Usefulness and limitations of dobutamine–atropine stress echocardiography for the diagnosis of coronary artery disease in patients with left bundle branch block

A multicentre study

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Background Patients with left bundle branch block exhibit abnormal septal motion which may limit the interpretation of stress echocardiograms. This study sought to assess the diagnostic value of dobutamine–atropine stress echocardiography in left bundle branch block patients.

Methods and Results Sixty-four left bundle branch block patients (mean age 59 years, 24 men) with suspected coronary artery disease underwent dobutamine–atropine stress echocardiography and coronary arteriography. Myocardial ischaemia was defined as new or worsening wall thickening abnormalities. Coronary artery disease was quantitatively defined as a diameter stenosis ≥50% in a major epicardial artery. Rest septal motion was normal (apart from the early systolic septal notch) in 34 patients (53%) and abnormal in 30 patients (47%). Rest septal thickening was normal in 32 patients (50%) and abnormal in 32 patients (50%). All seven patients with a QRS duration ≥160 ms and an abnormal QRS axis had abnormal rest septal motion and thickening. Inter-observer agreement for ischaemia was 88%. In all but one patient disagreement was in the septum. For the anterior and posterior circulation, respectively, sensitivity was 60% (9/15) and 67% (8/12), specificity was 94% (46/49) and 98% (51/52), and accuracy was 86% (55/64) and 92% (59/64). Sensitivity for the anterior circulation tended to be better in patients with normal rest septal thickening (83% vs 44%).

Conclusions Dobutamine–atropine stress echocardiography has excellent diagnostic specificity in left bundle branch block patients with suspected coronary artery disease. In patients with abnormal rest septal thickening, however, dobutamine–atropine stress echocardiography may lack good sensitivity for detection of coronary artery disease in the anterior circulation. Left bundle branch block patients who potentially most benefit from dobutamine–atropine stress echocardiography may initially be selected by their resting electrocardiogram.


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Key Words: Dobutamine, stress echocardiography, coronary artery disease, left bundle branch block.
Introduction

Left bundle branch block is most commonly associated with atherosclerotic coronary artery disease\[1\]. Other aetiopathologies are idiopathic dilated cardiomyopathy, hypertensive heart disease, aortic valvular disease or non-specific fibrosis of the cardiac conduction system. In a few patients, left bundle branch block may be rate related or idiopathic. Although the presence of left bundle branch block was associated with a three- to fourfold increase in cardiovascular mortality in the Framingham study\[1\], patients without clinically overt heart disease have an excellent short- and long-term prognosis\[2,3\]. Thus, it is important to determine whether left bundle branch block is associated with coronary artery disease or other underlying abnormalities. Unfortunately, most non-invasive stress tests have limited value for the detection of coronary artery disease in left bundle branch block patients. Exercise-induced ST segment changes are indeterminate for ischaemia\[4,5\], and myocardial perfusion studies, especially exercise perfusion studies, often suffer from false positive perfusion defects in the interventricular septum in the absence of left anterior descending coronary artery stenosis\[6-9\].

Echocardiographically, left bundle branch block is characterized by asynchronous contraction of the ventricles\[10\], resulting in the (M-mode) echocardiographic hallmarks of left bundle branch block, the early systolic posteriorly directed septal notch, first described by McDonald in 1973\[11\]. After the occurrence of this notch, several types of septal motion have been described. Classically, septal motion is anterior and described as paradoxical\[11-13\]. However, normal posterior motion and several intermediate types may also occur\[11-16\].

Dobutamine–atropine stress echocardiography is an established stress modality for the detection of coronary artery disease in patients without left bundle branch block\[17\]. It is capable of visualizing septal motion and assessing septal myocardial thickening which might be relatively preserved in left bundle branch block patients, especially in those patients without coronary artery disease\[16,18,19\]. To investigate the diagnostic accuracy of dobutamine–atropine stress echocardiography for the detection of coronary artery disease in left bundle branch block patients and the influence of rest septal motion and thickening on this accuracy we initiated a prospective, multicentre study in which left bundle branch block patients with chest pain and suspected coronary artery disease, who were referred for coronary arteriography, underwent dobutamine–atropine stress echocardiography.

