GUIDELINES AND RECOMMENDATIONS

Stress echocardiography in coronary artery disease: a practical guideline from the British Society of Echocardiography

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Abstract

Stress echocardiography is an established technique for assessing coronary artery disease. It has primarily been used for the diagnosis and assessment of patients presenting with chest pain in whom there is an intermediate probability of coronary artery disease. In addition, it is used for risk stratification and to guide revascularisation in patients with known ischaemic heart disease. Although cardiac computed tomography has recently been recommended in the United Kingdom as the first-line investigation in patients presenting for the first time with atypical or typical angina, stress echocardiography continues to have an important role in the assessment of patients with lesions of uncertain functional significance and patients with known ischaemic heart disease who represent with chest pain. In this guideline from the British Society of Echocardiography, the indications and recommended protocols are outlined for the assessment of ischaemic heart disease by stress echocardiography.

Key Words
▶ stress echocardiography
▶ coronary artery disease
▶ exercise
▶ pharmacological stress
▶ myocardial perfusion
▶ 3D echocardiography
▶ left ventricular opacification contrast

Introduction

Stress echocardiography (SE) is a well-established non-invasive technique that is most often used in the assessment of coronary artery disease (CAD). A recent survey by Bhattacharyya *et al.* highlights important themes that relate to quality and consistency in performance, including selection of the optimal method for stress and the number of studies that should be performed per year to maintain competency by individual operators ([1](#)). SE requires a high level of expertise to achieve accurate and reproducible results, and it is recognised that performing the technique requires additional training beyond proficiency in transthoracic echocardiography.

This is reflected in the recent development of a specific accreditation process for people undertaking SE (2). Furthermore, echocardiography services that provide SE are scrutinised during departmental accreditation, which requires standardised approaches to testing that is known to improve both quality of image acquisition and reporting (3). In the light of the need for a systematic approach to SE, this document sets out practical guidance for the performance of SE in CAD.

The aim of this document is to provide a framework for the practical aspects of performing and reporting SE for diagnosis and prognosis of CAD. The focus of this guideline is on 2D imaging with the assessment of changes in myocardial thickening as the marker of ischaemia. There is an increasing evidence base for advanced imaging techniques in SE including myocardial perfusion, coronary flow, strain and 3D SE, which will also be discussed, although these are not all yet in widespread clinical practice. The role of SE in non-ischaemic indications will be covered in future guidelines.

It is recognised that different stress modalities may be applicable in an individual patient and that the choice of stress modality may depend on clinician preference, availability of equipment and experience. In some patients, there may be technical or clinical reasons that make SE difficult or even impossible to perform. Indeed, patients will receive the greatest clinical benefit at the lowest risk when SE departments have access to a wide range of other functional tests, for example, stress cardiovascular magnetic resonance (CMR) imaging or nuclear perfusion techniques. One of the key aims of this document is to explain the practical and logistical difficulties that commonly arise in performing SE so that readers will have a useful and applicable template to disseminate amongst their staff.

Pathophysiology of ischaemia

Myocardial ischaemia results from a mismatch between myocardial oxygen consumption and oxygen delivery to the myocardium. Normally, in the setting of a fixed stenosis within the coronary arteries, the supply of oxygen to the myocardium is enough at rest but results in ischaemia at times of increasing workload. This is responsible for the typical presentation of exertional angina. The classical concept of ischaemia is that the effects alter myocardial physiology in such a way to produce a 'cascade' of changes to coronary perfusion, diastolic dysfunction, systolic dysfunction,

abnormalities on the electrocardiogram and finally symptoms of angina (4). Although the concept of a 'cascade' has recently been called into question, the advantage of SE is that it can detect each one of the abnormalities that make up the ischaemic 'constellation', whether that be abnormal perfusion, diastolic dysfunction, regional wall motion abnormalities, ECG changes or symptoms (4). It is this multiparametric capability that makes exercise SE a more attractive test to use with greater accuracy than the traditional exercise ECG (5, 6). Finally, contrast-enhanced SE has a good agreement with invasive fractional flow reserve when used with second generation contrast agents in predicting reversible myocardial ischaemia in patients with intermediate lesions (7). This increases the utility of SE as a 'gatekeeper' to reduce unnecessary invasive coronary procedures.

Indications for SE in CAD

1. The diagnosis of stable chest pain suspicious of angina in patients with intermediate probability of CAD. The European guidelines for the management of stable CAD indicate that stress imaging is the preferred modality for all patients with a pre-test probability of 15–85% if the expertise is available (8). While the National Institute for Health and Care Excellence Clinical Guideline 95 (2010) previously recommended functional testing (including SE) for patients with intermediate probability (30–60%) of CAD, this was rescinded in an update in 2016 in favour of CT coronary angiography (CTCA) as the first-line imaging modality in patients presenting with recent-onset typical or atypical angina (9). Although there are data to show equivalent outcomes from a functional compared to an angiographic approach (10) and there continues to be support for calculation of pre-test likelihood to select an imaging test (11), this is current NICE guidance.
2. The diagnosis of CAD in suspected acute coronary syndrome with non-diagnostic ECG and negative biomarkers of low-risk ACS (12).
3. The assessment of the functional significance of CAD of intermediate severity on CTCA or invasive coronary angiography.
4. The diagnosis of chest pain in patients with known CAD (including prior percutaneous coronary intervention and coronary artery by-pass grafting) who present with symptoms of angina.
5. The evaluation of a cardiac aetiology of dyspnoea. Dyspnoea is defined as difficult, laboured or

uncomfortable breathing, which is a non-specific symptom that can reflect several underlying diseases, including lack of physical fitness, obesity, lung disease, heart failure and ischaemia. The prevalence rate of angina increases with increasing severity of breathlessness (13), and approximately a third of patients referred for stress testing will have a positive test for ischaemia (14). Predictors for a positive test include male gender, history of CAD and abnormal wall motion on resting echocardiography (15).

