

## EAE GUIDELINES

# Stress echocardiography expert consensus statement

## European Association of Echocardiography (EAE) (a registered branch of the ESC)

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Received 11 May 2008; accepted after revision 11 May 2008

### KEYWORDS

Stress echocardiography

Stress echocardiography is the combination of 2D echocardiography with a physical, pharmacological or electrical stress. The diagnostic end point for the detection of myocardial ischemia is the induction of a transient worsening in regional function during stress. Stress echocardiography provides similar diagnostic and prognostic accuracy as radionuclide stress perfusion imaging, but at a substantially lower cost, without environmental impact, and with no biohazards for the patient and the physician. Among different stresses of comparable diagnostic and prognostic accuracy, semisupine exercise is the most used, dobutamine the best test for viability, and dipyridamole the safest and simplest pharmacological stress and the most suitable for combined wall motion coronary flow reserve assessment. The additional clinical benefit of myocardial perfusion contrast echocardiography and myocardial velocity imaging has been inconsistent to date, whereas the potential of adding – coronary flow reserve evaluation of left anterior descending coronary artery by transthoracic Doppler echocardiography adds another potentially important dimension to stress echocardiography. New emerging fields of application taking advantage from the versatility of the technique are Doppler stress echo in valvular heart disease and in dilated cardiomyopathy. In spite of its dependence upon operator's training, stress echocardiography is today the best (most cost-effective and risk-effective) possible imaging choice to achieve the still elusive target of sustainable cardiac imaging in the field of noninvasive diagnosis of coronary artery disease.

### Stress echo: a historical and socio-economic perspective

In 1935, Tennant and Wiggers<sup>1</sup> demonstrated that coronary occlusion immediately resulted in instantaneous abnormality of wall motion. Experimental studies conducted some 40 years later on the canine model with ultrasonic crystals and two-dimensional (2D) echocardiography proved that during acute ischaemia<sup>2</sup> and infarction,<sup>3</sup> reductions in regional flow are closely mirrored by reductions in

contractile functions, and set the stage for the clinical use of ultrasonic methods in ischaemic heart disease.

Initial reports describing echocardiographic changes during ischaemia dealt with the use of M-mode techniques in exercise-induced<sup>4</sup> and vasospastic, variant angina.<sup>5</sup> These studies recognized for the first time that transient dyssynergy was an early, sensitive, specific marker of transient ischaemia, clearly more accurate than ECG changes and pain. The clinical impact of the technique became more obvious in the mid-80s with the combination of 2D echocardiography with pharmacological stress, represented by dipyridamole<sup>6</sup> or dobutamine<sup>7</sup>—both much less technically demanding than treadmill exercise commonly used in the USA.<sup>8</sup>

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Stress echocardiography has evolved in Europe in a significantly different fashion from the USA. Pharmacological stress echo has been widely accepted in clinical practice, which has enabled us to collect a tremendous amount of data from large scale, multicentre, effectiveness studies, allowing to establish the safety and prognostic value of stress echo in thousands of patients studied under 'real world conditions'.<sup>9,10</sup> In European clinical practice, stress echo has been embedded in the legal and cultural framework of the existing European laws and medical imaging referral guidelines. The use of radiation for medical examinations and tests is the greatest man-made source of radiation exposure.<sup>11</sup> Small individual risks of each test performed with ionizing radiation multiplied by a billion examinations become significant population risks. For this reason, in Europe, both the law<sup>11</sup> and the referral guidelines for medical imaging<sup>12</sup> recommend a justified, optimized, and responsible use of testing with ionizing radiation. The Euratom Directive 97/43 establishes that the indication and execution of diagnostic procedures with ionizing radiation should follow three basic principles: the justification principle (article 3: 'if an exposure cannot be justified, it should be prohibited'); the optimization principle (article 4: according to the ALARA principle, 'all doses due to medical exposures must be kept As Low As Reasonably Achievable'), and the responsibility principle (article 5: 'both the prescriber and the practitioner are responsible for the justification of the test exposing the patient to ionising radiation'). European Commission referral guidelines were released in 2001 in application of the Euratom Directive and explicitly state that a non-ionizing technique must be used whenever it will give grossly comparable information with an ionizing investigation. For instance, 'because MRI does not use ionizing radiation, MRI should be preferred when both CT and MRI would provide similar information and when both are available'.<sup>12</sup>

In this perspective of the medical, as well as socio-economic and biological impact of medical imaging, it is imperative to increase all efforts to improve appropriateness<sup>13</sup> and minimize the radiation burden of stress imaging for the population and the individual patient.<sup>14</sup> The imperative of sustainability of medical imaging is likely to become increasingly important in the near future, from a US perspective also.<sup>15,16</sup> In the quest for sustainability, stress echocardiography has unsurpassed assets of low cost, absence of environmental impact, lack of biological effects for both the patient<sup>17</sup> and the operator compared with equally accurate, but less sustainable, competing techniques.<sup>18</sup>

