Detection of myocardial viability using stress echocardiography

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Asynergic myocardial regions in patients with coronary artery disease can be viable. They may have the ability to improve their function after restoring coronary blood flow. Asynergic but viable myocardial regions have a positive inotropic reserve which can be stimulated by catecholamines. Because echocardiography is an established method for evaluating regional left ventricular function, it has the potential to detect the inotropic response of asynergic myocardial regions. In the clinical setting, prediction of left ventricular functional improvement after revascularization is particularly important. Dobutamine stress echocardiography is the most frequently used stress echocardiographic test for detection of myocardial viability. Dobutamine is infused at low rates of 2.5 to 20 \mu g \cdot \text{kg}^{-1} \cdot \text{min}^{-1} to detect myocardial viability. This paper reports on the sensitivity and specificity of the method for the detection of viability and its usefulness for prediction of left ventricular functional improvement after revascularization.

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Key Words: Myocardial viability, dobutamine stress echocardiography, stunned myocardium, hibernating myocardium, left ventricular functional improvement following revascularization.

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Introduction

Clinical cardiologists used to define asynergic myocardial regions in severe coronary artery disease as scar. This traditional judgement is erroneous, as asynergic myocardial regions following myocardial ischaemia may be viable and may have the potential to recover function. Because two-dimensional echocardiography can detect regional myocardial wall motion, the echocardiographic approach appears to be valuable in diagnosing viability. This paper reports on the use of stress echocardiography as a diagnostic tool to evaluate myocardial viability in asynergic myocardial regions in patients with coronary artery disease.

Pathophysiological basis

Myocardial ischaemia following brief coronary artery occlusion can cause loss of regional contraction\cite{1}, but this is not always an all-or-nothing response with myocardial necrosis and irreversible myocardial damage. In 1982 Braunwald et al.\cite{2} described the ischaemic process after brief coronary occlusion as 'hit, run and stun': myocardial ischaemia acutely affects myocardial function (hit); after reestablishing myocardial perfusion (run) the myocardial function is impaired for a prolonged period. This prolonged, post-ischaemic ventricular dysfunction is called 'stunned myocardium'. Stunned myocardium is viable and able to recover its function; this holds also true for 'hibernating myocardium' as defined by Rahimtoola et al. in 1985\cite{3}; the term hibernating myocardium means viable myocardium in regions which are insufficiently perfused at rest and recover function after reestablishing adequate coronary blood flow. Hibernating and stunned myocardium have a positive inotropic reserve, which is in contrast to irreversibly damaged myocardium\cite{4}, i.e. necrosis or scar (Table 1).

<table>
<thead>
<tr>
<th>Table 1 Characteristics of clinical 'hibernating' and 'stunned' myocardium</th>
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<td>Wall motion abnormalities</td>
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The recruitment of this positive inotropic response can be provoked by nitroglycerin, catecholamines or by postextrasystolic potentiation\textsuperscript{[3,5-7]}. In echocardiography, chronic ischaemic (hibernation) and post-ischaemic (stunning) left ventricular dysfunction appear as severe wall motion abnormalities at rest. Stress echocardiography aims at detecting a stimulated positive inotropic response in segmental wall motion. The positive inotropic response leads to an improvement in impaired regional wall motion.

**Stress echocardiographic methods**

The most frequently used echocardiographic test of myocardial viability is dobutamine stress echocardiography. In this test low-dose dobutamine stimulation, without a marked increase in heart rate, is used to unmask myocardial viability. Dipyridamole stress echocardiography is an alternative test. The efficacy of the vasodilator dipyridamole is probably linked to the inotropic effect of increased coronary flow. This so-called 'Gregg phenomenon' also seems to exist in reduced coronary flow\textsuperscript{[8-10]}. However, the available literature on the use of dipyridamole stress echocardiography for detection of myocardial viability is limited.