6. The assessment of prognosis in patients with known CAD, e.g. risk stratification post myocardial infarction.
7. Stratification of risk prior to non-cardiac surgery. SE should be used in well-defined groups where the finding of an abnormal stress test will significantly alter the surgical and perioperative management (16). These patients will be undergoing intermediate or high-risk surgery but with poor functional capacity in addition to the presence of certain risk factors – angina, previous myocardial infarction, renal failure, previous stroke or insulin requiring diabetes.

Staffing requirements for safe performance of SE

A minimum of two individuals are required for every case. The first operator usually performs the echocardiography and can be any health professional with the appropriate skill and experience (17). The health professional should not only be fully trained in transthoracic echocardiography (BSE TTE Proficiency Accreditation or equivalent), but it is desirable for practitioners to undergo additional training in the acquisition of SE images, such as the BSE Accreditation in SE or international equivalent (2). The second operator oversees haemodynamic monitoring, ECG acquisition and drug administration if required. This person can be a clinician, nurse, healthcare scientist or cardiac physiologist.

Departments need to establish which operator is in overall charge of the test in terms of taking responsibility for decision making and maintaining patient safety. This division of labour will vary between departments depending on the personnel involved in SE. At least one of these individuals must have advanced life support competency. The second will have a minimum of intermediate life support competency. In units where SE is performed by non-medical health professionals (e.g. cardiac physiologists, nurses), it is expected that a crash (resuscitation) team will be available immediately

on activation of a cardiac arrest call. In addition, where SE is performed by non-medical health professionals, a named clinician trained in SE should be available to answer queries if required.

Patient information leaflets

SE is a low-risk, but not risk-free procedure and formal written consent should be obtained (18). Contemporary practice is for this to be obtained before the day of the test with the help of a written information leaflet, for patients to understand the risk involved and make an informed decision whether to proceed in their own time. For example, this could be done at the time when the SE is booked or by sending out the patient information leaflet sent out with the appointment, so that the patient has time to consider the issues involved. Consent before the day of the test may not always be practical or in the patients' interest, for example, when SE is done on request immediately within the context of a rapid access chest pain unit. In these circumstances, the patient should be given as much opportunity to read and consider the information supplied before consent is obtained. Examples of patient information leaflets relating to exercise and pharmacological stress are available (www.bsecho.org) and should be sent with the appointment letter or notification. These can be modified according to local practice. Patient information leaflets are also important to outline the preparations to be made by the patient prior to attending for the test. This will include advice on which medications to stop prior to the test, whether they need to fast and to clarify transport arrangements after the test.

Equipment requirements

This will depend on whether exercise or pharmacological stress is being used. It is expected that the designated room is fit for purpose and there are criteria for suitability within BSE Departmental Accreditation requirements (www.bsecho.org). Space should be available during scanning that will allow the immediate co-location of a crash trolley or defibrillator next to the patient in the event of an arrhythmia requiring shock. Space should also be adequate to run an arrest scenario with the full cardiac arrest team present, as well as standard monitoring and infusion equipment necessary to perform the test (Table 1).

Table 1 Equipment requirements for stress echocardiography.

All cases
1. Digital echocardiography machine with appropriate SE analysis package.
2. Automated blood pressure machine with manual back up if needed.
3. Continuous ECG monitoring.
4. Fully equipped resuscitation trolley with defibrillator.
5. Oxygen supply and suction.
6. Availability of transpulmonary contrast when echo window is suboptimal.
7. Drugs to manage severe allergic reactions and anaphylactic shock. To include – IV/IM adrenaline 1:1000, IV chlorpheniramine, IV hydrocortisone, salbutamol nebuliser – in dose and preparation to meet current Resuscitation UK guidelines
8. Cannulation equipment

Specific to exercise stress echo
1. Exercise treadmill and/or semi-supine bike with protocol options.

Specific to dobutamine stress echo
1. Dobutamine infusion and administration pump.
2. IV Atropine – up to 1.2 mg.
3. IV beta-blockers e.g. metoprolol.

Setup

Patient identification is established with three key identifiers – usually name, hospital or NHS number and date of birth. The basic history should be reassessed to confirm the indication and to ensure there has been no change in clinical status which may contraindicate the test for example crescendo angina. A list of patient medication should be available at the time of referral specifically mentioning rate slowing drugs. The sensitivity of detecting ischaemia is increased by achieving adequate workload and therefore in most patients it is sensible to stop rate slowing drugs 48 h prior to the test (19). In some patients, however, it may be necessary to continue all drugs for example in problematic hypertension or when assessing ischaemia in patients with known CAD on medical therapy, making note in the report whether this would affect the sensitivity of the SE. In other patients, for example, in assessment of risk of cardiovascular complications during non-cardiac surgery, it may be preferable not to stop drugs such as B-blockers when these would be continued through the proposed operation. Consideration should be given in patients who have a history of arrhythmia for example paroxysmal atrial fibrillation or ventricular tachycardia. Discontinuation of regular anti-arrhythmic medication may be problematic and, in some cases, potentially hazardous, particularly if the patient is undergoing a dobutamine stress study, due to the potential for promoting arrhythmia. Under such circumstances the clinician in charge should make a judgement, following discussion with the clinician referring the patient for the test and if necessary, consider an alternative stress test for example vasodilator stress with myocardial contrast SE (20), nuclear imaging or CMR.

Baseline blood pressure, heart rate and 12-lead ECG are obtained. Continuous 12-lead ECG monitoring may be performed during SE but the positions of the chest leads often need to be lower than usual to avoid interfering with the acoustic window. Moreover, whether using exercise or dobutamine, the ECG data do not add to the prognostic value of the SE result and there are no consistent data to indicate this improves accuracy (21, 22). Although the performance of 12-lead ECG monitoring during SE is not mandated, ECG monitoring for arrhythmia is necessary. The ECG leads attached to the echo machine must achieve a very clear tracing of the QRS complexes because well-demarcated imaging loops are critical at high heart rates, specifically for acquisition of correctly timed systolic images. One option can be to slave the ECG trace from the exercise machine if this is the stressor used. Left bundle branch block and pacing present challenges in SE due to the septal dyssynchrony seen during baseline imaging and is often accentuated at peak stress, so note must be made in such patients in the report (23).

