Stress echocardiography for assessing myocardial ischaemia and viable myocardium

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The electrocardiographic (ECG) ST segment response to exercise is perhaps the most commonly used functional test for the assessment of coronary artery disease. However, it has important limitations in the evaluation of myocardial ischaemia for two reasons. First, according to the theory of the ischaemic cascade, ECG changes and symptoms are preceded by flow heterogeneity followed by the development of regional myocardial dysfunction. Thus, unless the patient exercises to the level at which ECG changes occur, demand driven myocardial ischaemia may not occur. Second, resting ECG abnormalities may render changes occurring during stress uninterpretable. Furthermore, the presence of systemic hypertension, even in absence of any resting ECG abnormalities, may result in a false positive diagnosis of coronary artery disease. In a recent study only 35% of 1814 consecutive patients referred for stress testing had an interpretable ECG and a successful maximal exercise.

Echocardiography is currently the most widely used technique for the assessment of structure and function of the heart. Occurrence of abnormal regional systolic wall thickening during stress is perhaps the most specific sign of myocardial ischaemia. Echocardiography has been used during stress to assess the occurrence of myocardial ischaemia since the late 1970s. It was not until the advent of modern 90° scanners, however, together with the development of digital frame grabbing devices, that stress echocardiography became a practical diagnostic tool. Data analysis may be performed off line by review of recorded images from videotapes. This method requires that each view be recorded for a relatively long period and does not allow side by side comparison of resting versus peak stress images. In addition, respiratory artefacts, especially during dynamic exercise and translation motion of the heart during rapid heart rate, make interpretation very difficult. Recent stress echocardiographic studies have used digital acquisition techniques that enable high quality cardiac cycle from each image plane to be digitised and stored in a continuous loop format. The digitised recording of rest and stress images can then be simultaneously displayed in a quad screen format for analysis. Thus, the combination of improved transducer technology and digital methodologies has resulted in obtaining diagnostic images by most echocardiography laboratories in 90–100% of patients.

Definition of abnormal response to stress

A normal response to stress on echocardiography consists of an increase in systolic wall thickening and a reduction in cardiac volume (fig 1). During ischaemia, the systolic wall thickening is reduced in the ischaemic region with or without an overall increase in cardiac volume (fig 2). Failure to observe an increase in systolic wall thickening during stress, however, should not necessarily be regarded as a marker of ischaemia. Crouse et al correlated exercise echocardiography with coronary angiography in 228 patients. Systolic wall thickening was classified as normal only if the segment showed increased thickening after exercise. This resulted in a high sensitivity (97%) and an unacceptably low specificity (64%) for the detection of coronary artery disease. Failure to increase systolic wall thickening is not specific for coronary artery disease as it can also occur in cardiomyopathy, hypertensive heart disease, β blocker therapy, and a low workload. In the presence of abnormal resting systolic wall thickening, worsening systolic thickening is also a marker of myocardial ischaemia.

Several authors have suggested that stress echocardiography may fail to identify

Figure 1 Digitised quad screen display of normal dobutamine stress echocardiography. All images are obtained in short axis at end systole. (Upper left) rest, (upper right) during low dose of dobutamine, (lower left) high dose dobutamine, (lower right) recovery. Note the progressive increase in myocardial thickening with marked reduction in cardiac volumes. This patient had normal coronary arteries.
inducible ischaemia in regions of resting akinesia because of previous myocardial infarction, and that radionuclide perfusion techniques may be superior to echocardiography for detecting ischaemia in such patients.\textsuperscript{8,11} Pierard et al.\textsuperscript{12} observed that some of these infarcted segments showed an early improvement at low dose dobutamine followed by late deterioration at peak dose during dobutamine stress. These segments were mostly subtended by critically stenosed infarct related artery. In a recent study,\textsuperscript{13} it was observed that the presence or absence of this biphasic response (fig 3) closely agreed with the presence or absence of reversible perfusion defects (radionuclide marker of ischaemia) in regions of severe resting dysynergy. Thus, identification of biphasic response during dobutamine stress testing may enhance the detection of myocardial ischaemia in regions with severe resting myocardial dysfunction.