## Pathophysiological mechanisms

Stress echocardiography is the combination of 2D echocardiography with a physical, pharmacological, or electrical stress.<sup>19</sup> The diagnostic endpoint for the detection of myocardial ischaemia is the induction of a transient change in regional function during stress. The stress echo sign of ischaemia is a stress-induced worsening of function in a region contracting normally at baseline. The stress echo sign of myocardial viability is a stress-induced improvement of function during low levels of stress in a region that is abnormal at rest. A transient regional imbalance between oxygen demand and supply usually results in myocardial ischaemia, the signs and symptoms of which can be used

as a diagnostic tool. Myocardial ischaemia results in a typical 'cascade' of events in which the various markers are hierarchically ranked in a well-defined time sequence.<sup>20</sup> Flow heterogeneity, especially between the subendocardial and subepicardial perfusion, is the forerunner of ischaemia, followed by metabolic changes, alteration in regional mechanical function, and only at a later stage by electrocardiographic changes, global left ventricular (LV) dysfunction, and pain. The pathophysiological concept of the ischaemic cascade is translated clinically into a gradient of sensitivity of different available clinical markers of ischaemia, with chest pain being the least and regional malperfusion the most sensitive. This is the conceptual basis of the undisputed advantages of imaging techniques, such as perfusion imaging or stress echocardiography over electrocardiogram (ECG) for the noninvasive detection of coronary artery disease.<sup>21</sup> The reduction of coronary reserve is the common pathophysiological mechanism. Regardless of the stress used and the morphological substrate, ischaemia tends to propagate centrifugally with respect to the ventricular cavity:<sup>21,22</sup> it involves primarily the subendocardial layer, whereas the subepicardial layer is affected only at a later stage if the ischaemia persists. In fact, extravascular pressure is higher in the subendocardial than in the subepicardial layer; this provokes a higher metabolic demand (wall tension being among the main determinants of myocardial oxygen consumption) and an increased resistance to flow. In the absence of coronary artery disease, coronary flow reserve (CFR) can be reduced in microvascular disease (e.g. in syndrome X) or LV hypertrophy (e.g. arterial hypertension). In this condition, angina with ST segment depression can occur with regional perfusion changes, typically in the absence of any regional wall motion abnormalities during stress. Wall motion abnormalities are more specific than CFR and/or perfusion changes for the diagnosis of coronary artery disease.<sup>23–28</sup>

**Key point: Wall motion and perfusion (or CFR) changes are highly accurate, and more accurate than ECG changes, for detection and location of underlying coronary artery disease. However, wall motion is more specific and requires ischaemia; perfusion changes are more sensitive and may occur in the absence of true ischaemia.**

## Ischaemic stressors

The three most common stressors are exercise, dobutamine, and dipyridamole. Exercise is the prototype of demand-driven ischaemic stress and the most widely used. However, out of five patients, one cannot exercise, one exercises submaximally and one has an uninterpretable ECG. Thus, the use of an exercise-independent approach allows diagnostic domain of a stress test laboratory to be expanded.<sup>29,30</sup> Pharmacological stressors minimize factors such as hyperventilation, tachycardia, hypercontraction of normal walls, and excessive chest wall movement which render the ultrasonic examination difficult during exercise. All these factors degrade image quality and—in stress echo—worse image quality dramatically leads to higher interobserver variability and lower diagnostic accuracy.

Dipyridamole (or adenosine) and dobutamine act on different receptor populations: dobutamine stimulates adrenoceptors whereas dipyridamole (which accumulates endogenous adenosine) stimulates adenosine receptors.<sup>31</sup>

**Table 1** Pharmacological stresses

	Vasodilator	Dobutamine
Receptor targets	A <sub>2</sub> adenosine	Alpha1; beta1; beta2 adrenoreceptors
Haemodynamic mechanisms	Reduces supply	Increases supply
Physiological targets	Coronary arterioles	Myocardium
Cellular targets	Smooth muscle cells	Myocytes
Antidote	Aminophylline	β-blockers
Stress	Dipyridamole (adenosine)	Dobutamine
Contraindications	Asthma, bradyarrhythmias	Tachyarrhythmias, hypertension

They induce ischaemia through different haemodynamic mechanisms: dobutamine primarily increases myocardial oxygen demand<sup>32</sup> and dipyridamole (or adenosine) mainly decreases subendocardial flow supply<sup>33</sup> (Table 1). In the presence of coronary atherosclerosis, appropriate arteriolar dilation can paradoxically exert detrimental effects on regional myocardial layers or regions already well perfused in resting conditions at the expense of regions or layers with a precarious flow balance in resting conditions.