Intravenous access is established for all cases of pharmacological stress and in patients undergoing exercise SE in whom the images are suboptimal to allow administration of transpulmonary contrast (left ventricular opacification (LVO)). A suboptimal window is typically defined as difficulty in seeing two or more contiguous segments in any of the available echo windows (24). There should be a preference for use of LVO when there is a concern that image quality may not be optimal at peak stress, particularly when exercise is used as the stressor due to the likelihood of translational motion with respiration at peak (see current international guidelines on use of LVO) (20, 24). When a patient only has one arm that is available for IV access and monitoring, for example, haemodialysis fistula or lymphoedema, it may be necessary to measure the blood pressure on the same side. During pharmacological stress, it may be easier to make manual blood pressure recordings as this tends to reduce the time of cuff inflation which temporarily occludes the infusion.

Prior to acquisition of SE images, a baseline echocardiogram should be performed to assess ventricular function, chamber sizes, wall thickness, aortic root and valves unless this assessment has already been performed

within 6 months. Baseline assessment should always consider pathology which may not have been previously identified but which may be very important in the context of the patient's presenting symptoms. Two examples include:

1. Significant valve disease. If this is a new diagnosis, then further discussion with the referring clinician may be necessary to decide on the safety and indication for the stress test, for example severe aortic stenosis.
2. Flow acceleration in the LVOT may occur at baseline in association with basal septal hypertrophy, usually in the elderly. This may provide the substrate for systolic anterior motion of the mitral valve (SAM) with increasing heart rates which then exacerbates the degree of LVOT obstruction. The presence of a resting LVOT gradient is not an absolute contraindication to a SE study, however, increasing LVOT gradients may lead to hypotension or exacerbation of ischaemia and therefore may be a reason for terminating the test earlier than planned. Dobutamine infusions will often induce this mechanism of LVOT obstruction at higher doses which are much less common with physiological exercise. This needs to be considered when selecting the most appropriate method of stress.

Image acquisition

The core images to obtain are at baseline and at peak stress but during both bicycle exercise and dobutamine stress, it is usual to obtain additional images through the test. It is important for the machine to have a preset protocol to minimise acquisition time and to guarantee quad review. Standard images at each stage as a minimum include:

1. Apical four chamber
2. Apical two chamber
3. Parasternal long axis and/or apical three chamber
4. Parasternal short axis

The precise number of stages recorded varies depending on the indication and the method of stress but when reporting, it is important to indicate the heart rate and stage at which ischaemia first occurs. The addition of intermediate stages improves sensitivity and assessment of functional significance of CAD (25). It is essential to record the same views when recording multiple stages and it is this specific skill which is particularly demanding during SE. Images should be obtained in recovery to demonstrate normalisation of any regional changes in myocardial

thickening and/or wall motion. In dobutamine SE, administration of IV B-Blockers in recovery rapidly lowers the heart rate and acquisition of images in early recovery may improve the sensitivity of detecting regional changes in myocardial thickening and/or wall motion (26).

Technique

Exercise is the preferred method of stress for the assessment of CAD whenever possible, as the duration of exercise is a key marker of prognosis. Moreover, exercise SE has a better safety profile compared to pharmacological SE, although contraindications remain (Table 2). Pharmacological stress with dobutamine is the common alternative used in patients who are unable to exercise or when the assessment of contractile reserve and viability is the key clinical question. Although exercise SE is recommended, it is recognised that pharmacological stress minimises factors such as patient motion, hyperventilation and chest wall movement that can degrade image quality and make it much harder to acquire the same images at each stage. Hence, a lower threshold for the use of LVO is recommended (20).

Exercise stress

There are two main techniques to achieve exercise stress – (a) semi-supine bicycle exercise or (b) a conventional treadmill test. Semi-supine bicycle is more sensitive than post-treadmill exercise (27). There are limited data to indicate similar sensitivity of SE during treadmill exercise to semi-supine bicycle but this is technically difficult (28). The aim of exercise SE is to achieve both the maximum target heart rate which is calculated (220 – age), although sensitivity of the test does not appear to fall providing imaging is performed above 85% of the maximum heart rate and maximal exercise. If a patient fails to achieve a minimum of 85% maximum heart rate, the rate of

Table 2 Contraindications to exercise stress echocardiography.

1. Acute myocardial infarction (within 2 days)
2. Unstable angina not previously stabilised by medical therapy
3. Uncontrolled cardiac arrhythmias causing symptoms or haemodynamic compromise
4. Symptomatic severe aortic stenosis
5. Uncontrolled heart failure
6. Acute myocarditis or pericarditis
7. Hypertension >200/110 mmHg at baseline

Table 3 End points for stress echocardiography.

(a) Absolute	Drop in SBP† >10 mmHg from baseline with symptoms
	Sustained VT*
	ST elevation >1 mm with symptoms (other than aVR or V1)
	Central nervous system symptoms (ataxia, pre-syncope)
	Left ventricular thrombus
(b) Relative	Predicted maximum heart rate >1 and maximal effort
	New wall motion abnormality
	Progressive LV dilatation
	New onset or progressive global LV dysfunction
	Drop in SBP >10 mmHg from baseline without other evidence of ischaemia
	ST depression >2 mm or axis shift
	Stress-induced arrhythmia: AF, SVT, NSVT**
	Severe hypertension >230 mmHg
	HR falling >20% starting rate

†SBP, systolic blood pressure; *VT, ventricular tachycardia; **AF, atrial fibrillation; SVT, supraventricular tachycardia; NSVT, non-sustained ventricular tachycardia (47).

cardiovascular events in those who do not achieve their target but have normal images is higher than those who do achieve their target and have normal images (29). Similarly, failure to achieve a reasonable absolute level of exercise (defined as <7 metabolic equivalents (METs) for men and <5 METs for women) is a predictor of subsequent cardiac events even if SE is normal (30).

