Dobutamine Stress Echocardiography and Thallium-201 SPECT for Detecting Ischaemic Dilated Cardiomyopathy in Patients with Heart Failure*

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Aims: A diagnosis of ischaemic aetiology of a dilated cardiomyopathy has important therapeutic and prognostic implications. In such patients, abnormal ECG and atypical symptoms limit the usefulness of standard ECG-ergometry in detecting myocardial ischaemia. To assess the values of high-dose dobutamine stress echocardiography and of Thallium-201 SPECT (exercise-reinjection-rest protocol) in differentiating between ischaemic and non-ischaemic dilated cardiomyopathy, 37 patients with suspected myocardial ischemia, low ventricular ejection fraction (23 ± 5%) and heart failure were studied.

Methods and Results: Coronary artery disease was defined as >50% coronary stenosis in at least one coronary artery. By dobutamine stress echocardiography, ischaemic dilated cardiomyopathy was considered present when either an ischaemic response (biphasic response or direct deterioration) or a scar (fixed dyssynergy) was documented in at least two segments. By Thallium-201 SPECT, severe perfusion defects, either reversible (ischaemia) or fixed (scar), in at least two segments were considered markers of ischaemic dilated cardiomyopathy. Twenty-three patients had ischaemic dilated cardiomyopathy, while 14 had normal coronary arteries. The presence of myocardial ischaemia and/or scar by dobutamine stress echocardiography identified patients with ischaemic dilated cardiomyopathy with a sensitivity of 100% and a specificity of 86%. The sensitivity of Thallium-201 SPECT was 92%, its specificity was 69%. Three of the four false positive results occurred in patients with left bundle branch block.

Conclusion: Both dobutamine stress echocardiography and Thallium-201 SPECT are sensitive techniques for detecting the ischaemic aetiology of dilated cardiomyopathy. The specificity is lower, particularly by SPECT, when left ventricular branch block is present.

Key Words: congestive heart failure; dobutamine stress echocardiography, thallium-201 SPECT.

Introduction

Dilated cardiomyopathy, defined as a left ventricular dilatation associated with systolic dysfunction and diffuse wall motion abnormalities, is one of the most common causes of heart failure and is frequently associated with a high mid-term mortality.

Various aetiologies may underlie this condition1−3, ischaemia being the most frequent. The detection of significant coronary artery disease in a patient with dilated cardiomyopathy has important therapeutic implications since left ventricular dysfunction, being partly determined by the effects of chronic ischaemia, may recover after revascularization4,5. Furthermore, patients with ischaemic dilated cardiomyopathy generally have a poorer outcome than those with non-ischaemic dilated cardiomyopathy, but their prognosis improves greatly if a significant amount of ischaemic, but viable, myocardium can be revascularized6.

The diagnosis of ischaemic dilated cardiomyopathy is straightforward when patients have had large and/or multiple myocardial infarctions. However, in some patients the diagnosis of ischaemic aetiology can be
difficult, due to the limited sensitivity and specificity of clinical markers. In fact, a clear history of myocardial infarction and angina may be lacking even in patients with severe coronary artery disease, whereas 8–20% of patients with non-ischaemic dilated cardiomyopathy may experience ‘anginal’ pain. Furthermore, the interpretation of both rest and exercise echocardiograms can be complicated by intra-ventricular conduction defects, which are frequent in dilated cardiomyopathy of any cause. Regional wall motion abnormalities, as detected by rest echocardiography, are neither sensitive nor specific for ischaemic aetiology.

Stress echocardiography and nuclear imaging techniques have been proposed to improve the non-invasive diagnosis of ischaemic dilated cardiomyopathy. So far, however, the available data are limited and the values of dobutamine stress echocardiography and Thallium-201 SPECT in detecting ischaemic dilated cardiomyopathy have not been directly compared. This comparison was the aim of the present study.

All cardiac medications were continued, except beta-blockers, which were withdrawn before dobutamine stress echocardiography.

**Low–high Dose Dobutamine Stress Test**

Low–high dose dobutamine stress echocardiography was performed using the standard protocol, except that each step lasted 5 min to allow more accurate acquisition of images. Since patients with congestive heart failure are at high risk of arrhythmias, for reasons of safety we preferred not to add atropine at the end of the test, even when the heart rate was low.

Four electrocardiographic leads were continuously monitored during the test and for 20 min during the recovery. Criteria for stopping the test were:

(a) maximal dose of dobutamine;
(b) maximal heart rate for the patient’s age;
(c) angina and/or dyspnoea;
(d) new wall motion abnormalities;
(e) significant non-sustained arrhythmias (frequent ventricular premature beats; >two couplets per step; atrial tachycardia/fibrillation runs);
(f) sustained ventricular and supraventricular arrhythmias;
(g) hypotension and/or bradycardia;
(h) significant side effects.