Methods of stress echocardiography

EXERCISE ECHOCARDIOGRAPHY

Most studies employing exercise echocardiography have used treadmill or bicycle exercise. Each form of exercise has its advantages and disadvantages when used in conjunction with echocardiography. The advantage of treadmill exercise is that it is widely used, it is the most standardised and readily accepted by patients. However, when treadmill exercise is used, imaging is only performed before and immediately after exercise because of the difficulties in imaging in the upright position. The use of immediately post-exercise imaging is based on observations that exercise induced regional myocardial dysfunction persists between one and five minutes after exercise, and may persist longer in patients with multivessel disease.\textsuperscript{14-16} Nevertheless, image acquisition must be completed within 90 to 120 seconds following termination of exercise for optimal diagnostic accuracy.\textsuperscript{17,18} Supine bicycle exercise has the potential advantage of continuous imaging, this is off set by more limited imaging windows during exercise and the technique is less patient friendly.

PHARMACOLOGICAL STRESS ECHOCARDIOGRAPHY

The fact that approximately 42% of patients referred for exercise testing are unable to exercise adequately\textsuperscript{1} together with the ability of obtaining good quality serial echocardiographic images throughout the infusion has resulted in the widespread use of pharmacological stress echocardiography. The prevailing and most widely used drugs are dobutamine and adenosine. These are catecholamine derivatives that provoke ischaemia by increasing myocardial oxygen demand through raising heart rate, blood pressure, and contractility, mimicking the haemodynamic response of exercise. During dobutamine infusion, atropine is frequently required to achieve target heart rate as dobutamine has a weak chronotropic effect.\textsuperscript{19,20} Arbutamine, which exhibits more balanced chronotropic and inotropic effects, better mimics exercise haemodynamics.\textsuperscript{21} Vasodilator stress using dipyridamole or adenosine are less potent than inotropic agents in provoking abnormal wall thickening, and hence have lower sensitivity for the detection of coronary artery disease.\textsuperscript{22}

Accuracy of stress echocardiography

Accuracy of the varieties of stress echocardiography has been established in numerous laboratories.\textsuperscript{6,9,21,22} Using modern equipment, the sensitivity for detection of patients with coronary artery disease varies from 85% to 96% with specificity ranging from 78% to 95% (table). As with any technique in which a human observer element exists, the sensitivity and specificity tend to be inversely correlated.
Accuracy of stress echocardiography for detection of coronary artery disease

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Stress type</th>
<th>Total No. patients</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>No. MI</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crouse et al.</td>
<td>1991</td>
<td>TME</td>
<td>97</td>
<td>92%</td>
<td>100%</td>
<td>64%</td>
<td>124</td>
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<tr>
<td>Marcwick</td>
<td>1992</td>
<td>TME</td>
<td>179</td>
<td>84%</td>
<td>77%</td>
<td>93%</td>
<td>89%</td>
</tr>
<tr>
<td>Quiñones et al.</td>
<td>1992</td>
<td>TME</td>
<td>112</td>
<td>75%</td>
<td>58%</td>
<td>89%</td>
<td>88%</td>
</tr>
<tr>
<td>Marcwick</td>
<td>1993</td>
<td>Dob</td>
<td>97</td>
<td>95%</td>
<td>84%</td>
<td>86%</td>
<td>82%</td>
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<tr>
<td>Marcovicz et al.</td>
<td>1992</td>
<td>Dob</td>
<td>141</td>
<td>95%</td>
<td>95%</td>
<td>97%</td>
<td>82%</td>
</tr>
<tr>
<td>Senior et al.</td>
<td>1994</td>
<td>Dob</td>
<td>61</td>
<td>93%</td>
<td>94%</td>
<td>94%</td>
<td>82%</td>
</tr>
<tr>
<td>Ryan et al.</td>
<td>1993</td>
<td>UB</td>
<td>309</td>
<td>91%</td>
<td>86%</td>
<td>95%</td>
<td>78%</td>
</tr>
</tbody>
</table>

TME, treadmill exercise; Dob, dobutamine; UB, upright bicycle; SV, single vessel disease; MV, multivessel disease; MI, myocardial infarction.

Thus, the equivalence of stress echocardiography and perfusion scintigraphy is at variance from the ischaemic cascade model.

This apparent paradox lies in the fact that the relative accuracy of each modality is dependent on imaging characteristics as well as physiology. The development of dysfunction after perfusion abnormalities may be compensated by better spatial resolution and the ability to define wall motion independently in each segment (as opposed to comparison of relative flow used in perfusion imaging).