Methods

Patient selection

Patients with chest pain and permanent, complete left bundle branch block who were referred for coronary arteriography were eligible for the study if they did not meet any of the following excluding criteria: (1) known ventricular tachyarrhythmias, (2) history of myocardial infarction, (3) unstable angina, (4) uncontrolled hypertension (≥180/110 mmHg), (5) significant aortic valvular heart disease, or (6) poor quality echocardiogram (n=2). Sixty-four patients gave informed consent and were included in the study. All patients underwent dobutamine–atropine stress echocardiography within 1 month of coronary arteriography, without any preceding clinical event. Mean age of the patients was 59 ± 10 years (range 35 to 78), 24 were men (38%). Forty-seven patients (73%) had typical angina, 17 patients (27%) had atypical angina. Mean pre-test probability of coronary artery disease, calculated from age, gender and chest pain characteristics\[20\], was 74% ± 25%. At the time of the study 39 patients (61%) were receiving antianginal therapy including beta-blockers in five (8%). Relevant demographic data of all patients are displayed in Table 1.

Electrocardiography

Complete left bundle branch block was defined as a notching or slurring QRS ≥120 ms with an initial R wave in lead I and aVL, and the left precordial leads and displacement of the ST segment, and usually the T wave, in a direction opposite to that of the principal QRS deflection\[21\]. Electrocardiographic measurements from a standard 12-lead electrocardiogram included QRS duration, measured to the nearest 10 ms, and frontal QRS axis, measured to the nearest 15°. A frontal QRS axis between −30° and +90° was considered normal.

Dobutamine–atropine stress test

Dobutamine was administered intravenously by an infusion pump with an infusion rate of 10 μg · kg⁻¹ min⁻¹ for 3 min, increasing by 10 μg · kg⁻¹ min⁻¹ every 3 min up to a maximum of 40 μg · kg⁻¹ min⁻¹. In patients not achieving 85% of their age- and gender-predicted maximal heart rate and without symptoms or signs of myocardial ischaemia, atropine was administered, starting with 0.25 mg intravenously and repeated up to a maximum of 1.0 mg within 4 min with a continuation of the dobutamine infusion. Throughout the dobutamine infusion the electrocardiogram (three leads) was continuously monitored and recorded (12 leads) at 1 min intervals. Reasons for interruption of the test were: severe angina, symptomatic reduction in systolic blood pressure >40 mmHg from baseline, hypertension (blood pressure >240/120 mmHg), significant tachyarrhythmias and any serious side effect regarded as being due to dobutamine.

Echocardiographic imaging

Echocardiographic analysis of the left ventricular wall was performed according to the 16-segment model\[22\].
The anterior and septal segments were assigned to the anterior circulation, all other segments were assigned to the posterior circulation (right coronary artery and/or left circumflex artery). Isolated apical wall abnormalities were assigned to the anterior circulation. Isolated basal posterior septal wall abnormalities were assigned to the posterior circulation. Systolic wall thickening and/or wall motion were visually evaluated, and each segment was graded on a five-point scoring system (1=normal; 2=mild hypokinesis; 3=severe hypokinesis; 4=akinesis; and 5=dyskinesis). Resting wall motion score index was calculated by summing all individual segment scores and dividing the sum by the total number of segments. A test was considered positive for ischaemia in cases of new or worsening wall thickening (or motion) abnormalities at any dobutamine (or atropine) stage in 1 segment [23].

All echocardiograms were scored by two observers (P.M.F. and R.R.) who were blinded for the angiographic data. In case of disagreement, consensus was reached by the two observers, or a third observer’s (J.D.K.) scoring was decisive. Left ventricular end-diastolic diameter and septal motion were assessed from the baseline M-mode parasternal long axis view. Since it has been documented that septal motion assessment varies with the direction of the ultrasound beam [24], this motion was measured from the cross section in which parts of both mitral valve leaflets were visible. Systolic septal motion after the early notch was visually graded as (relatively) normal (posterior movement ≥3 mm) or abnormal (posterior movement <3 mm, flat [no movement] or paradoxical [anterior movement]). Likewise, systolic septal thickening was graded as (relatively) normal (more than 3 mm thickening) or abnormal (less than 3 mm thickening).