Rest, low and high dose dobutamine images displayed in quad screen format and videotape recordings were analysed by two experienced observers who were blind to the result of the coronary angiography. A standard left ventricular, 16-segment model was used and segmental wall motion was graded using a five point scale: 1 = normal; 2 = hypokinetic; 3 = severely hypokinetic; 4 = akinetic; 5 = dyskinetic.

By combining wall motion at rest and during low and high dose dobutamine, we identified four wall motion responses of dyssynergic segments at baseline: (i) improvement during both low- and high-dose dobutamine; (ii) biphasic response: improvement during low dose and worsening during high dose dobutamine; (iii) direct worsening of wall motion either during low- or high-dose dobutamine; (iv) no change–fixed dyssynergy during the entire test. Segments were classified as viable non-ischaemic when they showed the first pattern, viable ischaemic when they showed the second and third patterns, and as scar when they showed the fourth response. Patients with at least two ischaemic or scarred segments were diagnosed as having ischaemic dilated cardiomyopathy. Vascular territories, corresponding to the three major coronary artery branches, were assigned as described previously for both ultrasound and nuclear imaging.

To assess global left ventricular function, a wall motion score index was calculated by adding the indi-
vidual segment scores and dividing the resulting sum by the number of segments. Left ventricular ejection at rest and during dobutamine was also assessed using the apical views and applying the modified Simpson’s rule. A sphericity index was calculated as the ratio between the long axis and the short axis of the left ventricle in a four-chamber apical view.

**Thallium-201 SPECT**

Within 72 h of the echo-dobutamine test, patients underwent a bicycle symptom-limited exercise test in a semi-upright position with increasing workloads of 25 watts every 3 min. At the peak of the test, 100 MBq Thallium-201 were administered into an antecubital vein. Initial images were acquired immediately after exercise using a large field view, single crystal, rotating gamma camera (Elscint Apex SP-6), equipped with a ‘general purpose’ low energy collimator (window of 15% on peak of 68–80 KeV and additional window of 10% on peak of 167 KeV of Thallium-201). The ‘Step and Shoot’ modality was used (at 6-degree angular steps, 30 images of 40–50 seconds were acquired over a 180-degree arc from the 30-degree anterior oblique position to the 60-degree oblique posterior position); matrix of 64 × 64 pixels. Using the same modality, an additional dose of 30 MBq of Thallium-201 was administered at rest and reinjection images were acquired 180–240 min later.

Transaxial reconstruction was performed with ‘filtered backprojection’ (Butterworth filters with 0.35 cut off, of order 5/0). Reconstructed tomographic slices were then reoriented in the standard horizontal long and short axes and vertical long axis. From a short axis slice, circumferential profile analysis images were analysed by reconstructing a polar map (bull’s eye). To simplify the comparison with the echographic method, the polar map was subdivided into 16 segments corresponding to those evaluated by echocardiography. Quantitative analysis of the computed data obtained for each segment (normalized for the number of pixel components), was performed on the percentage value of uptake in segments with maximal activity. A ‘cut off’ of 55% of maximum was used to evaluate viability. Transient myocardial ischaemia was diagnosed when at least two segments showed severe perfusion defects (<55% of maximum uptake) after stress and increased uptake (partial or total) at rest (reperfusion). Regions with irreversible severe perfusion defects in two or more segments were considered to be scarred.

As for dobutamine stress echocardiography, patients who had at least two ischaemic or scarred segments were diagnosed as having ischaemic dilated cardiomyopathy.

**Statistical Analysis**

Data are expressed as mean values ± 1 S.D. Proportions of parametric variables between two groups of patients with and without coronary disease were compared using Student’s t-test or unpaired data. Fisher’s exact test was used to compare categoric variables. The agreement between techniques was assessed by calculating the k value.

**Results**

**Coronary Angiography**

Thirteen patients had normal coronary arteries, one had non-significant coronary lesions, and 23 had significant coronary artery disease. Single vessel disease was present in three patients; two-vessel disease in six patients and the remaining 14 had triple-vessel disease.

**Clinical and ECG data**

As shown in Table 1, age, left ventricular dysfunction, presence of bundle branch block and frequency of
principal risk factors, except for family history of coronary artery disease, did not differ between the two groups. Only a history of myocardial infarction and the presence of Q waves >40 ms in the ECG were significantly more frequent in patients with ischaemic dilated cardiomyopathy (Table 1). Their sensitivity was, however, low (Fig. 1). Of the two patients who had previously had a MI and were classified as patients with non-ischaemic DCM, one had entirely normal coronary arteries and one had minimal (<30% diameter) lesions of the left anterior descending coronary artery.