**Dobutamine stress-echocardiography**

At present two different groups of dobutamine test protocols are used; in the first group, dobutamine is given at a low dose ranging from 2.5 or 5 \( \mu \)g kg\(^{-1}\) min\(^{-1}\) up to 10 or 20 \( \mu \)g kg\(^{-1}\) min\(^{-1}\). The second group of test protocols provides high doses of dobutamine (up to 40 \( \mu \)g kg\(^{-1}\) min\(^{-1}\)), with the optional addition of atropine, and also includes low infusion rates of dobutamine. Both groups of test protocols can detect myocardial viability. Pathophysiological findings in a short-term hibernation animal model demonstrated that provocation of increased severity of ischaemia produces irreversible myocardial damage\textsuperscript{[11]}. These findings have been put forward as one argument for using dobutamine at only low infusion rates, because the heart rate does not significantly increase, thus avoiding provoking ischaemia. But this short-term hibernating animal model cannot be easily transferred to human pathophysiological conditions. Another reason for low-dose testing is the shorter test duration. A recent investigation using a high-dose of dobutamine for testing viability in humans failed to show any myocardial enzymatic damage\textsuperscript{[12]}. This is important, because the high-dose test protocols yield more information: they not only demonstrate viability at low doses of dobutamine, they also show ischaemic worsening of myocardial wall motion at high doses of dobutamine within the same or other myocardial regions caused by heart rate increases during the higher dobutamine dosage. Improvement in wall motion at low doses followed by impairment of wall motion at high doses within the same myocardial region during dobutamine stimulation is called a 'biphasic response' and seems to have the highest predictive value for functional recovery of clinical hibernating myocardium after revascularization\textsuperscript{[13]}. Whether this biphasic response detects actual hibernation or repetitive stunning\textsuperscript{[9]} associated with stress-induced ischaemia caused by coronary artery stenosis (e.g. after thrombolysis) has not been conclusively established. However, this is of minor importance for clinical decision making with respect to revascularization; in this process the detection of coronary lesions, which could benefit from interventions, is the major focus.

In our stress echocardiography laboratory we use a high-dose dobutamine stress protocol. It begins with 5 \( \mu \)g kg\(^{-1}\) min\(^{-1}\), with increases in dose every 3 min in steps 10, 20, 30, 40 \( \mu \)g kg\(^{-1}\) min\(^{-1}\), with the addition of 0.25-1.0 mg atropine until a test endpoint is reached. Test endpoints are the detection of new wall motion abnormalities in >1 segment with a decrease in wall motion scoring of >1, reaching the target heart rate \((220 - \text{age}) \times 0.85\), or the occurrence of complications. During the whole low-dose phase, improvement in segmental wall motion has to be checked carefully, using a side-by-side simultaneous quad screen technique, in order to detect viability before heart rate increases significantly. Viability is defined as an improvement in wall motion score \( \geq 1 \) in \( \geq 1 \) segment in a 4-grade score system with normokinesia=1, hypokinesia=2, akinesia=3 and dyskinesia=4. Other investigators subdivided hypokinesia into mild and severe hypokinesia resulting in a 5-grade score system.

**Clinical impact of detection of viability**

The evidence of viability predicts post-revascularization improvement of left ventricular function\textsuperscript{[13,16]}. There is an inverse relationship between mortality rates and reduction of left ventricular function. In the GISSI-2 study this was shown in 2813 patients for the 6 month mortality rate and in echocardiographically measured left ventricular ejection fraction within 2 weeks after thrombolysed myocardial infarction (Fig. 1); mortality rates were mainly greater in patients with left ventricular ejection fraction below 40\%\textsuperscript{[14]}. Some limited prognostic data are available in the literature concerning patients with advanced coronary artery disease, impaired left ventricular function and a positive viability marker based on positive fluorodeoxyglucose (FDG) positron emission computed tomography (PET).\textsuperscript{[15-18]} The authors concluded, after a follow-up period of 12 to 36 months, that detection of viability predicts more cardiac events. Evidence of viability was associated with a significantly poorer prognosis\textsuperscript{[19]} and a reduced survival rate\textsuperscript{[15]} in patients in whom revascularization had not been performed. Similar results were recently provided by Williams \textit{et al.} using dobutamine stress echocardiography\textsuperscript{[19]}, in their study on 130 patients with a
Detection of myocardial viability

20% Si10 - (< 30%)
(30-39%)
40-49%
50-59%
≥ 60%
Not available

49% (50-59%)

Mortality % (deaths/total)
15.2 (25/164)
8.6 (35/405)
2.2 (17/772)
1.3 (12/916)
1.1 (6/556)
3.6 (264/7406)

LVEF

Echocardiographic ejection fraction (%)

Figure 1  Plot of 6 months all-cause mortality in five categories of echocardiography measured left ventricular ejection fraction. (Reprinted with permission from Volpi et al., and the American Heart Association.)

follow-up of 16 ± 8 months, the patients with a positive test for ischaemia or viability had a worse prognosis (Fig. 2)[19]. Because the diagnosis of myocardial viability and the prediction of left ventricular improvement after revascularization seem to have an important clinical impact, Thomas and Topol articulated it as 'wanted: dead or alive'[20]. However, trials analysing the prognostic value of myocardial viability from the data of large numbers of patients are not available. Furthermore, there is no information indicating the 'minimum amount of viable myocardium' to have an impact on prognosis.