In 'vertical steal', the anatomical requisite is the presence of an epicardial coronary artery stenosis and the subepicardium 'steals' blood from the subendocardial layers. The mechanisms underlying vertical steal is a fall in perfusion pressure across the stenosis. In the presence of a coronary stenosis, the administration of a coronary vasodilator causes a drop in post-stenotic pressure and, therefore, a critical drop in subendocardial perfusion pressure, which in turn provokes a decrease in absolute subendocardial flow, even with subepicardial overperfusion. Regional thickening is closely related to subendocardial rather than transmural flow and this explains the regional asynergy with ischaemia, despite regionally increased transmural flow. Since endocardial oxygen demands are greater than epicardial, the resistance vessels of the endocardium are more dilated than those of the subepicardium, ultimately resulting in selective subendocardial hypoperfusion. 'Horizontal steal' requires the presence of collateral circulation between two vascular beds with the victim of the steal being the myocardium fed by the more stenotic vessel. The arteriolar vasodilatory reserve must be preserved, at least partially, in the donor vessel and abolished in the vessel receiving collateral flow. After vasodilation, the flow in the collateral circulation is reduced in comparison with resting conditions. Despite the different pathophysiological mechanism, ischaemia induction when appropriately high doses with state-of-the-art protocols are used, dipyridamole and dobutamine tests show a similar diagnostic accuracy.<sup>34-37</sup>

**Key point:** Exercise, dobutamine, and vasodilators (at appropriately high doses) are equally potent ischaemic stressors for inducing wall abnormalities in the presence of a critical epicardial coronary artery stenosis. Dobutamine and exercise mainly act through increased myocardial oxygen demand and dipyridamole and adenosine through reduced subendocardial flow supply subsequent to inappropriate arteriolar vasodilation and steal phenomena.

**Table 2** Stress echocardiography in four equations

Rest + Stress = Diagnosis

Normokinesis + Normo-Hyperkinesis = Normal  
 Normokinesis + Hypo, A, Dyskinesis = Ischaemia  
 Akinesis + Hypo, Normokinesis = Viable  
 A-, Dyskinesis + A-, Dyskinesis = Necrosis

## Diagnostic criteria

All stress echocardiographic diagnoses can be easily summarized into equations centred on regional wall function describing the fundamental response patterns as normal, ischaemic, viable- and necrotic myocardium. In the normal response, a segment is normokinetic at rest and normal or hyperkinetic during stress. In the ischaemic response, a segment worsens its function during stress from normokinesis to hypokinesis, akinesis, or dyskinesis (usually at least two adjacent segments for test positivity are required) (Table 2). In the necrotic response, a segment with resting dysfunction remains fixed during stress. In the viability response, a segment with resting dysfunction may show either a sustained improvement during stress indicating a non-jeopardized myocardium (stunned) or improve during early stress with subsequent deterioration at peak (biphasic response). This response would indicate a jeopardized region (hibernating myocardium) often improving after revascularization.<sup>19,38</sup> A resting akinesis which becomes dyskinesis during stress usually reflects a purely passive, mechanical consequence of increased intraventricular pressure developed by normally contracting walls and should not be considered a true active ischaemia.<sup>39</sup>

As with most imaging techniques, patient-dependent factors can limit image quality in stress echocardiography, which can adversely affect accuracy. Obesity and lung disease, for example, may lead to poor acoustic windows in ~10% of patients. Harmonic imaging and ultrasound contrast agents for LV opacification are now recommended to enhance endocardial border detection. Given that the interpretation of contractile function is subjective, improved image quality can reduce interreader variability.

**Key point:** All stress echo responses follow four basic patterns: normal (rest=stress=normal function); ischaemia (rest=normal; stress=abnormal); necrotic (rest=stress=abnormal); and viability (rest=abnormal; stress=normal or biphasic).

Clear endocardial definition is crucial for optimal interpretation and it is recommended that harmonic imaging, when available, be routinely used for optimal endocardial border detection. Contrast-enhanced endocardial border detection could be used when suboptimal imaging is present.

## Methodology

### General test protocol

During stress echo, electrocardiographic leads are placed at standard limb and precordial sites, slightly displacing (upward and downward) any leads that may interfere with the chosen acoustic windows. A 12-lead ECG is recorded in

resting condition and each minute throughout the examination. An ECG lead is also continuously displayed on the echo monitor to provide the operator with a reference for ST segment changes and arrhythmias. Cuff blood pressure is measured in resting condition and each stage thereafter. Echocardiographic imaging is typically performed from the parasternal long- and short-axis, apical long-axis, and apical four- and two-chamber views. In some cases, the subxyphoid and apical long-axis views are used. Images are recorded in resting condition from all views and captured digitally. A quad-screen format is used for comparative analysis. Recording on video tape alone is not sufficient and may be used as a back-up medium only in cases of technical failure.<sup>40</sup>

Echocardiography is then continuously monitored and intermittently stored. In the presence of obvious or suspected dyssynergy, a complete echo examination is performed and recorded from all employed approaches to allow optimal documentation of the presence and extent of myocardial ischaemia. These same projections are obtained and recorded during the recovery phase, after cessation of stress (exercise or pacing) or administration of the antidote (aminophylline for dipyridamole,  $\beta$ -blocker for dobutamine, nitroglycerine for ergometrine),<sup>40,41</sup> an ischaemic response may occasionally occur late, after cessation of drug infusion.<sup>41</sup> In this way, the transiently dyssynergic area during stress can be evaluated by a triple comparison: stress vs. resting state; stress vs. recovery phase; and at peak stress. It is critical to obtain the same views at each stage of the test. Analysis and scoring of the study are usually performed using a 16- or 17-segment model of the left ventricle<sup>42</sup> and a four-grade scale of regional wall motion analysis.