Baseline Echocardiography

Patients with ischaemic dilated cardiomyopathy had akinetic or dyskinetic segments more frequently than those with non-ischaemic dilated cardiomyopathy (Table 2). However, the specificity of these severe wall motion abnormalities for identifying ischaemic dilated cardiomyopathy was low, since they were also seen in five of 14 patients with non-ischaemic dilated cardiomyopathy (Fig. 1). The left ventricle tended to be less spherical in patients with ischaemic dilated cardiomyopathy than those with non-ischaemic disease, but the difference was of borderline statistical significance.

Dobutamine Stress Echocardiography

High dose dobutamine stress echocardiography was performed in all patients without major complications.

Table 2. Baseline and dobutamine-stress echocardiography.

<table>
<thead>
<tr>
<th></th>
<th>Ischaemic DCM n=23</th>
<th>Non-ischaemic DCM n=14</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wall motion score index</td>
<td>2.8 ± 0.4</td>
<td>2.4 ± 0.5</td>
<td>0.05</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>26 ± 9</td>
<td>27 ± 9</td>
<td>ns</td>
</tr>
<tr>
<td>Left ventricular end diastolic volume (ml)</td>
<td>177 ± 64</td>
<td>207 ± 70</td>
<td>ns</td>
</tr>
<tr>
<td>Regional severe dyssynergy (n) (≥2 akinetic/dyskinetic segments)</td>
<td>20</td>
<td>5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sphericity index of left ventricle</td>
<td>1.5 ± 0.2</td>
<td>1.3 ± 0.1</td>
<td>ns</td>
</tr>
<tr>
<td>Dobutamine maximal dose (µg/kg/min)</td>
<td>25 ± 8</td>
<td>29 ± 8</td>
<td>ns</td>
</tr>
<tr>
<td>Maximal systolic blood pressure (mmHg)</td>
<td>119 ± 32</td>
<td>131 ± 24</td>
<td>ns</td>
</tr>
<tr>
<td>Maximal heart rate (beats/min)</td>
<td>114 ± 29</td>
<td>114 ± 19</td>
<td>ns</td>
</tr>
<tr>
<td>Ischaemic response (n) (biphasic response or direct worsening)</td>
<td>17</td>
<td>2</td>
<td>0.05</td>
</tr>
<tr>
<td>Ischaemic response and/or scar (n)</td>
<td>23</td>
<td>2</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1; WMSI: wall motion score index.

Table 3. End points of dobutamine stress echocardiography.

<table>
<thead>
<tr>
<th></th>
<th>Ischaemic DCM n=23</th>
<th>Non-ischaemic DCM n=14</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial ischaemic/angina (n)</td>
<td>13</td>
<td>2</td>
<td>0.001</td>
</tr>
<tr>
<td>Arrhythmias (n)</td>
<td>5</td>
<td>5</td>
<td>ns</td>
</tr>
<tr>
<td>Side effects (n)</td>
<td>3</td>
<td>3</td>
<td>ns</td>
</tr>
<tr>
<td>Maximal dose (n)</td>
<td>2</td>
<td>3</td>
<td>ns</td>
</tr>
<tr>
<td>Target heart rate (n)</td>
<td>0</td>
<td>1</td>
<td>ns</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
The maximum dose of dobutamine was 25 \( \pm \) 9 mg/kg/min. Dobutamine dose, heart rate and blood pressure were not different between the two groups (Table 2). As shown in Table 3, the test was frequently terminated because an ischaemic endpoint was achieved. Ischaemia required administration of intravenous beta-blockade in three patients, while in the remaining 12 patients spontaneous resolution of ischaemia occurred after interrupting the dobutamine infusion. Non-sustained arrhythmias were fairly frequent end points of the test in both groups, but no patients experienced sustained arrhythmias.

At baseline, regional wall motion score index was slightly worse in patients with ischaemic dilated cardiomyopathy than in those with non-ischaemic dilated cardiomyopathy. However, the values overlapped greatly between the two groups. During high-dose dobutamine, wall motion score index improved in patients with non-ischaemic dilated cardiomyopathy, but markedly worsened in those with ischaemic dilated cardiomyopathy (Fig. 2). Thus, at high-dose dobutamine wall motion score index was markedly different (virtually without overlap) in the two groups.