Diagnostic value of dobutamine stress-echocardiography

Before considering the diagnostic value of a new method we must define the point of reference to prove this method. The point of reference in the diagnosis of viability is improvement of impaired left ventricular function. In hibernating myocardium, ventricular function improves after revascularization and in stunned myocardium ventricular function improves in the course of time. Sensitivity for detecting myocardial viability in patients with coronary artery disease using dobutamine stress echocardiography in relationship to post-revascularization improvement of ventricular function is about 80% (74-86%). Specificity is about 90% (86-95%)[10,13,21-23]. In one study, sensitivity and specificity for detection of viability after thrombolysis were only 79% and 68%, respectively[24] (Table 2). Sensitivity and specificity of dobutamine stress echocardiography were 82-94% and 80-92%, respectively[25-29] with respect to segmental wall motion analysis and to improvement of every left ventricular segment after revascularization (Table 3). These data were obtained using transthoracic echocardiography.

Few data are available on the use of transoesophageal echocardiography. This technique often has a better image quality, and therefore seems to be superior at detecting viability. Baer et al. reported a sensitivity of 91% and a specificity of 100% in their study[30]. However, despite its better image quality, transoesophageal echocardiography has the disadvantage of being invasive.

Nuclear medicine tests

Many scintigraphic studies with FDG-PET, or thallium-201 in various settings, have been reported. They demonstrated accurate results in the detection of viability and the prediction of left ventricular recovery[22,25,27,30,31]. FDG-PET is currently reputed to be the
definitive non-invasive imaging method. However, recently some small studies found that scintigraphic techniques had a low specificity in predicting myocardial recovery [21-25,32-33]. The assumption was that small islands of viable myocytes in a predominantly infarcted region were not capable of functional improvement after revascularization [21-25].

Experience at the Wuppertal Heart Centre

We studied the diagnostic value of dobutamine stress echocardiography for detection of viability and prediction of left ventricular improvement after revascularization.

Patients studied

We examined 26 patients, 20 men and six women, with an average age of 56 years (range: 36–74 years). Twenty-four patients had a history of myocardial infarction, 17 patients had an anterior, six a posterior and one an anterior and posterior myocardial infarction. The mean period after myocardial infarction was 7 months (range 0.5–58). Successful coronary angioplasty (LAD 14, RCX 5, RCA 4) was performed in 23 patients; three patients underwent aortocoronary bypass grafting.

Methods

Left heart catheterization, including coronary angiography, a left ventriculogram and echocardiography at rest, were performed prior to revascularization. In all patients, impaired regional or global left ventricular function and coronary artery disease with a diameter stenosis ≥75% (often ≥90%) of the corresponding artery were demonstrated. A dobutamine test was performed to detect viability and a biphasic response of segmental wall motion, as described above. After revascularization, left ventricular function was analysed 3 and 6 months later using echocardiography. Three months after revascularization a left ventriculogram was performed in patients who had had coronary angioplasty. Left ventricular function was compared before and after revascularization. At the time of the stress echocardiographic test, a scintigraphic investigation was performed. In 23 patients, we used a thallium-201/technetium-99m sestamibi rest-test protocol with thallium as a metabolic and technetium as a perfusion marker. The single photon emission tomography (SPECT) examination was done 1 h after radionuclide...
Results and discussion

Dobutamine stress echocardiography proved useful in the diagnosis of myocardial viability and the prediction of left ventricular improvement after revascularization. With respect to left ventricular improvement, we found a sensitivity of 94%, a specificity of 70%, an accuracy of 85%, a positive predictive value of 83% and a negative predictive value of 88% in all 26 patients (Table 4).

As regards left ventricular improvement after revascularization, we calculated for dobutamine stress echocardiography vs thallium/technetium scans a sensitivity of 93% vs 60%, a specificity of 88% vs 38%, a positive predictive value of 93% vs 64% and a negative predictive value of 88% vs 33% (n = 23) (Table 5). Comparing FDG/technetium SPECT with dobutamine stress echocardiography in seven patients we found a correct prediction of left ventricular improvement in three patients with FDG/technetium SPECT (three FDG positive patients without ventricular recovery) and in five patients with dobutamine stress echocardiography. Our stress echocardiographic data corresponded well to other reported results (Table 3) on dobutamine stress echocardiography. Results obtained by scintigraphic scans as regards prediction of left ventricular improvement were less impressive. In particular, the sensitivity of the thallium/technetium SPECT scan was lower in our investigation than reported in the current literature21,22,27,30,34. These reported studies used other scintigraphic test protocols.

Conclusions

Dobutamine stress echocardiography is a valuable diagnostic method for detection of myocardial viability and prediction of left ventricular functional improvement following revascularization. Further work is needed to establish its position for detecting viability in comparison to established thallium or FDG protocols.

References
