, tended to be lower in patients with CAD compared with those without CAD, which is consistent with hibernating myocardium.21 The presence of myocardial viability has been shown to be one of the important predictors of success after cardiac resynchronization therapy.22

We also demonstrated that despite changes in regional myocardial structure and function, MCE was able to detect CAD accurately. The reason is that MCE has excellent spatial (2 to 4 mm) and temporal resolution.12,13,15 MBFR was markedly reduced in patients with LBBB and CAD compared with those without LBBB and CAD. MCE could exclude nearly all patients (>90%) without CAD and detected all patients with multivessel disease. We also have shown that as a result of partial volume effects, the specificity of SPECT for detecting CAD was significantly reduced compared with MCE. Our study, similar to other studies, found SPECT to have lower accuracy for predicting CAD in patients with LBBB because of a high percentage of false-positive antero-septal and septal perfusion defects.3–7 This also was shown in a smaller study comparing MCE and SPECT.23 No difference in sensitivity between the 2 techniques was noted for the detection of CAD. However, because reversible defects (suggesting myocardial ischemia) occurred in only 57% of CAD patients, a significant proportion of patients undergoing SPECT would inadvertently be denied revascularization. The low incidence of reversibility in patients with CAD is due to a low tracer count (partial volume effect) at rest and thus an indiscernible reduction in tracer uptake during stress because at least a 20% to 30% change in myocardial blood volume is required to produce a perfusion defect. On the other hand, because MCE does not suffer from partial volume effects and because it tracks blood flow, unlike SPECT, it demonstrated reversible perfusion defects in ≈85% of patients with CAD. Furthermore, the reversible defects were larger compared with SPECT in patients with CAD.

Comparison With Other Competing Techniques
Stress echocardiography also has reduced accuracy for detecting CAD in patients with LBBB because it relies on changes in regional wall thickening and motion, both of which are affected even in LBBB without CAD.24 Because MCE assesses myocardial perfusion, it is a function-independent technique and thus is unlikely to be affected by the unique functional effects of LBBB. This is reflected in the excellent diagnostic accuracy of MCE for the detection of CAD in our study. Another emerging noninvasive technique that can reliably assess CAD is multislice computed tomography.25 However, assessment of symptomatic patients with LBBB not only requires demonstration of CAD but also must include assessment of its functional significance and evaluation of the presence or absence of myocardial viability. Echocardiography with MCE has the advantage in that it can provide a comprehensive assessment of cardiac structure, cardiac function, presence or absence of flow-limiting CAD, and status of myocardial viability in a single examination in patients presenting with symptomatic LBBB.

Study Limitations
Most patients with LBBB in the present study demonstrated LV systolic dysfunction; thus, the conclusions drawn from the present study pertain largely to this specific population. In our study population, shortness of breath was the predominant symptom that may explain the low mean LVEF. Presence of LV dysfunction also explains the lower MBFR in this group compared with normal control subjects; MBFR was further reduced in LBBB patients with CAD. Thus, our results do not apply to patients with LBBB and normal LV systolic function. However, in a smaller study of asymptomatic LBBB patients who demonstrated predominantly normal LV function, the performance of MCE and SPECT for the detection of CAD was similar to our study.23

The control group in our study was small, and multiple comparisons were performed, which may have led to a false-positive result. To minimize the possibility of type I error rate, we performed a 1-way ANOVA with post hoc adjustment for multiple comparisons with the Tukey method. In our study, factors that may affect cardiac structure,
function, and perfusion are represented reasonably in the study versus control groups. The main variables likely to affect cardiac structure are age, hypertension, diabetes mellitus, and gender. In the 3 groups, age, hypertension, and diabetes mellitus were well represented. Furthermore, any discrepancy was minimized by measurement of the ratios of the SWT to PWT. The latter specifically negates any bias that may have occurred with the discrepant gender distribution in the 3 groups. The main demographic factors that may affect function and perfusion include age, hypertension, diabetes mellitus, hyperlipidemia, and smoking history; most of these factors are not discrepantly distributed. To further negate any possible errors when categorical variables are compared between relatively small groups, we assessed Framingham risk score, which incorporates all the above variables into a continuous variable. Framingham risk scores were similar across all 3 groups.

Finally, for normal control subjects, we have included patients presenting with chest pain but with normal cardiac enzymes and normal resting and stress function, which classifies them as having a low probability of significant cardiac disease. However, cardiac disease cannot be entirely excluded in this group.

Conclusions
Despite a reduction in SWT and function compared with the PW, myocardial perfusion at rest is preserved and homogenous in patients with LBBB without CAD and LV systolic dysfunction. However, MBFR is reduced, albeit homogenous. Because MCE is a partial volume– and function-independent technique, the accuracy of MCE for detecting CAD is not compromised compared with SPECT.

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Disclosures
None.

References
CLINICAL PERSPECTIVE

The present study is the first to simultaneously assess cardiac structure, function, perfusion, and perfusion reserve using quantitative myocardial contrast echocardiography in patients with symptomatic left bundle-branch block who predominantly had left ventricular dysfunction. In these patients, regardless of coronary artery disease (CAD), there were asymmetrical reductions in septal wall thickness and function compared with the posterior wall; however, resting myocardial blood volume and flow were homogeneously preserved. Single-photon emission computed tomography (SPECT) is widely used for the detection and risk stratification of CAD. However, we demonstrated that because of asymmetrical reductions in septal thickness and function, SPECT has a significantly higher incidence of false-positive perfusion defects resulting from partial volume effects as a consequence of its poorer spatial and temporal resolution compared with myocardial contrast echocardiography. Despite no difference in sensitivity between the 2 techniques for the detection of CAD, because of partial volume effects, reversible defects (suggesting myocardial ischemia) occurred in only 57% of CAD patients with SPECT imaging compared with 92% with myocardial contrast echocardiography. This finding has both cost and safety implications in that patients would be inappropriately referred for coronary arteriography after SPECT and a significant proportion of patients undergoing SPECT would inadvertently be denied revascularization. Compared with other imaging techniques such as multislice computed tomography, SPECT, or stress echocardiography, myocardial contrast echocardiography has the advantage of providing an accurate comprehensive assessment of cardiac structure and function and denoting the presence or absence of flow-limiting CAD and the status of myocardial viability in a single examination in patients presenting with symptomatic left bundle-branch block.
Effects of Left Bundle-Branch Block on Cardiac Structure, Function, Perfusion, and Perfusion Reserve: Implications for Myocardial Contrast Echocardiography Versus Radionuclide Perfusion Imaging for the Detection of Coronary Artery Disease

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