(a) Semi-supine bike – the recommended protocol to use is the World Health Organisation 25 Watt programme with load increased in increments of 25 Watts every 2 or 3 min, with the patient maintaining a cadence of approximately 60 revolutions per minute (25). It is standard practice to acquire images at rest and at peak stress, but the acquisition of additional images at 25W and 50W during semi-supine bicycle improves diagnostic performance (25). The major consideration is to ensure that the patient achieves their maximum workload, since this is an important discriminator of outcome irrespective of protocol (31). Protocols should therefore be tailored to the physical capability of the patient and supplemented with hand-grip exercise or atropine to optimise heart rate response (32).

(b) Treadmill – the recommended protocol to use is the standard Bruce exercise treadmill protocol, with the modified Bruce for the less physically able patient or an accelerated Bruce (first stage skipped) for a super fit patient. Images are taken at baseline and within 90 s of termination of exercise, although as discussed above, there is some evidence of improved sensitivity by imaging during exercise. The main issue is to avoid missing abnormalities when patient recovery is rapid or by inappropriate delay to imaging.

End points for exercise SE are listed in Table 3.

Dobutamine stress echocardiography

Dobutamine is a sympathomimetic agent that increases myocardial oxygen demand by increasing heart rate (chronotropic effect) and the force of contraction (inotropic effect) through action on β1 adrenoceptors. In addition, it has weaker action on β2 adrenoceptors resulting in a degree of vasodilatation. Use in SE requires infusion of supra-pharmacologic doses (up to 40 µg/kg/min), frequently with the addition of atropine (which improves sensitivity of the test) (33) and requires a degree of caution and expertise. Every test carries a definite risk of complications, although the administration of these agents in the era of LVO has been shown to be safe, with a risk of myocardial infarction and life-threatening arrhythmia below 1% (34). Moreover, there is evidence that dobutamine-atropine (DA) SE can

Table 4 Contraindications to dobutamine-atropine SE.

Absolute
1. Previous hypersensitivity/allergy to dobutamine or atropine
2. Recent myocardial infarction (within 3 days)
3. Ongoing unstable angina
4. Acute heart failure
5. Left ventricular thrombus
6. Recent significant ventricular arrhythmia (within 3 days)
7. Recurrent persistent supraventricular arrhythmias
8. High-grade AV block (second or third degree)
9. Active endocarditis or myocarditis
10. Severe arterial hypertension – systolic >200 mmHg, diastolic >110 mmHg

Relative contraindications/cautions
1. Paroxysmal supraventricular arrhythmia
2. Moderate aortic stenosis
3. Resting left ventricular outflow tract obstruction >30 mmHg
4. Aortic aneurysm >4 cm

Table 5 Common drugs in SE: dosage and supplementary information.

Drug	Dose
Atropine	300 µg aliquots; up to 1.2 mg in total Side effects: dry mouth, constipation, mydriasis Contraindications: angle closure glaucoma, prostate hypertrophy (difficulty in micturition)
Dobutamine	5–40 µg/kg/min; dilution as an infusion via syringe driver Side effects: nausea, tremor, palpitations, chest pain, hyper/hypotension, arrhythmia, myocardial infarction Contraindications: see Table 4
Adenosine	140 µg/kg/min; often diluted as an infusion 1 mg/mL Side effects: flushing, chest pain, shortness of breath, metallic taste, bradyarrhythmia Contraindications: sinus node disease, high-grade AV block (second or third degree); reversible airways disease. Note: effect antagonised by methylxanthines, e.g. coffee.
Dipyridamole	0.56 mg/kg over 4 min; followed after 2 min by 0.28 mg/kg over 2 min (low dose enough for perfusion assessment; high dose may also invoke RWMA) Side effects: chest pain, flushing, arrhythmia, hypersensitivity reactions, bronchospasm, hypotension Contraindications: prior hypersensitivity, unstable angina
Regadenoson	400 µg in 5 mL pre-loaded syringe IV bolus over 5–10 s Side effects: chest pain, nausea, dizziness, headache, conduction abnormalities. Contraindications: sinus node disease, high-grade AV block (second or third degree); prior hypersensitivity. Note: effect antagonised by methylxanthines, e.g. coffee.
Aminophylline	240 mg IV; routinely infused at end of dipyridamole infusion Side effects: Contraindications
Metoprolol	1 mg aliquots Up to 5 mg if required Side effects: Contraindications: asthma or severe airways disease of any kind. Caution with pre-existing high-grade AV block or known tachybrady syndrome
Anaphylaxis	
Adrenaline	0.5 mg–1 mg (1:1000 strength) intramuscular injection
Chlorpheniramine	10 mg
Hydrocortisone	100 mg
Salbutamol Nebuliser	5 mg – may be given repeatedly

This Table lists common and major risks, but is not exhaustive, and any operator must have a full working knowledge of the side effects and contraindications of these drugs. Local hospital administration requirements must be met.

be supervised by doctors, nurses and physiologists when adequately trained with equivalent risk and safety (35). Contraindications to SE with DA are listed in Table 4 and risk factors of common pharmacological agents, doses and contraindications used in SE are given in Table 5.

Dobutamine is infused continuously through an intravenous cannula according to a weight-adjusted dose (Fig. 1). The aim of DA SE is to achieve the maximum target heart rate which is calculated (220 – age), although sensitivity of the test does not appear to fall *providing* imaging is performed above 85% of the maximum heart rate. Atropine is often required in 300 µg aliquots up to 1.2 mg to augment the heart rate response, improves sensitivity compared to the use of dobutamine alone, and can be helpful in reducing the likelihood of adverse hypotensive and vagal reactions (Fig. 1).

The latter adverse effects of dobutamine are due to mixed action at β1 and β2 adrenoceptors. At low doses, the inotropic and chronotropic effects of dobutamine lead to a slight augmentation of blood pressure.