Diagnostic endpoints of stress echocardiographic testing are: maximum dose (for pharmacological) or maximum workload (for exercise testing); achievement of target heart rate; obvious echocardiographic positivity (with akinesis of  $\geq 2$  LV segments); severe chest pain; or obvious electrocardiographic positivity (with  $>2$  mV ST segment shift). Submaximal non-diagnostic endpoints of stress echo testing are non-tolerable symptoms or limiting asymptomatic side effects such as hypertension, with systolic blood pressure  $>220$  mmHg or diastolic blood pressure  $>120$  mmHg, symptomatic hypotension, with  $>40$  mmHg drop in blood pressure; supraventricular arrhythmias, such as supraventricular tachycardia or atrial fibrillations; and complex ventricular arrhythmias, such as ventricular tachycardia or frequent, polymorphic premature ventricular beats.

**Key point:** Standardized protocols for stress echocardiography are required to conduct a safe study with optimal diagnostic accuracy. Careful monitoring of vital signs (clinical status, heart rate, blood pressure, and ECG beyond echo) is required during stress echocardiography, which should be done by cardiologists with Basic Life Support and Advanced Cardiac Life Support training.

### Specific test protocols

The most frequently used stressors for echocardiographic tests are exercise, dobutamine, and dipyridamole.

#### Exercise

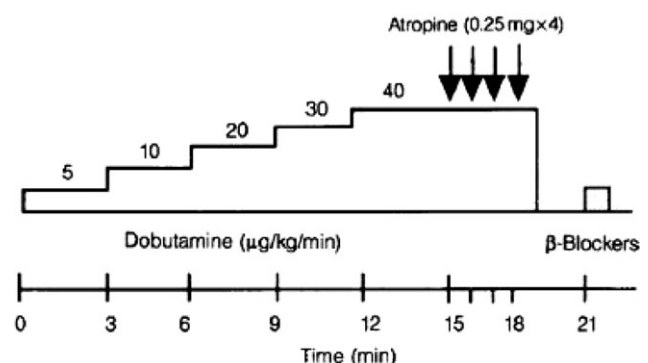
Exercise echocardiography can be performed using either a treadmill or a bicycle protocol. When a treadmill test is performed, scanning during exercise is not feasible, so most

protocols rely on immediate post-exercise imaging. It is imperative to accomplish post-exercise imaging as soon as possible ( $\leq 1$  min from cessation of exercise). To accomplish this, the patient is moved immediately from the treadmill to an imaging bed and placed in the left lateral decubitus position so that imaging may be completed within 1–2 min. This technique assumes that regional wall motion abnormalities will persist long enough into recovery to be detected. When abnormalities recover rapidly, false-negative results occur. The advantages of treadmill exercise echocardiography are the widespread availability of the treadmill system and a greater feasibility due to the fact that a number of patients are unable to cycle. Information on exercise capacity, heart rate response, and rhythm and blood pressure changes are analysed and, together with wall motion analysis, become part of the final interpretation.

Bicycle exercise echocardiography is performed during either an upright or a recumbent posture. The patient pedals against an increasing workload at a constant cadence (usually 60 rpm). The workload is escalated in a stepwise fashion while imaging is performed. Successful bicycle stress testing requires co-operation of the patient (to maintain the correct cadence) and co-ordination (to perform pedalling action). The most important advantage of bicycle exercise is the chance to obtain images during the various levels of exercise (rather than relying on post-exercise imaging). Although imaging can be done throughout the exercise protocol, in most cases, interpretation is based on a comparison of resting and peak exercise images. In the supine posture, it is relatively easy to record images from multiple views during graded exercise. With the development of ergometers that permit leftward tilting of the patients, the ease of image acquisition has been further improved. In the upright posture, imaging is generally limited to either apical or subcostal views. By leaning the patient forward over the handlebars and extending the arms, apical images can be obtained in the majority of patients. To record subcostal views, a more lordotic position is necessary and care must be taken to avoid foreshortening of the apex.

#### Dobutamine

The standard dobutamine stress protocol usually adopted consists of continuous intravenous infusion of dobutamine in 3 min increments, starting with 5  $\mu\text{g}/\text{kg}/\text{min}$  and increasing to 10, 20, 30, and 40  $\mu\text{g}/\text{kg}/\text{min}$  (Figure 1). If no endpoint is reached, atropine (in doses 0.25 mg up to a



**Figure 1** State-of-the-art protocol of dobutamine stress echocardiography.



maximum of 1 mg) is added to the 40  $\mu\text{g}/\text{kg}/\text{min}$  dobutamine infusion. Other more conservative protocols—with longer duration of steps and peak dobutamine dosage of 20–30  $\mu\text{g}/\text{kg}/\text{min}$ —have been proposed but are limited by unsatisfactory sensitivity. More aggressive protocols—with higher peak dosage of dobutamine up to 50–60  $\mu\text{g}/\text{kg}/\text{min}$  and atropine sulphate up to 2 mg—have also been proposed, but safety concern remains and to date no advantages have been shown in larger studies.