Moreover, abnormal wall thickening resulting from subendocardial ischaemia may be evident before malperfusion is sufficient to be seen by scintigraphy. Conversely, wall thickening abnormality may falsely occur when the heart rate is over 150 beats/min. The status of myocardial perfusion as assessed by SPECT in conjunction with myocardial contraction assessed by echocardiography may be the optimal way of assessing patients with coronary artery disease. We have demonstrated a synergistic value of combining the results of simultaneously performed stress echocardiography and scintigraphy for predicting coronary artery disease, multivessel disease, and disease extent. It is possible that in future, myocardial perfusion could also be assessed during echocardiography with intravenous contrast injection.

In a recent study it was demonstrated that myocardial contrast echocardiography had a high concordance with scintigraphy for the detection of normal perfusion and irreversible or reversible defects. This would make stress echocardiography an even more powerful modality in assessing the functional significance of coronary artery stenosis.

Prognostic value of stress echocardiography

It is imperative that a test be able to provide not only diagnostic results but also prognostic information. The one to two year prognosis following a normal exercise or dobutamine stress echocardiography is excellent and equivalent to that seen following normal 201Tl scintigraphy. Hard event rates of 0.8% to 1.5% per patient per year have been reported following normal stress echocardiography. Mazeika et al demonstrated that patients with inducible ischaemia during dobutamine stress have a significantly higher incidence of myocardial infarction compared with those without demonstrable ischaemia. This was further borne out in a larger group of patients...
Assessment of viable myocardium

It is important to recognise the presence of viable myocardium when resting myocardial dysfunction is present because of the potential for recovery of function following revascularisation. Several studies in patients following acute myocardial infarction have suggested that in chronic heart failure secondary to coronary artery disease, those with non-revascularised dysfunctional but viable myocardium may be worse off than those with revascularised myocardium.46 It is conceivable that assessment of left ventricular systolic function at rest may underestimate the presence of viability. Most left ventricular wall thickening occurs as a result of subendocardial motion while the contribution of the subepicardium is minimal.46 Increased myocardial thickening of the middle and outer myocardial layers following catecholamine stimulation contributes to overall wall thickening during exercise without necessarily indicating improved subendocardial function. Conversely, lack of improvement of systolic function following revascularisation may result from inadequate revascularisation, the presence of comorbid conditions such as hypertensive heart disease and diabetes mellitus, or lack of sufficient viable cells that can trigger contraction. However, the basic characteristics of viable myocardium are that it is metabolically functional (detected by PET), has a permeable cell membrane (detected by 201thallium or sestamibi uptake), that it is responsive to catecholamine stimulation during echocardiography or magnetic resonance imaging, and that the microcirculation is present (seen with myocardial contrast echocardiography).

Acute myocardial infarction

In the thrombolytic era, the important question following acute myocardial infarction is whether the dysfunctional myocardium in the infarct zone is viable and, if so, whether it is subtended by significantly stenosed artery. Dobutamine echocardiography has the potential to answer these questions. If an infarct related artery is not significantly narrowed, the improvement in wall thickening during dobutamine infusion will be inversely related to infarct size.46 If the infarct is small, 5 µg/kg/min of dobutamine is usually adequate to trigger wall thickening. Higher doses will be required in larger infarcts, but doses higher than 15 µg/kg/min are rarely necessary.49 Deterioration of wall thickening is also a sign of viable myocardium as ischaemia cannot occur in necrosed tissue. Thus, it is not surprising that Smart et al.49 showed that the greatest sensitivity for predicting spontaneous improvement of resting wall thickening follow-

Figure 5 Event free survival curve analysis showed a clear separation between patients with and without inducible ischaemia during dobutamine stress.