**Coronary angiography**

Coronary angiography was performed, using the Judkins technique, within 1 month from dobutamine–atropine stress echocardiography in all patients. Significant coronary artery disease was defined as a diameter stenosis ≥50% in a major epicardial artery at quantitative coronary angiography [25].

**Statistical analysis**

Values were expressed as mean value ± standard deviation, when appropriate. Comparison between variables was performed with the Student’s t-test for continuous variables and chi-square test for discrete variables. Differences of P<0.05 were considered significant.

**Results**

**Haemodynamic and adverse effects of dobutamine–atropine**

Dobutamine–atropine increased the heart rate from 79 ± 13 beats . min⁻¹ to 136 ± 13 beats . min⁻¹, systolic blood pressure from 135 ± 17 mmHg to 145 ± 25 mmHg, and double (rate-pressure) product from 10 704 ± 2248 mmHg × beats . min⁻¹ to 19 741 ± 3915 mmHg × beats . min⁻¹. Test end-points were target heart rate in 55 patients (86%), maximal dose dobutamine–atropine in five patients (8%), severe angina in three patients (5%), and hypotension in one patient (2%). None of the patients had a tachyarrhythmia during dobutamine infusion or recovery. Typical angina was induced in six patients (9%).

**Baseline electrocardiographic and echocardiographic results**

QRS duration was positively correlated with rest left ventricular end-diastolic diameter (r=0.69, Fig. 1(a))
Rest septal motion was normal in 34 patients (53%) and abnormal in 30 patients (47%). Abnormal septal motion was severely hypokinetic in 20, flat in 9 and true paradoxical in 1. Rest septal thickening was normal in 32 patients (50%) and abnormal in 32 patients (50%). As shown in Table 2, patients with normal septal thickening had a shorter QRS duration ($P<0.001$), lower numbers of abnormal frontal QRS axes ($P<0.02$), smaller left ventricular end-diastolic diameter ($P<0.001$), lower wall motion score index ($P<0.001$), and more often normal septal motion ($P<0.0001$). The presence of left anterior descending coronary artery disease did not differ significantly. Of 30 patients without evidence of coronary artery disease or cardiomyopathy (normal coronary arteriography, left ventricular end-diastolic diameter $\leq 56$ mm, and normal resting wall thickening apart from septal wall abnormalities), 26 (87%) had (relatively) normal septal motion and 25 (83%) normal septal wall thickening.

**Inter-observer agreement for ischaemia**

Inter-observer agreement for myocardial ischaemia was 88% (56/64). In all but one patient disagreement was in the septum. Disagreement was present in 9% (3/32) of septums with normal thickening and in 13% (4/32) of septums with abnormal thickening. Ischemia in the anterior circulation was detected in the septum in nine patients, in the anterior wall in one patient, and in both the septum and the anterior wall in two patients.

**Diagnostic accuracy**

Significant coronary artery disease was present in 19 of 64 patients (30%). Of the 45 patients (70%) without significant coronary artery disease, 38 patients had normal coronary arteries and seven patients had non-significant lesions. Overall sensitivity for the detection of coronary artery disease was 68% (13/19), specificity was 91% (41/43), and diagnostic accuracy was 84% (54/64). Sensitivity for one, two, and three-vessel coronary artery disease was 50% (5/10), 80% (4/5), and 100% (4/4), respectively. For the anterior circulation sensitivity was 60% (9/15), specificity 94% (46/49), and accuracy 86% (55/64). For the posterior circulation sensitivity was 67% (8/12), specificity 98% (51/52), and accuracy 92% (59/64) (Fig. 2).