### Dipyridamole

The standard dipyridamole protocol consists of an intravenous infusion of 0.84 mg/kg over 10 min, in two separate infusions: 0.56 mg/kg over 4 min ('standard dose'), followed by 4 min of no dose and, if still negative, and additional 0.28 mg/kg over 2 min. If no endpoint is reached, atropine (doses of 0.25 mg up to a maximum of 1 mg) is added. The same overall dose of 0.84 mg/kg can be given over 6 min—the shorter the infusion time, the higher the sensitivity<sup>43</sup> (Figure 2). Aminophylline (240 mg iv) should be available for immediate use in case an adverse dipyridamole-related event occurs and routinely infused at the end of the test independent of the result.

### Adenosine

Adenosine can be used in a similar manner and is typically infused at a maximum dose of 140  $\mu\text{g}/\text{kg}/\text{min}$  over 6 min. Imaging is performed prior to and after starting adenosine infusion.

### Pacing

The presence of a permanent pacemaker can be exploited to conduct a pacing stress test in a totally non-invasive manner by externally programming the pacemaker to increasing frequencies.<sup>44</sup> Pacing is started at 100 bpm and increased every 2 min by 10 bpm until the target heart rate (85% of age-predicted maximal heart rate) is achieved or until other standard endpoints are reached. The same protocol can also be followed in an accelerated fashion, with faster steps (20–30 s each), up to the target heart rate. A limiting factor is, however, that several pacemakers cannot be programmed to the target heart rate. This should be checked before the patient is scheduled for such a test. Two-

dimensional echocardiographic images are obtained before pacing and throughout the stress test with the final recording being obtained after 3 min of pacing at the highest rate reached (usually 150 bpm) or the target heart rate.

### Test for vasospasm: ergometrine

A bolus injection of ergometrine (50  $\mu\text{g}$ ) is administered intravenously at 5 min intervals until a positive response is obtained or a total dose of 0.35 mg is reached. The 12-lead ECG is recorded after each ergonovine injection and LV wall motion is monitored continuously. Positive criteria for the test include the appearance of transient ST-segment elevation or depression  $>0.1\text{ mV}$  at 0.08 s after the J point (ECG criteria) or reversible wall motion abnormality by 2D echocardiography (echocardiographic criteria). The criteria for terminating the test are as follows: positive response defined as ECG or echocardiographic criteria, total cumulative dose of 0.35 mg ergonovine, or development of significant arrhythmia or changes in vital signs (systolic blood pressure  $>200\text{ mmHg}$  or  $<90\text{ mmHg}$ ). An intravenous bolus injection of nitroglycerin is administered as soon as an abnormal response is detected; sublingual nifedipine (10 mg) is also recommended to counter the possible delayed effects of ergometrine.<sup>45,46</sup> These drugs can be administered as required.

**Key points: Maximal, symptom-limited tests are required to optimize accuracy of stress echo. Semi-supine exercise is the preferred option for physical exercise. Both dobutamine and dipyridamole should be performed with high-dose protocols to obtain high sensitivities, comparable with maximal exercise.**

### Diagnostic accuracy

Exercise,<sup>47–66</sup> high-dose dobutamine,<sup>30,34,58,63–110</sup> and high-dose (accelerated or with atropine) dipyridamole<sup>6,29,34,50,64,70,74,92–120</sup> have not only similar accuracies, but also similar sensitivities<sup>36,120</sup> (Tables 3 and 4). Familiarity with all forms of stress is an index of the quality of the echo lab. In this way, indications in the individual patient can be optimized, thereby avoiding the relative and absolute contraindications of each test. For instance, a patient with severe hypertension and/or a history of

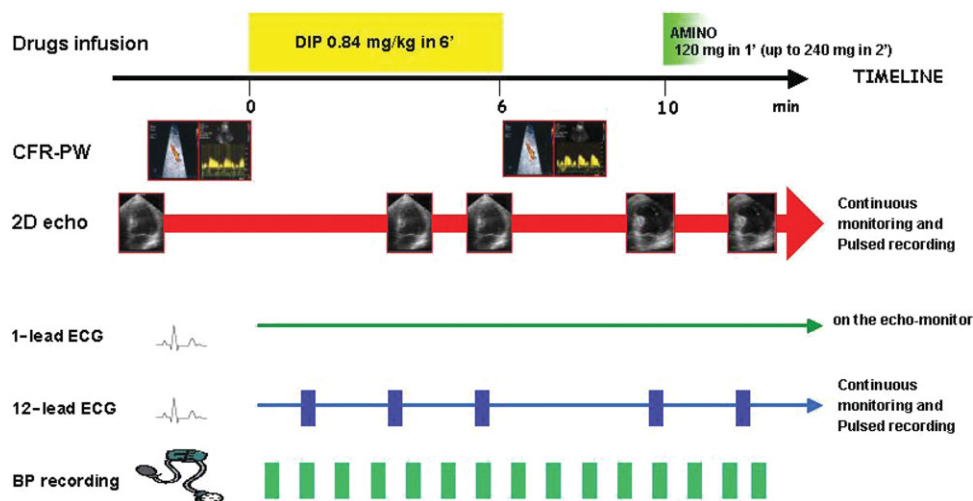


Figure 2 State-of-the-art protocol of dipyridamole stress echocardiography.