At higher doses, however, the β2 agonism can result in peripheral vasodilation resulting in a fall in blood pressure, particularly in the diastolic component. Occasionally, there can be a paradoxical slowing of heart rate during high-dose dobutamine. This is typically mediated via the Bezold-Jarisch reflex that results in increased parasympathetic activity and inhibition of sympathetic activity. This results in a 'vagal' response and can lead to a precipitous fall in blood pressure. This can be avoided by monitoring carefully for any paradoxical slowing of heart rate and if this occurs to administer atropine and/or to ask the patient to undertake hand-grip exercises by repeatedly squeezing a ball or similar object.

Myocardial perfusion stress echocardiography

Myocardial perfusion stress echocardiography (MPSE) improves detection of ischaemia, since perfusion abnormalities occur before the occurrence of loss of wall
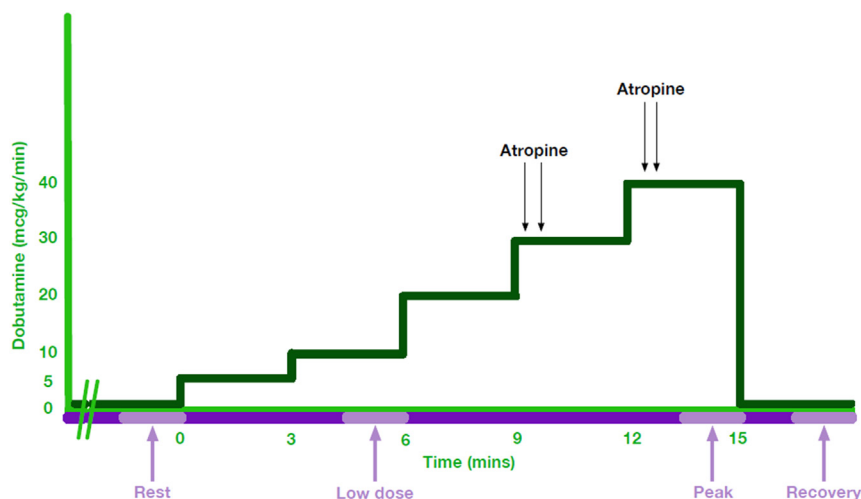
Figure 1
Dobutamine infusion schedule.

thickening (36). The addition of perfusion imaging to regional wall motion analysis improves the sensitivity for detection of ischaemia and improves prediction of risk (37). The incremental value of MPSE has been demonstrated on exercise (38), with DA, and following vasodilator stress without significant addition to the risk of the test (34). MPSE may also have particular advantages in improving sensitivity in the context of resting wall motion abnormalities, such as left bundle branch block (39). Multiple studies have been performed using vasodilator stress, which has the advantages of being quick to perform, providing good image quality at lower heart rate, while avoiding the issue of translational motion of the heart with rapid breathing and producing equivalent accuracy to other stress agents. Vasodilator stress agents induce abnormalities in wall thickening by enhancing flow inhomogeneity due to underlying stenosis, and do not increase heart rate and blood pressure significantly. The most common agents used are adenosine and dipyrimadole, although studies have also confirmed equivalent accuracy of MPSE with regadenoson (40) and perfusion can also be done during DA SE (refer to Table 5 for common side effects). Quantitative analysis of perfusion and myocardial blood flow may be performed using steady-state infusion and flash replenishment, and there is some evidence of additional accuracy compared to qualitative perfusion analysis, although data are limited (41). Moreover, visual assessment is easier and faster.

MPSE is performed at rest and during stress immediately after standard images for wall motion analysis have been acquired. Standard protocols are below (Figs 2, 3 and 4). The key to obtaining high-quality MPSE images is to ensure optimal machine settings and to familiarise yourself with the adjustable settings:

(a) Setup. A contrast-specific preset should be selected specifically for perfusion, which will involve very low mechanical index imaging <0.2 (preferably <0.1 (SonoVue) or <0.15 (Optison/Luminity)). The depth should be adjusted so that the left ventricle fills in screen. Overall gain should be between 60 and 65%. The transitional and lateral gain compensation controls
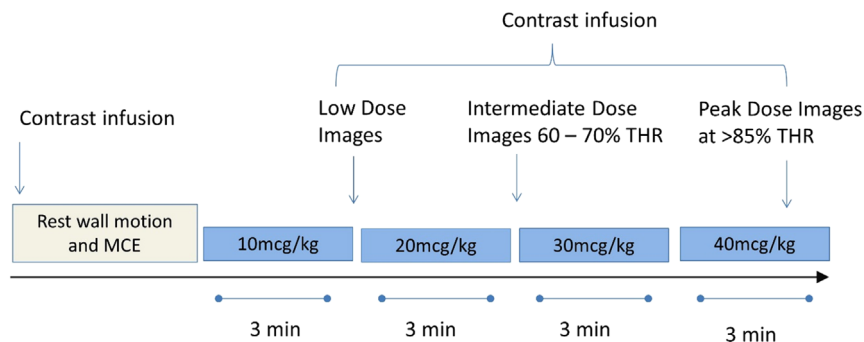
Treadmill exercise MCE
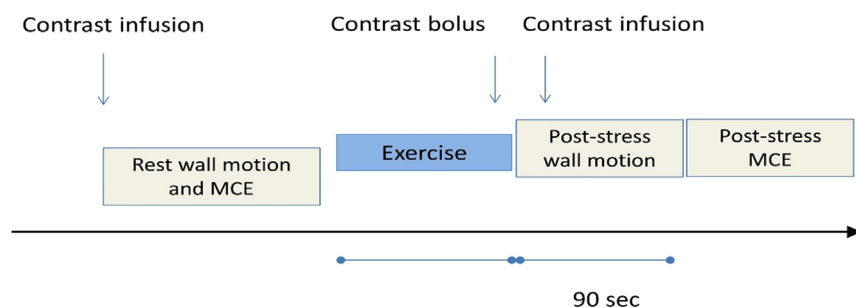
Figure 2
Myocardial perfusion stress echocardiography protocol during exercise stress.

