Dobutamine stress echocardiography

W. Krahwinkel, T. Ketteler, J. Gödke, J. Wolfertz, L. J. Ulbricht, I. Krakau and H. Gülker

Wuppertal Heart Centre, Department of Cardiology, University of Witten/Herdecke, Wuppertal, Germany

Dobutamine is a synthetic catecholamine with predominant β-stimulation. Its half-life is approximately 2 min. The positive chronotropic and inotropic effects of dobutamine induce myocardial ischaemia if significant coronary artery obstruction is present. Regional ischaemia produces regional wall motion abnormalities which can be detected by echocardiography. Most dobutamine stress protocols start at an infusion rate of 5 μg kg⁻¹ min⁻¹ and increase to a peak dose of 40 or 50 μg kg⁻¹ min⁻¹; to further increase heart rate, a bolus injection of 0.25–1.0 mg atropine is added. Test endpoints are the detection of new wall motion abnormalities, the occurrence of severe complications or achievement of the target heart rate. Viable myocardial regions have a positive inotropic reserve, which can be stimulated by dobutamine and detected by echocardiography. Indications for the use of dobutamine stress echocardiography are to prove stress-inducible myocardial ischaemia and to detect myocardial viability. The test should only be performed for the detection of stress-induced myocardial ischaemia if patients are unable to undergo exercise echocardiography, or if patients fail to reach their required test level in exercise echocardiography. (Eur Heart J 1997; 18 (Suppl D): D9–D15)

Key Words: Dobutamine stress echocardiography, coronary artery disease, stress-induced myocardial ischaemia, myocardial viability.

Introduction

Two-dimensional echocardiography is an accepted non-invasive method for evaluating global and regional left ventricular function. Left ventricular regional wall motion is analysed using the 16-segment model recommended by the American Society of Echocardiography11. Since the first report 10 years ago12, numerous investigations have been performed using dobutamine stress echocardiography. Today the method has become a useful and established diagnostic tool to indicate the presence of stress-inducible myocardial ischaemia in patients with known or suspected coronary artery disease and is valuable in the detection of myocardial viability.

Pharmacology

Dobutamine is a sympathomimetic agent with predominant β-receptor stimulation. Its effect on the β₁-receptor is more pronounced than on the β₂-receptor. The effects on α-receptors are minor. β-receptor stimulation causes positive inotropic, chronotropic and dromotropic effects on the heart. The peripheral arteries and the bronchial system react with dilatation. The half-life of the drug in the plasma is 2 min143.

Basic pathophysiological principles

Oxygen and metabolic supplies to the myocardium depend on coronary blood flow. Reduced coronary blood flow provides myocardial ischaemia as a result of oxygen and metabolite deprivation. Under resting conditions, basal coronary artery flow is maintained at normal levels until coronary artery stenosis becomes severe. Under conditions of stress, coronary blood flow normally increases, mediated by the increased demand for oxygen and metabolites. The ability of coronary arteries to increase coronary blood flow is reduced in significantly stenosed vessels. A 70% coronary artery stenosis is usually associated with reduced maximal coronary flow under stress conditions144. Myocardial alterations provoked by ischaemia demonstrate a typical pathophysiological continuum called ‘the ischaemic cascade’. At first, perfusion heterogeneity occurs, then metabolism is altered, followed by diastolic dysfunction, systolic dysynchrony, ECG changes and angina pectoris144. The purpose of echocardiography is to detect ischaemically induced regional systolic wall motion abnormalities.
Asynergic myocardial areas need not necessarily be irreversibly damaged or scarred. Brief coronary artery occlusion causes myocardial dysfunction; following subsequent reperfusion within a certain time contractile function has the potential to recover. This phenomenon is termed ‘stunned myocardium’. Chronic ischaemic myocardial dysfunction with the potential to restore contractile function after normalizing coronary blood flow is called ‘hibernating myocardium’. Stunned and hibernating myocardium have a positive inotropic reserve, which can be stimulated by dobutamine, and the improvement in wall motion can be detected by echocardiography.