**Table 3** Dipyridamole-stress vs dobutamine-stress echocardiography for detection of coronary artery disease

	Sn (%), n		Sn 1 v (%), n		Sn multiv (%), n		Sp (%), n		Acc (%), n	
	Dip	Dop	Dip	Dop	Dip	Dop	Dip	Dop	Dip	Dop
Salustri <i>et al.</i> <sup>70</sup>	82, 23/28	79, 22/28	50, 5/10	40, 4/10	72, 13/18	67, 12/18	89, 16/18	78, 14/18	85, 39/46	72, 36/46
Pingitore <i>et al.</i> <sup>34</sup>	82, 75/92	84, 77/92	71, 29/41	78, 32/41	91, 46/51	87, 44/51	94, 17/18	89, 15/18	84, 92/110	84, 92/110
San Roman <i>et al.</i> <sup>115</sup>	81, 54/66	78, 52/66	68, 22/32	75, 24/32	94, 32/34	82, 28/34	94, 34/36	88, 32/36	86, 88/102	82, 82/102
Loimaala <i>et al.</i> <sup>118</sup>	93, 41/44	95, 42/44	92, 24/26	92, 24/26	94, 17/18	100, 18/18	75, 12/16	63, 10/16	87, 53/60	88, 52/60
Nedeljovic <i>et al.</i> <sup>119</sup>	96, 66/69	93, 64/69	95, 54/57	95, 54/57	100, 12/12	100, 12/12	92, 44/48	92, 44/48	91, 107/117	94, 110/117
Total	87, 259/299	86, 257/299	81, 134/166	83, 138/166	90, 120/133	86, 114/133	90, 123/136	84, 115/136	87, 379/435	85, 372/435

**Table 4** Dipyridamole (DIP) stress vs exercise (EXE) stress echocardiography for detection of coronary artery disease

Study	Sensitivity			Specificity	Accuracy	Feasibility						
	Single vessel DIP	Multivessel EXE	Global DIP			EXE	DIP	EXE	DIP	EXE	DIP	EXE
Picano <i>et al.</i> <sup>23</sup>	6/13 (46%)	8/13 (62%)	12/12 (100%)	11/12 (92%)	18/25 (72%)	19/25 (76%)	15/15 (100%)	13/15 (87%)	33/40 (83%)	32/40 (80%)	55/55 (100%)	40/55 (73%)
Deutsch <i>et al.</i> <sup>117</sup>	19/30 (63%)	20/30 (67%)	18/21 (86%)	18/21 (86%)	37/51 (73%)	38/51 (75%)	13/15 (87%)	12/15 (80%)	50/66 (76%)	50/66 (76%)	74/80 (95%)	66/80 (84%)
Marangelli <i>et al.</i> <sup>52</sup>	4/16 (25%)	13/16 (81%)	11/19 (58%)	18/19 (95%)	15/35 (43%)	31/35 (89%)	23/25 (92%)	22/25 (88%)	38/60 (63%)	53/60 (88%)	80/82 (92%)	84/100 (84%)
Beleslin <i>et al.</i> <sup>51</sup>	78/108 (72%)	95/108 (88%)	10/11 (91%)	10/11 (91%)	88/119 (74%)	105/119 (88%)	16/17 (94%)	14/17 (82%)	105/136 (77%)	118/136 (87%)		
Dagianti <i>et al.</i> <sup>64</sup>	3/10 (30%)	7/10 (70%)	10/15 (70%)	12/15 (80%)	13/25 (52%)	19/25 (76%)	34/35 (97%)	33/35 (94%)	47/60 (78%)	52/60 (87%)	60/60 (100%)	57/60 (95%)
Bjornstad <i>et al.</i> <sup>59</sup>					21/31 (68%)	26/31 (84%)	6/6 (100%)	4/6 (67%)	27/37 (73%)	30/37 (81%)		
Schroder <i>et al.</i> <sup>95</sup>					50/65 (77%)	35/65 (53%)	8/9 (89%)	8/9 (89%)	58/74 (78%)	43/74 (58%)	119/121 (98%)	74/83 (89%)
Loimaala <i>et al.</i> <sup>118</sup>	24/26 (92%)	23/26 (88%)	17/18 (94%)	17/18 (94%)	41/44 (93%)	40/44 (91%)	12/16 (75%)	7/16 (44%)	53/60 (88%)	47/60 (78%)		
Total	134/203 (66%)	166/203 (72%)	78/96 (81%)	86/96 (90%)	283/395(72%)	313/395 (79%)	127/138 (92%)	113/138 (82%)	411/533 (77%)	425/533 (80%)	388/398 (97%)	321/398 (81%)

significant atrial or ventricular arrhythmias can more reasonably undergo to the dipyridamole stress test which, unlike dobutamine, has no arrhythmogenic or hypertensive effect. In contrast, a patient with severe conduction disturbances or advanced asthmatic disease should undergo the dobutamine stress test, since adenosine has a negative chronotropic and dromotropic effect, as well as a documented bronchoconstrictor activity. Patients either taking xanthine medication or under the effect of caffeine contained in drinks (tea, coffee, and cola) should undergo the dobutamine test. Both dipyridamole and dobutamine have overall tolerance and feasibility. The choice of one test over the other depends on patient characteristics, local drug cost, and the physician's preference. It is important for all stress echocardiography laboratories to become familiar with all stresses to achieve a flexible and versatile diagnostic approach that enables the best stress to be tailored to individual patient needs. Antianginal medical therapy (in particular, beta-blocking agents) significantly affects the diagnostic accuracy of all forms of stress; therefore, it is recommended, whenever possible, to withhold medical therapy at the time of testing to avoid a false-negative result.