Dobutamine MCE

Figure 3
Myocardial contrast echocardiography during dobutamine stress echocardiography.

should be in mid-positions, and the focus should be at the mitral valve level but can be moved to the near field when apical perfusion is being evaluated. The default loop length should be set to 15 beats. Images can be obtained in real-time (40 frames per RR interval) and using triggered imaging (1 frame per RR interval).

(b) Flash Parameters. The flash setting involves delivering a brief (5–10 flash frames) high mechanical index (MI > 0.8) impulse to clear contrast within the myocardium, following which replenishment is analysed on the end-systolic images. The flash power button will increase the flash power. The flash frames button can be used to adjust the number of flash frames per beat.

(c) Myocardial Contrast. Although small bolus injections with saline flush given slowly can create periods when steady-state kinetics are achieved to examine flash-replenishment, most MPSE is performed with contrast infusion via a pump or IV giving set 0.7–1 mL/min. It is important to ensure homogenous opacification of the left ventricular cavity and myocardium (Fig. 5). Once the endocardial/epicardial borders are well visualised, press acquire to start recording of images.

Wait 2–3 beats then press flash. The loop length should be 15 beats so images should be optimised until the end of the acquisition.

(d) Check Images. It is important ensure adequate microbubble destruction in all segments of the myocardium (the myocardium will appear almost black) with minimal amount of microbubble destruction in the LV cavity. If there is incomplete bubble destruction (Fig. 6), consider the following steps:

- Increase flash frames for example from 8 to 15 to 20 if still incomplete destruction;
- Increase flash power for example from 0.8 to 1.0;
- Reduce overall gain while maintaining opacification of the myocardium;
- Reducing infusion rate for example 0.8 mL/min to 0.7 mL/min if above fails.

If there is too much bubble destruction in LV cavity, consider the following:

- Reduce flash frames, for example from 8 to 6;
- Reduce flash power, for example from 0.8 to 0.6.

Dipyridamole MCE
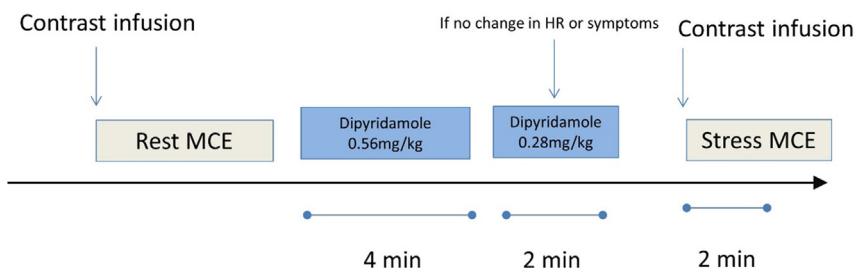
Figure 4
Vasodilator stress echocardiography. Note: low dose enough for perfusion assessment; high dose may also invoke RWMA, so that infusion dose may be modified accordingly.
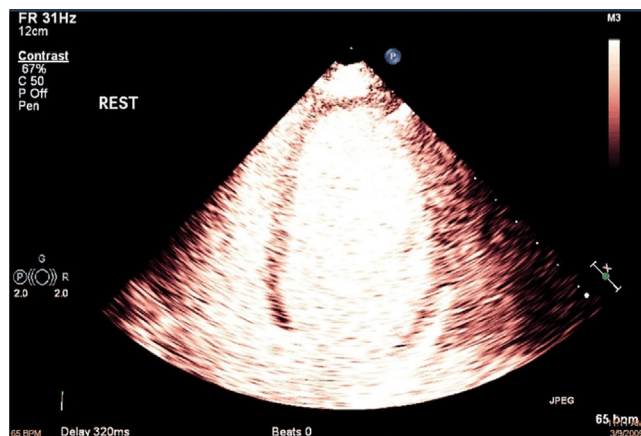
Figure 5
Initial settings optimised for myocardial contrast echocardiography.

Once image quality and microbubble destruction are considered satisfactory, the above steps can be repeated using triggered imaging. If the wall motion is normal at rest, perfusion will always be normal. Thus, to save time, only the apical four-chamber view need be obtained to optimise image at rest. The settings after optimisation must be held constant during acquisition of stress imaging. The only parameters which can be changed during stress are the number of flash frames and flash MI for optimisation of bubble clearance.

When reviewing images following MPSE, freeze the cine loop on the frame exactly after the flash and ensure that there has been adequate bubble destruction (i.e. myocardium should be black). Review both real-time and triggered image, and when starting, it may be helpful to analyse each cine-loop frame by frame. At rest, complete
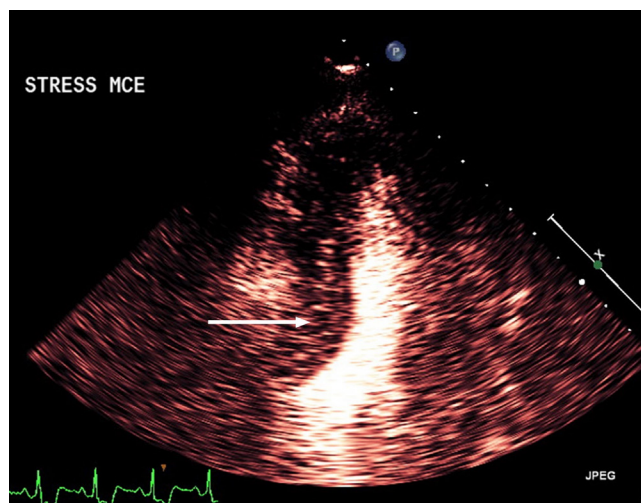
Figure 6
Incomplete microbubble destruction basal/mid-infero-septum (arrow).

bubble replenishment following bubble clearance is expected within 5 s or five beats if the heart rate is 60 bpm. At peak stress, bubble replenishment is expected within 1–2 s. If the heart rate is 120 bpm replenishment is expected within 2–3 beats. Video 1 shows an example of a perfusion defect identified during MPSE.

Video 1

Real-time myocardial contrast echocardiography. After two beats a perfusion defect remains in the mid–to-apical infero-septum and lateral wall. This eventually resolves after a further 10–12 beats. View Video 1 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0068/video-1.