**Dobutamine stress test**

In dobutamine stress testing, various similar test protocols are used. In the protocol used in our hospital and by many other investigators the dobutamine infusion is started at a dose of 5 µg kg⁻¹ min⁻¹ and increased in steps of 10, 20, 30, 40 µg kg⁻¹ min⁻¹ every 3 min. At peak dobutamine dose, 0.25 mg atropine is added as a bolus at intervals of 1 min up to a maximum dose of 1 mg (Fig. 1). The test is terminated if one of the test endpoints is reached. These are the detection of new wall motion abnormalities in more than one segment, an increase in end-systolic volume, reaching the target heart rate [(220 – age) x 0.85] or the occurrence of severe complications. In test protocols used by other investigators, the maximum dobutamine dose is set at 50 µg kg⁻¹ min⁻¹, or atropine is added at lower doses of dobutamine. To antagonize the cardiovascular effects of dobutamine a short lasting β-blocker, i.e. esmolol, can be given intravenously. During the test, regional and global left ventricular function are monitored by echocardiography, and heart rate and rhythm by continuous ECG. Every 3 min blood pressure is measured and a 12-lead ECG is registered. Images are acquired in a digital processed endless cineloop in our laboratory at rest, at low dose, at peak dose of dobutamine, and in the post peak period (Fig. 1). Cineloops in simultaneous on-line quad screen format are preferred. The entire stress echocardiographic examination, as well as specific views, can optionally be recorded on additional videotapes.

**Haemodynamic response to dobutamine infusion**

In a study group of 257 patients, we found that the heart rate remained constant at 5 and 10 µg kg⁻¹ min⁻¹ dobutamine. On average the heart rate increased at the 20 µg kg⁻¹ min⁻¹ step (Fig. 2). Mean systolic and diastolic blood pressures did not change significantly during the test within a certain blood pressure range (Fig. 3). Symptomatic hypotension was seen in one of 257 patients. In this study no test was terminated because of a hypertensive reaction. Several studies have shown a mild decrease in blood pressure in 5% to 20% of patients during the dobutamine test. In contrast to exercise where hypotension is a potential marker for severe coronary artery disease, dobutamine-induced hypotension is not a predictor of advanced coronary artery disease or an adverse prognosis. Consequently, a dobutamine stress echocardiographic study does not have to be terminated because of an asymptomatic, mild decrease in blood pressure.
Dobutamine stress echocardiography

Clinical value of dobutamine stress echocardiography in detecting myocardial ischaemia

In the diagnostic course of coronary artery disease, the first step in exercise testing should be a bicycle or treadmill exercise ECG. This should be followed by exercise echocardiography if the exercise ECG test result is inconclusive or a more accurate test is necessary in patients with a negative exercise ECG test. About 35% of the patients were unable to undergo exercise testing because of neurological, orthopaedic or vascular diseases, or failed to reach the required test level\(^{[11]}\). These patients are prime candidates for pharmacological stress echocardiography using dobutamine.

Indications for dobutamine stress echocardiography

Indications for dobutamine stress echocardiography are listed in Table 1.

Table 1 Indications for dobutamine stress echocardiography

<table>
<thead>
<tr>
<th>Indications</th>
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<tbody>
<tr>
<td>Suspected coronary artery disease</td>
</tr>
<tr>
<td>Non-diagnostic bicycle or treadmill exercise tests</td>
</tr>
<tr>
<td>Known coronary artery disease to define the ischaemic reaction before and after interventional or operative revascularization</td>
</tr>
<tr>
<td>Known coronary artery disease to assess the area of ischaemia</td>
</tr>
<tr>
<td>Risk stratification: before major surgery, post myocardial infarction</td>
</tr>
<tr>
<td>Detection of myocardial viability</td>
</tr>
</tbody>
</table>