**Key point:** Physical or pharmacological (inotropic or vasodilator) stress echocardiography have comparable diagnostic accuracies. The choice of one test over the other will depend on relative contraindications. Large-volume laboratories should be fully acquainted with all the three main forms of stress in order to apply the test in all patients. In the presence of a submaximal first-line stress for limiting side effects, the second choice should be applied, since submaximal (physical or pharmacological) stresses have suboptimal diagnostic value.

### Prognostic value of inducible myocardial ischaemia

The presence (or absence) of inducible wall motion abnormalities separates patients with different prognoses. Information has been obtained from data banks of thousands of patients—also with multicentre design—for exercise,<sup>121–137</sup> dobutamine,<sup>83,138–191</sup> and dipyridamole.<sup>34,158,159,164,167–169,188,192–222</sup> A normal stress echocardiogram yields an annual risk of 0.4–0.9% based on a total of 9000 patients,<sup>137</sup> the same as for a normal stress myocardial perfusion scan. Thus in patients with suspected coronary artery disease, a normal stress echocardiogram implies excellent prognosis and coronary angiography can safely be avoided. The positive and the negative response can be further stratified with interactions with clinical parameters (diabetes, renal dysfunction, and therapy at the time of test), resting echo (global LV function), and additive stress echo parameters (LV cavity dilatation, CFR, and previous revascularization).<sup>223–229</sup>

The established prognostic stress echo parameters with their relative event rate are shown in *Tables 5 and 6*.

**Key point:** Physical or pharmacological (inotropic or vasodilator) stress echocardiography have a comparable prognostic power of stratification. The most extensive evidence is available with dipyridamole, dobutamine, and exercise tests. A normal baseline and stress echocardiogram gives an annual risk for death of 0.4–0.9%, the same as for a normal stress myocardial perfusion scan. Thus, in patients with suspected coronary artery

**Table 5** Stress echo risk titration of a positive test

1-year risk (hard events)	Intermediate (1–3% year)	High (>10% year)
Dose/workload	High	Low
Resting EF	>50%	<40%
Anti-ischaemic therapy	Off	On
Coronary territory	LCx/RCA	LAD
Peak WMSI	Low	High
Recovery	Fast	Slow
Positivity or baseline dyssynergy	Homozonal	Heterozonal
CFR	>2.0	<2.0

LAD, left anterior descending artery; LCx, left circumflex; RCA, right coronary artery.

disease, a normal stress echocardiogram implies an excellent prognosis and coronary angiography can safely be avoided.

### Indications and prognostic value of myocardial viability assessment

By far, the widest experience is available with low-dose dobutamine stress echocardiography,<sup>7,230–266</sup> the preferred stressor for assessing myocardial viability. However, it is also possible to assess the presence of myocardial viability using low-dose dipyridamole or low-level exercise or enoximone.<sup>267–272</sup>

In the setting of ischaemia, loss of myocardial contractile function may be due to myocardial necrosis, stunning, or hibernation. Whereas myocardial necrosis usually alludes to irreversible myocardial dysfunction, stunning and hibernation reflect reversibility of myocardial function. Revascularization of chronically, but reversibly, dysfunctional myocardium, often referred to as hibernating or viable, has emerged as an important alternative in the treatment of heart failure secondary to coronary artery disease. Observational studies have indeed suggested that patients with ischaemic LV dysfunction and a significant amount of viable myocardium (at least five segments or a WMSI >0.25)<sup>250–266</sup> have lower perioperative mortality, greater improvements in regional and global LV function, fewer heart failure symptoms, and improved long-term survival after revascularization than patients with large areas of non-viable myocardium.

**Table 6** Stress echo risk titration of a negative test

1-year risk (hard events)	Very low (<0.5% year)	Low (1–3% year)
Stress	Maximal	Submaximal
Resting EF	>50%	<40%
Anti-ischaemic therapy	Off	On
CFR	>2.0	<2.0

CFR, coronary flow reserve.

The protocol in most stress echocardiography laboratories uses dobutamine infusion at two low-dose stages (5 and 10  $\mu\text{g}/\text{kg}/\text{min}$ ), with each stage lasting 3 min. Some advocate using an even lower starting dose of 2.5  $\mu\text{g}/\text{kg}/\text{min}$  since in patients with critical coronary stenosis, myocardial ischaemia may be precipitated even with doses as low as 5  $\mu\text{g}/\text{kg}/\text{min}$ . The benefit of proceeding to higher doses of dobutamine, even if contractile reserve is demonstrated at lower doses, is to observe a 'biphasic response'. It is not surprising that the biphasic response has the best predictive value of all the possible responses to dobutamine in determining improvement in LV function following revascularization. In a recent study, <15% of myocardial segments demonstrating either no change or sustained improvement with low- and high-dose dobutamine had functional recovery with revascularization, whereas 72% of segments with a biphasic response recovered function.<sup>266</sup> Thus, the combined low- and high-dose approach in all patients who do not have contraindications should be recommended.