Figure 6 201Thallium scintigraphy (top) and dobutamine stress echocardiographic images (bottom) demonstrating marked improvement of the regional and overall ventricular function after revascularisation. GTN, glyceryl trinitrate; ANT, anterior view; LAO 40, left anterior oblique view; LAT, lateral view; LVEF, left ventricular ejection fraction.
Severe stenosis, where resting flow is normal but repeated episodes of mild ischaemia could leave the myocardium perpetually stunned. In the presence of severe left ventricular dysfunction, demonstration of contractile reserve by low doses of dobutamine is predictive of recovery in both regional and global left ventricular systolic function following revascularisation. In a study by Baer et al. it was shown that 18F-fluorodeoxyglucose uptake on PET in akinetic segments with contractile reserve on dobutamine echocardiography was similar to that in normal segments, whereas akinetic segments with no contractile reserve have significantly lower glucose uptake. In another study, a high concordance (81%) was noted between 201-thallium uptake (a marker of viable myocardium) and low dose (5–15 μg/kg/min) dobutamine echocardiography for the detection of viable and non-viable segments (fig 6). In this study, dobutamine echocardiography showed a sensitivity of 87% and a specificity of 82% for the recovery of regional function, similar to that of other studies in the same group of patients. Furthermore, using the criterion of improvement of at least one grade in at least two contiguous segments as an indicator of existing contractile reserve, left ventricular ejection fraction improved from 27-8% to 38-9% (P < 0.001) (fig 7).

However, it is important to determine whether these viable segments also demonstrate ischaemia at high doses of dobutamine. In a study by Afridi et al. a biphasic response alone had a specificity of 88% for the recovery of a segment after revascularisation. Sustained improvement throughout the infusion had a very poor predictive value as it can be seen in cardiomyopathic ventricle from other causes. Williams et al. showed that presence of viable myocardium, as suggested by both presence of contractile reserve and biphasic response during dobutamine, was highly predictive of cardiac events in patients with severe left ventricular dysfunction. Thus, when investigating patients with left ventricular dysfunction, it is important to detect not only whether the dysfunctional myocardium demonstrates any contractile reserve but also whether there is evidence of inducible ischaemia. This may be shown by performing dobutamine echocardiography at both low and high doses during continuous imaging. Whether revascularisation of dysfunctional but viable myocardium results in significant clinical benefits can only be answered through an adequately powered study randomising patients with and without dobutamine responsive dysfunctional myocardium to medical treatment and revascularisation.

**Emphasis on training**

The advantage of echocardiography being safe and inexpensive has become a disadvantage as it is now being increasingly used by inappropriately trained people with resultant inaccu-rate reports. Recently, the British Society of Echocardiography issued guidelines for train-
Stress echocardiography for assessing myocardial ischaemia and viable myocardium

Stress echocardiography is a non-invasive diagnostic tool that is used in conjunction with other cardiac imaging techniques to assess the extent of myocardial ischemia and viability. It plays a vital role in risk stratification, patient management, and the decision-making process for further diagnostic procedures.


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vascular disease, risk factors, interventions, and prognosis, fulfilling criteria for a suitable non-invasive assessment of endothelial function. Furthermore, several groups have targeted this molecule as a means of intervening in the thrombotic process.16 The next five years will tell if this approach is successful.

The non-invasive approach outlined by Mullen and colleagues has provided invaluable opportunities to dissect the pharmacology of the endothelium. However, by its very nature such an approach is unlikely to provide epidemiological data or even data to compare groups with large numbers of subjects. We submit that plasma markers such as von Willebrand factor and soluble thrombomodulin are likely candidates for providing data of this nature.

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12 Blann AD, Amiraj J, McCollum CN. Prognostic value of increased soluble thrombomodulin and increased E-selectin in ischaemic heart disease. Eur J Haem. [In press.]

This letter was shown to the authors, who reply as follows:

We read with interest the letter from Drs Blann and Lip regarding the advantages and limitations of plasma markers of endothelial cell function. We share their interest in this area of research and its potential clinical application. We feel, however, that evaluation of nitric oxide mediated arterial physiology in large conduit arteries using the non-invasive techniques described may provide insight into the pathophysiology of vascular disease, be an early marker of endothelial injury, and a means of evaluating interventions early in the natural history of atherogenesis.

The value of these measures in predicting disease development and outcome is not known and is central to current research efforts. Our published data, however, indicate that this technique can be used to study endothelial function in large groups of subjects from early in childhood, to provide epidemiological data, compare groups of subjects with risk factors, and demonstrate beneficial response to interventions.1-5

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CORRECTION
Pregnancy and congenital heart disease
C M Oakley Heart 1997;78:12-14.

The first sentence of the section Atrial septal defects should have read:

“The only frailty of patients with un repaired atrial septal defects is intolerance of blood loss that can force left to right shunting, to the sudden detriment of left ventricular and coronary flow.”

And not as published. The error is regretted.