Diagnosis of relevant coronary artery disease

Dobutamine stress echocardiography is more efficient in detecting significant coronary artery stenosis than exercise ECG and is comparable with myocardial perfusion scintigraphy. In comparison with coronary angiographic results, the overall sensitivity, specificity and accuracy of dobutamine stress echocardiography, with maximal doses of 40 $\mu$g . kg$^{-1}$. min$^{-1}$ dobutamine, is about 72–86%, 77–95% and 76–89%, respectively (Table 2). With lower dobutamine doses, diagnostic accuracy decreases\(^{[12]}\). Sensitivity is better in multivessel than in single-vessel disease (Tables 3 and 4) and higher in 70% than 50% diameter stenosis\(^{[13,14]}\). Maximum sensitivity seems to be obtained for ischaemic wall motion abnormalities in the area perfused by the left anterior descending coronary artery; however, there are some contradictory results\(^{[15,16]}\). The addition of atropine enhances the sensitivity of dobutamine stress echocardiography\(^{[17]}\). The incidence of myocardial ischaemia is reduced by $\beta$-blockade\(^{[18]}\). Special consideration must be given to patients with wall motion abnormalities at rest. Assumption that all wall motion abnormalities, even at rest, represent coronary artery disease reduces the specificity of dobutamine stress echocardiography in detecting coronary artery disease\(^{[19]}\). Whether the sensitivity in the detection of stress-induced myocardial ischaemia...
Table 2  Sensitivity, specificity and accuracy of dobutamine stress echocardiography in the detection of significant coronary artery stenosis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
<th>Patients (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beleslin et al.</td>
<td>82</td>
<td>77</td>
<td>82</td>
<td>136</td>
</tr>
<tr>
<td>Boccanelli et al.</td>
<td>86</td>
<td>94</td>
<td>87</td>
<td>109</td>
</tr>
<tr>
<td>Cohen et al.</td>
<td>86</td>
<td>95</td>
<td>89</td>
<td>70</td>
</tr>
<tr>
<td>Hoffmann et al.</td>
<td>79</td>
<td>81</td>
<td>80</td>
<td>64</td>
</tr>
<tr>
<td>Marwick et al.</td>
<td>72</td>
<td>83</td>
<td>76</td>
<td>217</td>
</tr>
<tr>
<td>Previtali et al.</td>
<td>79</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
</tbody>
</table>

*(+0.5-1.5 mg atropine).

Table 3  Dobutamine stress echocardiography: sensitivity for the detection of significant coronary artery stenosis in single-vessel disease

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sensitivity (%)</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beleslin et al.</td>
<td>82</td>
<td>108</td>
</tr>
<tr>
<td>Hoffmann et al.</td>
<td>78</td>
<td>27</td>
</tr>
<tr>
<td>Marwick et al.</td>
<td>66</td>
<td>68</td>
</tr>
<tr>
<td>Previtali et al.</td>
<td>62</td>
<td>24</td>
</tr>
</tbody>
</table>

\[x=75\%\].

Table 4  Dobutamine stress echocardiography: sensitivity for the detection of significant coronary artery stenosis in multivessel disease

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sensitivity (%)</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen et al.</td>
<td>94</td>
<td>35</td>
</tr>
<tr>
<td>Hoffmann et al.</td>
<td>81</td>
<td>21</td>
</tr>
<tr>
<td>Marwick et al.</td>
<td>77</td>
<td>74</td>
</tr>
<tr>
<td>Previtali et al.</td>
<td>91</td>
<td>33</td>
</tr>
</tbody>
</table>

\[x=84\%\].