An ischaemic response and/or a scar in at least two segments, as detected by dobutamine stress echocardiography, identified all 23 patients with ischaemic dilated cardiomyopathy. Two patients with non-ischaemic DCM had an ischaemic response. Therefore, the sensitivity of this sign was 100% and its specificity 86% (Fig. 1).

**Thallium-201 SPECT**

Symptom limited bicycle exercise test was performed in all patients without major complications. Exercise tolerance, maximal heart rate and blood pressure were similar in both groups. Table 4 sets out the end points of the tests. Thallium-201 SPECT showed an ischaemic response in 20 of the 23 patients with ischaemic dilated cardiomyopathy, and in three of the 14 patients without coronary artery disease (Table 4). Severe perfusion defect, either fixed (scar) or reversible (ischaemia) during stress, increased the sensitivity of TL SPECT up to 92% with a specificity of 69% (Fig. 1). Three of the four false positive results were in patients who had a left bundle branch block on ECG. The fourth had a fixed perfusion defect at rest (scar), normal coronary artery and an history of previous myocardial infarction. This particular patient had also been mistakenly diagnosed by dobutamine, making him the only double false positive in the two tests.

**Agreement between Dobutamine Stress Echocardiography and Thallium-201 SPECT**

Figure 3 shows the relation between the diagnoses provided by dobutamine stress echocardiography and Thallium-201 SPECT. The criterion used for diagnosing

<table>
<thead>
<tr>
<th>Wall motion score index</th>
<th>Baseline</th>
<th>Low-dose</th>
<th>Peak-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ns</td>
<td>2</td>
<td>2.5</td>
<td>3</td>
</tr>
</tbody>
</table>

\[ P = 0.5 \]

\[ P < 0.001 \]

**Table 4.** Bicycle stress test end-points and Thallium-201 SPECT.

<table>
<thead>
<tr>
<th></th>
<th>Ischaemic DCM n=23</th>
<th>Non-ischaemic DCM n=14</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue/dyspnoea (n)</td>
<td>10</td>
<td>6</td>
<td>ns</td>
</tr>
<tr>
<td>Angina (n)</td>
<td>11</td>
<td>6</td>
<td>ns</td>
</tr>
<tr>
<td>Target heart rate (n)</td>
<td>2</td>
<td>2</td>
<td>ns</td>
</tr>
<tr>
<td>Maximal work capacity (watts)</td>
<td>77 ± 26</td>
<td>84 ± 33</td>
<td>ns</td>
</tr>
<tr>
<td>Maximal systolic blood pressure (mmHg)</td>
<td>150 ± 28</td>
<td>160 ± 31</td>
<td>ns</td>
</tr>
<tr>
<td>Maximal heart rate (beats/min)</td>
<td>128 ± 20</td>
<td>133 ± 21</td>
<td>ns</td>
</tr>
<tr>
<td>Perfusion defects at rest (n)</td>
<td>20</td>
<td>3</td>
<td>0.001</td>
</tr>
<tr>
<td>Ischaemic response (n)</td>
<td>20</td>
<td>3</td>
<td>0.0001</td>
</tr>
<tr>
<td>(reversible perfusion defects in ( \geq 2 ) segments)</td>
<td>22</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Ischaemic response and/or scar (n)</td>
<td>22</td>
<td>4</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
ischaemic dilated cardiomyopathy by both techniques was the occurrence of an ischaemic response and/or the demonstration of a scar. Thirty-two patients were concordantly classified (agreement 86%, $k=0.73$). The detection of an individual narrowed coronary artery by each technique was: Thallium-201 SPECT–sensitivity 90%, specificity, 73%; dobutamine stress echocardiography–sensitivity 80%; specificity, 79%.

### Discussion

This study confirms that ischaemic and non-ischaemic dilated cardiomyopathy can be clinically indistinguishable, and that electrocardiograms and echocardiograms are of limited value in differentiating the two conditions, but it also shows that both low–high dose dobutamine stress echocardiography and Thallium-201 SPECT with a stress-reinjection protocol are highly sensitive and moderately specific techniques for detecting coronary artery disease in patients with dilated cardiomyopathy and heart failure.

The excellent diagnostic accuracy of dobutamine stress echocardiography, using the high-dose dobutamine-atropine protocol, in detecting coronary artery disease in various groups of patients with normal or moderately depressed left ventricular dysfunction has been proved by several studies\[14 - 16\] and this technique is now widely used such patients whenever an exercise test is unfeasible or provides equivocal results. Dobutamine stress echocardiography has been extensively used in patients with severe left ventricular dysfunction and known coronary artery disease to identify and quantify viable and ischaemic myocardium and to predict its functional recovery after revascularization\[17\]. However, limited data is available regarding the diagnostic value of dobutamine stress echocardiography for detecting coronary artery disease in patients presenting with dilated left ventricle and diffuse wall motion abnormalities of unknown origin\[18 - 19\].