**Analysis of false-negative results**

Of four patients with a false-negative dobutamine–atropine stress echocardiography study for the posterior circulation, three patients had one-vessel coronary artery disease (left circumflex coronary artery stenosis of 55%, 69%, and 75%, respectively), and one patient had two-vessel coronary artery disease (right coronary artery stenosis of 100% and left circumflex coronary artery stenosis of 57%).
stenosis of 60%). Achieved heart rates (percentage of 'maximal' heart rate) in these four patients were 92%, 104%, 117%, and 65%, respectively. Of six patients with a false-negative dobutamine–atropine stress echocardiography study for the anterior circulation, one patient had normal rest septal thickening (left anterior descending coronary artery stenosis of 53%) and five patients had abnormal septal thickening (left anterior descending coronary artery stenosis of 58%, 63%, 66%, 75%, and 100%, respectively). Achieved heart rates in these six patients were 92%, 91%, 102%, 107%, 92% and 75%, respectively. In the 32 patients with normal rest septal thickening, sensitivity, specificity and accuracy for the detection of left anterior descending coronary artery disease was 44% (4/9), 100% (23/23), and 84% (27/32), respectively. Sensitivity for the detection of left anterior descending coronary artery disease tended to be better in patients with normal rest septal thickening (5/6=83% vs 4/9=44%, P<0·10). When only septal ischaemia was considered diagnostic for left anterior descending coronary artery disease this difference was significant (5/6=83% vs 3/9=33%, P<0·05).

**Analysis of false-positive results**

The only patient with a false-positive dobutamine–atropine stress echocardiography study for the posterior circulation had normal resting wall thickening and mildly impaired basal and mid inferoposterior wall thickening at peak stress. All three patients with a false-positive dobutamine–atropine stress echocardiography study for the anterior circulation had relatively normal rest septal wall motion and stress-induced wall thickening abnormalities in the septum. Peak heart rate of the latter three patients with a false positive study was comparable to the 46 patients with a true negative study for the anterior circulation (136 ± 7 vs 138 ± 12 beats per minute, P=ns). All patients with a false-positive dobutamine–atropine stress echocardiography study had angiographically normal coronary arteries.

**Discussion**

The present study addressed the diagnostic value of dobutamine–atropine stress echocardiography in left bundle branch block patients with chest pain and suspected coronary artery disease. The main finding of the study is that dobutamine–atropine stress echocardiography is a moderately sensitive and highly specific test for the detection of coronary artery disease in left bundle branch block patients, both in the anterior and posterior circulation. Inter-observer agreement for detection of coronary artery disease in the left anterior descending coronary artery artery, however, seems somewhat lower compared to patients without left bundle branch block[17]. Additionally, sensitivity for the detection of coronary artery disease in the left anterior descending coronary artery artery seems lower in patients with abnormal rest septal thickening.

**Echocardiographic characteristics of left bundle branch block**

In left bundle branch block patients ventricular activation starts in the right ventricle and the right side of the septum. Transseptal activation from right to left is transmyocardial and thus slow. Activation of the left ventricle proceeds also from right to left, with the basal
and posterolateral wall activated last, although activation of the latter is relatively rapid because of impulse entrance in the distal Purkinje network. Thus, whereas in normal subjects the onset of right and left ventricular contraction occurs nearly simultaneously, in left bundle branch block patients there is an asynchronous onset of right and left ventricular contraction. This mechanical asynchrony, resulting in dynamic changes in pressure and volume between the ventricles, continues throughout the cardiac cycle[10]. During early systole, right ventricular isovolumic contraction is unopposed by left ventricular contraction, causing the septum to move passively posteriorly (explaining the early systolic septal notch). Abrupt anterior septal motion occurs at the time of normalization of the transseptal pressure gradient by a decrease in right ventricular volume with pulmonic ejection and a rise in left ventricular pressure with isovolumic contraction. During simultaneous right and left ventricular ejection several types of septal motion can be encountered. Classically, septal motion is anterior and described as paradoxical[11–13]; however, normal posterior motion and several intermediate types may also occur[11–16]. Septal motion seems related to both contraction capability (e.g. presence of septal infarction, cardiomyopathy) as well as activation sequence. Several right ventricular pacing studies, simulating left bundle branch block, have indicated that apical pacing results in an early systolic notch followed by (near) normal posterior septal motion and thickening[18,19], whereas midventricular pacing results in an early systolic notch followed by paradoxical anterior septal motion without thickening[19,20]. Likewise, the proximal or more distal site of left bundle branch block may influence septal motion and thickening[21]. In contrast to the initial studies describing septal motion[11–13], many left bundle branch block patients in the present study had (apart from the early systolic notch) relatively normal septal motion and thickening. In particular, patients without evidence of coronary artery disease or cardiomyopathy usually had normal septal motion and thickening. In the largest (resting) echocardiographic studies in consecutive left bundle branch block patients by Strasberg et al.[15] and Curtius et al.[16], relatively normal septal motion was also present in the majority of patients. Grines et al.[10] stated that left bundle branch block patients with a more prolonged right/left ventricular filling ratio (interventricular asynchrony) had increased abnormal septal motion. In concordance with the studies of Strasberg et al.[15] and Curtius et al.[16] we found that patients with abnormal septal thickening (and usually motion) had a longer QRS duration, more often an abnormal QRS axis, and larger left ventricular end-diastolic diameter. These findings were, although not specifically analysed, also present in the classic study of McDonald[11].