Table 5  Dobutamine stress echocardiography in patients with rest wall motion abnormalities (RWMA)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients</th>
<th>Specificity (%)</th>
<th>Sensitivity (%)</th>
<th>No. of patients</th>
</tr>
</thead>
</table>
| Detection of CAD — lower specificity, if all wall motion abnormalities incl. RWMA were assumed to represent CAD
  Marcovitz et al. | All      | 66              | 96              | 141             |
  (Dobutamine dose — max 30 μg . kg⁻¹ . min⁻¹)
  Normal rest wall motion | 91       | 87              | 53              |
| Remotely diseased vessel — accuracy 83%
  Sawada et al.    | RWMA — remote vessel disease | 81       | 87              | 41              |
  (Dobutamine dose — max 30 μg . kg⁻¹ . min⁻¹)
  Normal rest wall motion | 89       | 85              | 55              |
| Diagnosis of stress-induced ischaemia
  Authors          | Suspected CAD | No. of patients | Post M1 | No. of patients |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Beleslin et al.</td>
<td>77%</td>
<td>59</td>
<td>89%</td>
<td>37</td>
</tr>
</tbody>
</table>
  (Dobutamine dose — max 40 μg . kg⁻¹ . min⁻¹)
| Hoffmann et al.  | Sensitivity   | 91%             | 50      | 63%            | 50             |

CAD=coronary artery disease; post M1=post-myocardial infarction (see text).
echocardiography is a valuable diagnostic tool, especially in patients unable to undergo exercise testing. Pre-operative dobutamine stress testing was performed in patients undergoing vascular surgery, including patients with aortic aneurysms and in a smaller number of patients undergoing general surgery. The reported results in the literature show that patients with new wall motion abnormalities, as revealed by dobutamine stress echocardiography before surgery, have a higher perioperative risk for cardiac events than those with a negative test result. The positive and negative predictive value of the test for peri-operative cardiac events were reported in a range of 20%–40% and 100%, respectively.

### Detection of viability

Dobutamine stress echocardiography can be used to detect myocardial viability and to predict functional improvement in viable myocardium after revascularization, with a sensitivity of about 80% and specificity of about 90%.[25-35] For further details see the article 'Detection of myocardial viability using stress-echocardiography' in this Supplement.

### Contraindications

The contraindications for dobutamine stress echocardiography are similar to those for other stress tests and are listed in Table 6.

### Complications and side effects

As with other stress tests in coronary artery disease, dobutamine stress echocardiography has a certain risk of serious complications. This risk is due to the coronary artery disease itself and to side effects of the drugs. In the reported studies no death, two myocardial infarctions and a small number of other serious complications occurred (Table 7). In our study group of 312 patients, the most serious complications could be managed only by test interruption. Arrhythmias take, with respect to frequency, first place in the list of serious complications; they include ventricular and supraventricular tachycardias (Tables 7 and 8), monomorphic and polymorphic ventricular and supraventricular extrasystolic beats, couplets, junctional and idioventricular rhythms, AV-block, rate-dependent left or right bundle branch block and relevant sinus bradycardia. Other cardiovascular complications and side effects are hypotension, vasovagal reactions and left ventricular intracavitary or outflow tract obstruction.[7,9,36,37,41]

In our experience coronary vasospasms have to be seen as another cardiac complication of dobutamine stress testing. In three of 1105 patients we documented severe angina pectoris, extensive new echocardiographic wall motion abnormalities and ischaemic ECG changes with abrupt onset and long duration despite application of antianginal drugs. In one patient a large area of left ventricular myocardium became hypo- and akinetic, suggesting significant stenosis of the left main stem; however, this patient failed to show any signs of atherosclerosis in coronary angiography and had a history of cerebral vasospasms. The two other patients showed atherosclerotic intracoronary plaques without significant coronary artery stenosis at coronary angiography and intracoronary ultrasound. We assume that a dobutamine-induced mediated vasospasm could have been responsible for the symptoms[38,39].