Coronary flow reserve

Coronary blood flow can increase approximately four-to-six-fold in the healthy individual to meet increasing myocardial oxygen demands. This effect is mediated by vasodilation of the arteriolar bed, which reduces vascular resistance, thereby increasing coronary flow. Coronary flow reserve (CFR) represents the capacity of the coronary circulation to dilate following an increase in myocardial metabolic demands and can be expressed by the difference between hyperaemic flow and resting flow. It has long been known that there is an inverse curvilinear relationship between the narrowing of the lumen of coronary artery and hyperemic capacity, up to a complete annulment or absence of CFR for stenosis >90% significance (42). Although in clinical practice, there are a number of factors that affect the curvilinear nature of the link between CFR and stenosis severity, for example arterial spasm, left ventricular hypertrophy and pharmacotherapy, Doppler-derived CFR can be measured reproducibly and in agreement with values from positron emission tomography, which is considered gold standard (43). Doppler-derived CFR adds incremental diagnostic and prognostic value to wall motion analysis (44) and perfusion (45) in the assessment of patients with known or suspected CAD and can be used whether or not anti-ischaemic medication is continued at the time of the test (46).

Doppler-derived CFR is possible not only for the left anterior descending (LAD) artery but also in the right and left circumflex arteries (47). In experienced hands, CFR by echocardiography is achievable within the LAD artery in >90% cases, and in nearly all with the use of intravenous contrast agents. In difficult cases, the intravenous injection of small boluses of transpulmonary

contrast helps to improve both the colour Doppler signal for location of the arterial segment and/or to obtain clear Pulse Doppler signals in the artery in question, particularly in the overweight and obese (48). Measurement of CFR is technically challenging, particularly since the measurement of absolute blood velocity is dependent on the incident angle between the Doppler beam and blood flow and reliability requires a consistent position throughout assessment. As a result of this and other technical reasons, including the use of velocity ratio as a surrogate for CFR, it is recommended that Doppler measurement of CFR is performed using vasodilator stress, ideally used as a first step in a multiparametric study that includes assessment of regional wall thickening/motion and/or perfusion (49). A cut-off value of two for detecting significant epicardial coronary stenosis or ischaemia has been demonstrated in a number of studies of CFR (46).

Myocardial strain, diastolic function and SE

The term strain is used to describe the shortening and thickening of myocardium during the cardiac cycle in the longitudinal, circumferential and radial planes as a reflection of contractility. Strain is a dimensionless change in length of tissue between two points, whereas strain rate is the change of strain over time. Strain can be measured by tissue Doppler imaging, which was the method used for initial validation (50, 51), but this has largely been replaced by speckle tracking echocardiography, which avoids some of the issues relating to angle dependency. Characteristic changes in diagnosis of ischaemia include reduction in peak strain, systolic lengthening and post-systolic shortening (52). The advantage of adding strain imaging to standard regional thickening and wall motion is that this replaces qualitative assessment with quantitative assessment and reduces inter-observer variability (53). Strain imaging can be performed during pharmacological stress or during bicycle exercise, although the stable positioning of the patient during DA make this an ideal format in which to combine strain imaging with wall thickening and motion (54). There are data to indicate incremental value of reduction in peak strain, systolic lengthening and post-systolic shortening in addition to wall motion analysis (55). More documentation of added clinical value is needed, however, before strain imaging can be recommended for routine use in the evaluation of patients with chest pain, particularly in linking the adoption of strain in SE to improved outcomes (56).

As discussed earlier in indications for SE, dyspnoea on exertion is a common symptom that may often reflect ischaemia but the differential diagnosis may be wide. Exercise SE can unmask diastolic dysfunction and can provide an explanation for breathlessness by estimating changes in filling pressure in the form of E/e′ and maximal tricuspid regurgitant velocity (57). This can better be performed using a semi-supine bicycle ergometer to enable estimation throughout low-dose exercise, with abnormality defined by increased transmitral E-wave velocity, reduced A wave velocity, unchanged e′ and increased E/e′ (usually >14).

3D acquisitions in SE

The use of 3D echocardiography during SE reduces the time taken for image acquisition (58), improve foreshortened imaging planes (58) and increase reproducibility between imaging planes acquired at different stages of stress (59). New and relatively fast 3D ultrasound imaging devices are entering the market offering superior image quality, higher frame (3D volume) rates and ever-expanding capabilities that increase the potential for routine use.

Modes of 3D SE

3D systems offer several different imaging modes:

(a) Real-Time 3D (RT3D) Multislice Imaging. Detection of haemodynamically-significant CAD with RT3D relies on the detection of changes in wall motion and thickening between rest and peak stress in the same way as 2D SE. The availability of multislice and multiplane RT3D permits simultaneous viewing of standard parasternal long, parasternal short and apical volumetric data, such that specificity and accuracy may be better than 2D SE (60). In fact, any chosen imaging plane of the LV can theoretically be visualised allowing a more detailed wall motion analysis than is currently available from standard 2D imaging planes. This improves detection of wall motion abnormalities in the apical segments and allows off-axis images to be interrogated, while preserving overall accuracy (60). Moreover, since the whole LV is imaged simultaneously, image acquisition becomes greatly simplified and faster (61).

(b) Real-Time 3D Full Volume Data Acquisition (RT3DFV): With RT3DFV, full volume 3D datasets are acquired with the transducer positioned over the apex with the volume size adjusted to incorporate the entire left

Table 6 Interpretation of images according to wall motion in individual segments.

Rest	Stress	Diagnosis
Normal	Hyperdynamic	Normal
Normal	Hypokinetic/akinesia/dyskinesia	Ischaemia
Hypokinetic	Hypokinetic	Partial thickness infarction
Hypokinetic/akinetic	Normal	Viability
Hypokinetic/akinetic	Normal at low dose followed by hypokinesia/akinesia at high dose	Viability and ischaemia – 'biphasic response'
Akinetic	Akinetic/dyskinetic	Scar
LV size and function	LV dilatation/fall in EF with regional WMA	Extensive ischaemia

ventricle. Initial studies involving dobutamine stress echocardiography show shorter image acquisition times for 3D imaging than 2D imaging (62). There is no need to acquire parasternal images. As yet, data predominantly show equivalent overall accuracy compared to 2D SE with RT3DFV datasets (63).