It is believed that, within these patients, those with non-ischaemic dilated cardiomyopathy should have more spherical and homogeneously hypokinetic left ventricles, whereas heterogeneous akinetic or dyskinetic areas would suggest ischaemic dilated cardiomyopathy\[20\]. These beliefs were in part confirmed by our results, but left ventricular shape was too variable in the two groups to distinguish between patients with ischaemic and non-ischaemic dilated cardiomyopathy and, in line with the results of a previous study\[27\], akinetic segments at baseline were present in up to 40% of patients with non-ischaemic dilated cardiomyopathy.

Although the contractile response to $\beta$-adrenergic stimulation is generally reduced in patients with dilated cardiomyopathy and heart failure\[21\], dobutamine infusion produced a marked, progressive improvement of global left ventricular wall motion in patients who had normal coronary arteries, while in those with ischaemic dilated cardiomyopathy, wall motion either deteriorated or did not change from low to peak dose of dobutamine infusion. Similar results were reported by Sharp et al\[18\]. Furthermore, in addition, regional wall motion analysis revealed that dobutamine produced either wall motion deterioration (ischaemic response) or no change (scar) in at least one area of the left ventricle (corresponding fairly well to the site of the coronary stenosis) in all patients with ischaemic dilated cardiomyopathy. In contrast, patients who had non-ischaemic dilated cardiomyopathy showed a sustained improvement of most segments during dobutamine. The reason why two patients in the non-ischaemic dilated cardiomyopathy group had false positive results may be explained by the reduced coronary flow reserve which occurs in some patients with dilated cardiomyopathy even in the absence of significant coronary artery stenosis.

Several studies have investigated the value of nuclear techniques for differentiating between ischaemic and non-ischaemic dilated cardiomyopathy providing conflicting results, possibly because of differences in stress protocols, radiotracers and radionuclide imaging techniques. In our study, with an exercise-reinjection-rest protocol and quantitative analysis, the nuclear technique was highly sensitive for diagnosing and localizing coronary artery disease. Despite the fact that we applied a rather restrictive criterion diagnosing ischaemic dilated cardiomyopathy (fixed or reversible, severe and relatively large perfusion defects), four false positive diagnoses were made. Three of these patients had left bundle branch block, which is a well known cause of false positive septal and anterior perfusion defects, particularly after exercise. According to a recent report\[22\] the use of dobutamine in conjunction with Thallium-201 SPECT is associated with a higher specificity than exercise scintigraphy and should overcome this limitation.

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**Figure 3.** Agreement in ischaemic or non-ischaemic dilated cardiomyopathy (DCM) diagnosis between Thallium-201 SPECT and dobutamine stress echocardiography.
Other limitations of the present study need to be acknowledged. First, the number of patients with non-ischaemic dilated cardiomyopathy was small so that no firm conclusions regarding the comparison of the specificities of dobutamine stress echocardiography and Thallium-201 SPECT can be drawn. Second, the classification of patients into the two groups based on the presence of at least one >50% narrowing of coronary diameter is imprecise. In fact, on one hand a single coronary stenosis may not justify global left ventricular dysfunction and dilatation and, although the cardiomyopathy is classified as ischaemic, there is probably a co-existent non-ischaemic aetiology. On the other hand, the absence of significant coronary stenoses (particularly with a history of myocardial infarction) may be the result of late recanalization and does not, therefore, totally exclude ischaemic disease. Finally, dobutamine stress echocardiography was analysed visually. It is possible that new methods for quantifying wall motion or for assessing perfusion by means of echocardiographic contrast agents will improve the accuracy of dobutamine stress echocardiography in complicated cases.

Despite these limitations, this study demonstrates that both dobutamine stress echocardiography and exercise Thallium-201 SPECT are highly sensitive techniques for non-invasively identifying coronary artery disease in patients presenting with dilated cardiomyopathy and heart failure. This result may have practical implications. There is evidence that patients with ischaemic dilated cardiomyopathy and heart failure who have a sufficient amount of viable myocardium may gain relevant functional and survival benefits from myocardial revascularization, which means that this condition must be systematically searched for and diagnosed. Thanks to their high sensitivity, dobutamine stress echocardiography and Thallium-201 SPECT can be used to select patients to be submitted to coronary angiography: those with positive results should undergo invasive evaluation to confirm the diagnosis of ischaemia, while in those with negative results coronary angiography can probably be safely avoided.

Acknowledgments

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References