### Table 6 Contraindications for dobutamine stress echocardiography

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Acute myocardial infarction ≤4–10 days</td>
</tr>
<tr>
<td>Unstable angina pectoris</td>
</tr>
<tr>
<td>Manifest congestive heart failure</td>
</tr>
<tr>
<td>Severe, life threatening tachyarrhythmias</td>
</tr>
<tr>
<td>Severe valvular stenosis</td>
</tr>
<tr>
<td>Hypertrophic obstructive cardiomyopathy</td>
</tr>
<tr>
<td>Acute peri-/myocarditis, endocarditis</td>
</tr>
<tr>
<td>Aortic dissection</td>
</tr>
</tbody>
</table>

Reported data on the use of dobutamine stress echocardiography early (within 4–10 days) after acute myocardial infarction are very limited. In two studies with 37 and 59 patients, respectively, there were no complications; dobutamine was used up to a maximum of 40 µg · kg⁻¹ · min⁻¹[12,34].

### Table 7 Dobutamine stress echocardiography: serious complications

<table>
<thead>
<tr>
<th>Authors</th>
<th>Death</th>
<th>Myo. infarct (%)</th>
<th>VF (%)</th>
<th>s VT (%)</th>
<th>ns VT (%)</th>
<th>No. of patients (total)</th>
<th>Dob/A (maximum dose) (µg · kg⁻¹ · min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mertes et al[7]</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3-5</td>
<td>1-8</td>
<td>1118</td>
<td>30-50</td>
</tr>
<tr>
<td>Poldermans et al[9]</td>
<td>0</td>
<td>0</td>
<td>0.15</td>
<td>0.5</td>
<td>1.8</td>
<td>650</td>
<td>40</td>
</tr>
<tr>
<td>Picano et al[17]</td>
<td>0</td>
<td>0.07</td>
<td>0.07</td>
<td>1</td>
<td>1.8</td>
<td>2949</td>
<td>40</td>
</tr>
<tr>
<td>Krahwinkel et al[36]</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.9</td>
<td></td>
<td>312</td>
<td>40</td>
</tr>
<tr>
<td>Zahn et al[44]</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
<td>1.8</td>
<td></td>
<td>1000</td>
<td>50</td>
</tr>
</tbody>
</table>

*Complex ventricular tachyarrhythmias 4-7%.
Myo. infarct = Myocardial infarction; VF = ventricular fibrillation; VT = ventricular tachycardia; s = sustained; ns = non-sustained; Dob/A = dobutamine/atropine.
Non-cardiac side effects occur in about 10–25% of patients, but most of them are well-tolerated without requiring test termination. They include palpitations, nausea, vertigo, headache, tremor, anxiety, flush, urgency, allergic reactions, intravenous access malfunction and other rare side effects. In one study, atropine intoxication was reported following the application of 0.5–1.0 mg atropine in addition to the maximum dobutamine dose, causing discomfort and stupor in five of 2799 patients.

Some investigations focused on safety in specific groups. In elderly patients there was no difference in the occurrence of side effects compared with younger subjects. Advanced left ventricular dysfunction (ejection fraction ≤25%) did not seem to pose a higher risk for cardiac arrhythmias and does not represent a contraindication for dobutamine-atropine stress testing; however, a correlation was found between dobutamine stress-induced severe cardiac arrhythmias and a history of severe spontaneously occurring arrhythmias.

Because of the complications documented above, it is necessary to have emergency equipment immediately accessible and to be well-trained in emergency situations and of course in dobutamine stress echocardiography itself.

### Future aspects

At present, dobutamine stress testing using high-dose dobutamine infusion rates up to 40 μg . kg⁻¹ . min⁻¹ is contraindicated in the presence of severe valvular stenosis and hypertrophic obstructive cardiomyopathy. The value of dobutamine stress echocardiography for specific indications in valvular heart diseases, heart failure and cardiomyopathies is an object of ongoing investigations. Currently, only a few studies have been performed; some data are presented by Schwammenthal et al. in this Supplement. They suggest that the indications for the use of this test may be expanded in the near future.

### Conclusions

Dobutamine stress echocardiography is a valuable diagnostic tool in patients with suspected or known coronary artery disease for the detection of myocardial ischaemia and of myocardial viability. The test is especially useful in patients who cannot exercise adequately. Dobutamine stress echocardiography is a safe method with only few contraindications.

### References