3D volume data acquisition

The patient should be asked to stop breathing at end-expiration during the full volume acquisition to minimise issues with 'fault lines' between sub-volumes after reconstruction. Care should be given to ensure good-quality ECG gating and currently obtaining good-quality RT3DFV studies is difficult in patients with arrhythmias, particularly atrial fibrillation. With exercise SE, RT3DFV is more challenging and stitching artefacts due to hyperventilation and cardiac translation are more likely to occur, so much of the data acquired in existing publications relate to pharmacological stress.

In an otherwise suboptimal harmonic 3D SE study, LVO contrast has been shown to improve endocardial border delineation to a similar level to that achieved by contrast-enhanced 2D (64). A limitation to the use of LVO in 3D SE is that this does cause a reduction in temporal resolution (65). This has significance during peak exercise, when the heart rate is high and the number of 3D volumes per cardiac cycle is at levels that may be too low for diagnostic use.

Workflow and display

Present workflow issues for 3D stress analysis include cropping the 3D datasets to create a multiplane reconstruction equivalent to standard 2D image planes. However, this takes time and despite initially acquiring a 3D image, the time taken to create the necessary anatomical views may have an impact on the clinical workflow of SE. There are commercially available 3D stress software packages for processing 3D stress images that improve workflow,

producing whole volume short axis slices for analysis. These derived 2D images can be 'shuffled' and displayed side by side for visual analysis in any format required. The key, however, to improving workflow for 3D SE will be the automation of the cropping and reconstruction process, and the quantification of LV wall motion and thickening.

Reporting

A comprehensive report should include:

1. The indications for the study;
2. Details of stress technique used to include heart rate and blood pressure at rest and peak, workload achieved, dose of pharmacological agents, with the addition of other relevant changes such as a fall in blood pressure during the test;
3. Use of contrast, including dose and type;
4. Symptoms occurring during the test e.g. whether the patient had their typical symptoms during stress;
5. Assessment of the 12-lead ECG findings if used;
6. Image quality: good/moderate/poor;
7. LV size and function at rest and peak;
8. Wall motion assessment/scoring at each stage. Most modern echo systems have a template for reporting based on a 16-segment model. The 17-segment model which includes the LV apex is less commonly used in SE since the apex is stationary in the true long axis and therefore wall motion is less applicable. Reporting is based on the development of delay in onset of contraction (tardokinesis), reduction in systolic thickening (hypokinesis), absent wall thickening in systole (akinesis) and paradoxical wall motion in systole (dyskinesis). The interpretation of wall motion abnormalities is given in Table 6. Examples of regional abnormalities are given in Videos 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15;
9. Qualitative perfusion at rest and peak stress;
10. Interpretation and diagnosis including a conclusion regarding risk stratification.

Video 2

Quad screen for normal SE (peak stress images). View Video 2 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0068/video-2.

Video 3

Quad screen for normal SE (resting images). View Video 3 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0068/video-3.

Video 4

Apical four-chamber images from stress echocardiogram with left ventricular opacification contrast demonstrating ischaemia in the left anterior descending artery. View Video 4 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0068/video-4.

Video 5

Apical two-chamber images from stress echocardiogram with left ventricular opacification contrast demonstrating ischaemia in the left anterior descending artery. View Video 5 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0068/video-5.

Video 6

Invasive coronary angiogram confirming flow-limiting stenosis in the left anterior descending artery. View Video 6 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0068/video-6.

Video 7

Stress echocardiogram (apical four-chamber) demonstrating ischaemia in the circumflex artery. View Video 7 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0068/video-7.

Video 8

Stress echocardiogram (apical two-chamber) demonstrating ischaemia in the circumflex artery. View Video 8 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0068/video-8.

Video 9

Stress echocardiogram (apical three-chamber) demonstrating ischaemia in the circumflex artery. View Video 9 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0068/video-9.

Video 10

Invasive coronary angiogram confirming flow-limiting stenosis in the circumflex artery. View Video 10 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0068/video-10.

Video 11

Stress echocardiogram (apical four-chamber) demonstrating ischaemia in the right coronary artery. View Video 11 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0068/video-11.

Video 12

Stress echocardiogram (apical two-chamber) demonstrating ischaemia in the right coronary artery. View Video 12 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0068/video-12.

Video 13

Stress echocardiogram (apical three-chamber) demonstrating ischaemia in the right coronary artery. View Video 13 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0068/video-13.

Video 14

Invasive coronary angiogram confirming flow-limiting stenosis in the circumflex artery. View Video 14 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0068/video-14.

Video 15

Rest and stress images in the apical two chamber view demonstrating thinning and loss of systolic thickening in the inferior wall consistent with completed myocardial infarction. View Video 15 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-18-0068/video-15.

Audit

Departments should regularly audit and review the indications, safety and outcomes of SE. This is important to demonstrate a high-quality service with accurate and reproducible results. The findings of any further investigations for example coronary angiography or clinical events such as hospital admissions with an

acute coronary syndrome should be fed back to the echo department to cross check SE data. Joint reporting and review of studies on a regular basis contributes to achieving high standards. Audits should be considered in a cycle and may include:

- Audit of outcomes following SE, e.g. using Hospital Episode Statistics (death, myocardial infarction, angiography, admission with angina) to review of outcomes at 1 or 2 years. One such audit every 5 years to be considered reasonable;
- Quality of tests (e.g. review of non-diagnostic tests or sub-maximal exercise). One such audit every year to be considered reasonable;
- Double-reading or review of 10% of studies, e.g. on a recurrent basis at weekly meeting.

Conclusion

SE for the assessment of coronary disease remains a commonly requested investigation. Adherence to recommended guidelines for performing and reporting SE together with robust quality assurance process is vital to ensure patient safety and best results from SE.

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