Detection of myocardial ischaemia

In left bundle branch block patients, exercise-induced ST segment changes are non-specific for ischaemia[4,5] and myocardial perfusion studies, especially when exercise stress is used, and often suffer from false positive perfusion defects in the interventricular septum in the absence of left anterior descending coronary artery stenosis[6–9]. Pacing studies in dogs have indicated that regional myocardial blood flow and thallium-201 uptake during (mid) right ventricular pacing induced left bundle branch block was reduced in the septum compared to the lateral wall, whereas in right atrial pacing and normal ventricular depolarization myocardial blood flow and thallium-201 uptake was equal in the lateral and septal wall[6,26]. True ischaemia, as measured by lactate extraction, was not present. Several mechanisms have been proposed to explain these perfusion defects. In left bundle branch block patients, septal contraction occurs at the very end of systole. The regional myocardial compressive effect may restrict coronary blood flow during early diastole, when most perfusion normally occurs[20]. As heart rate increases and diastole shortens, the relative septal hypoperfusion may even become more apparent. Alternatively, with markedly delayed septal contraction, the myocardium in this region encounters a decreased afterload relative to that of other left ventricular segments. This may result in a relative reduction in coronary septal blood flow as a result of coronary autoregulatory mechanisms[21]. Other proposed mechanisms include coronary spasm or small vessel coronary artery disease, septal fibrosis[22], and technical factors, including wall motion artifact[23]. Because of the suspected major role of heart rate, an increase in the development of septal defects, vasodilator (dipyridamole, adenosine) perfusion imaging, which causes only a moderate increase in heart rate, is advocated as the stress test of choice in left bundle branch block patients to detect coronary artery disease[10,9].

Echocardiographically, myocardial ischaemia in the left anterior descending coronary artery territory can be assessed by stress-induced wall thickening abnormalities in the septum or anterior wall. Stress-induced wall thickening abnormalities in the septum are relatively easy to detect because of the well delineated endocardium compared to the anterior wall endocardium and are important because they may reflect proximal or mid left anterior descending coronary artery stenosis. Our study shows that in left bundle branch block patients septal (and anterior) dobutamine–stress induced wall thickening abnormalities are very specific for the detection of coronary artery disease in the left anterior descending coronary artery. Unfortunately, interobserver agreement for septal ischaemia in the present study was relatively low. Additionally, in patients with abnormal rest septal thickening, septal ischaemia was detected less frequently and the sensitivity of dobutamine–atropine stress echocardiography for the detection of coronary artery disease in the left anterior descending coronary artery seemed lower. The false negative studies could not be explained by less severe left anterior descending coronary artery stenosis, lower achieved heart rates or double products. Other
investigators have shown that in patients without left bundle branch block but with abnormal rest wall thickening or dilated cardiomyopathy, dobutamine–atropine stress echocardiography is still an accurate test for the diagnosis of coronary artery disease\cite{23,31,32}. However, despite the use of the biphasic response\cite{33}, the combination of impaired baseline wall thickening and left bundle branch block-induced abnormal wall motion seems to make the assessment of septal ischaemia difficult. In this respect, we anticipate that in left bundle branch block patients with septal infarction, who usually have a flat septum without wall thickening\cite{34}, assessment of infarct-related artery patency will also be very difficult. Recently, Mairesse et al\cite{35} reported in eight left bundle branch block patients with prior myocardial infarction and left anterior descending coronary artery stenosis a sensitivity of dobutamine–atropine stress echocardiography for the detection of coronary artery disease in the left anterior descending coronary artery of 88%. However, in their study infarct (or rest wall thickening abnormality) localization was not specified and failure to improve wall thickening during dobutamine infusion was considered an additional criterion for ischaemia. Opinions about the use of this latter criterion diverge\cite{34}. Application of this criterion to our 32 left bundle branch block patients with abnormal septums would have increased sensitivity for the detection of coronary artery disease in the left anterior descending coronary artery from 44% to 89%, at the sacrifice of a decrease in specificity from 100% to 17%. As mentioned before, vasodilator (dipyridamole, adenosine) perfusion scintigraphy is nowadays considered as the diagnostic stress test of choice in left bundle branch block patients. Unfortunately, there are no studies reported in the literature specifically addressed to the sensitivity of perfusion scintigraphy for the detection of left anterior descending coronary artery disease in left bundle branch block patients with abnormal rest septal thickening. Although left bundle branch block-induced septal abnormalities do not concur with the detection of coronary artery disease in the posterior circulation, some patients had false negative results for this circulation. All these patients had significant left circumflex coronary artery stenosis, a finding consistent with the general literature on false negative results\cite{17}.

Interestingly, the likelihood of having relatively normal rest septal thickening was higher in patients with a shorter QRS duration and normal QRS axis. Only three of 19 patients (16%) with a QRS duration $\geq 160$ ms had relatively normal septal thickening, as opposed to 29 of 45 patients (64%) with a QRS duration $\leq 150$ ms. All seven patients with a QRS duration $\geq 160$ ms and abnormal QRS axis had abnormal rest septal thickening (and motion). If other studies confirm our findings, left bundle branch block patients who potentially most benefit from dobutamine–atropine stress echocardiography may initially be selected by their resting electrocardiogram.

**Limitations**

The number of patients was relatively small and despite a mean pre-test probability of coronary artery disease of $74\% \pm 25\%$ only $30\%$ of the patients had significant coronary artery disease. Twelve patients (19%) in our study group had evidence of non-ischaemic dilated cardiomyopathy by left ventricular end-diastolic diameter $>56$ mm, global hypokinesis and angiographically normal coronary arteries. It is well known that patients with dilated cardiomyopathy can experience typical, exertional angina in the absence of epicardial coronary artery disease\cite{35}. Importantly, the main issue in left bundle branch block patients is the rather low specificity of most non-invasive stress tests. Since $70\%$ of our patients did not have significant coronary artery disease, this important issue could adequately be addressed. In fact, our left bundle branch block study population is the largest reported in the literature without angiographic referral bias.

**Conclusions**

Despite suboptimal inter-observer agreement on septal ischaemia, we believe that the diagnostic accuracy of dobutamine–atropine stress echocardiography establishes this stress modality as one of the stress tests of choice in left bundle branch block patients with relatively normal rest septal thickening. In patients with abnormal rest septal thickening dobutamine–atropine stress echocardiography may lack good sensitivity for left anterior descending coronary artery disease detection, although the test remains highly specific. Future studies should confirm our findings and, preferably in head-to-head comparisons, assess whether stress perfusion scintigraphy has better diagnostic accuracy (or may be complimentary) in these latter patients with abnormal rest septal thickening.

**References**


Stress echocardiography in left bundle branch block


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Appendix

Investigators, number of patients, participating centres

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