**Key point:** Dobutamine stress echocardiography is by far the most widely used method for assessing viable myocardium. This is mandatory in patients with LV dysfunction who may benefit from coronary revascularization. When dobutamine is contraindicated or not well tolerated, several other stresses (low-level exercise, adenosine, dipyridamole, and enoximone) can be used to elicit a regional inotropic reserve in viable myocardium.

### The diagnostic and prognostic value of CFR during vasodilator stress testing

Stress testing of CFR introduces a change in the choice of stress, the use of transducers, and the methodology of testing.<sup>273–275</sup> Besides the classic projections for stress echocardiography testing, specific projection for left anterior descending (LAD) coronary artery imaging should be integrated into the cardiac imaging sequence. The posterior descending artery and the left circumflex artery can be imaged with dedicated imaging projections, but with greater difficulty and a lower success rate. The use of CFR as a 'stand-alone' diagnostic criterion suffers from so many structural limitations that render it little more than an academic assumption: first, only the LAD is sampled; and secondly, the CFR cannot distinguish between microvascular and macrovascular coronary disease.<sup>276</sup> Therefore, it is much more interesting (and clinically realistic) to evaluate the additive value over conventional wall motion for LAD detection. The assessment of CFR adds sensitivity for LAD disease—with a modest loss in specificity. Coronary flow reserve and wall motion analysis offer, under many aspects, complementary information during stress echo. From the pathophysiological viewpoint, wall motion positivity requires ischaemia as a necessary pre-requisite, whereas CFR can be impaired in the absence of induced ischaemia. A normal CFR has a higher negative predictive value. Therefore, the two pieces of information on flow and function can complement each other, since a wall motion abnormality is more efficient to include coronary artery disease and a normal CFR is more efficient to exclude it.<sup>273–275</sup> In patients with idiopathic dilated cardiomyopathy,<sup>277,278</sup> an abnormal CFR during dipyridamole infusion identifies a subgroup at high risk of developing progressive ventricular deterioration

and heart failure. In the same subset of patients, the combination of the two parameters has an added value and is complementary in its power of prognostication.<sup>278</sup> The combination of conventional wall motion analysis with 2D-echo and CFR with pulsed Doppler flowmetry of mid-distal LAD artery has been shown to provide an added and complementary power of prognostication in patients with known or suspected coronary artery disease.<sup>279,280</sup> A reduced CFR is an additional parameter of ischaemia severity in the risk stratification of the stress echocardiographic response whereas patients with a negative test for wall motion criteria and normal CFR have a favourable outcome during dipyridamole stress echocardiography.

**Key point:** Whenever suitable technology and dedicated expertise are available, it is recommended to perform dual imaging vasodilator stress echocardiography for diagnostic and prognostic purposes. Coronary flow reserve on LAD territory is highly feasible in expert hands, and is not useful as a stand-alone diagnostic criterion due to low specificity and LAD-limited information; however, it does add critical prognostic value when added to conventional wall motion analysis exploring all LV territories.

### Safety of pharmacological stress echocardiography

Minor, but limiting, side effects preclude the achievement of maximal pharmacological stress in <10% of patients with dobutamine<sup>9</sup> and <5% in patients with dipyridamole stress.<sup>281–295</sup> The most frequent minor and major complications during stress echo and their frequencies are shown in Tables 7–9. The data emphasize some obvious, albeit sometimes neglected, points. First, pharmacological stress tests should always be performed with an attending

**Table 7** Life-threatening complications in single-center experience (>1000 patients), multicenter studies (EDIC), and multicenter registries for dobutamine stress echocardiography

Study	Patients	Complication(s)
<i>Single institution experience</i>		
Mertes <i>et al.</i> <sup>283</sup>	1118	None <sup>a</sup>
Pellikka <i>et al.</i> <sup>284</sup>	1000	1 AMI, 4 VT, 1 prol ischaemia
Zahn <i>et al.</i> <sup>285</sup>	1000	1 VF, 1LVF, 1 seizure
Seknus and Marwick <sup>286</sup>	3011	5 VT, 1 AMI, 1 prol ischaemia, 1 hypo
Elhendy <i>et al.</i> <sup>287</sup>	1164	7 VT
Bremer <i>et al.</i> <sup>288</sup>	1035	1 VF, 1 VT
Poldermans <i>et al.</i> <sup>289</sup>	1734	3 VF, 13 VT, 6 hypo
Mathias <i>et al.</i> <sup>290</sup>	4033	1 VFm 8 VT, 1 MI; 5 atropine intoxications
<i>Multicenter registry</i>		
Picano <i>et al.</i> <sup>9</sup>	2949	2 VF, 2 VT, 2 AMI, 1 prol ischaemia, 1 hypo
Pezzano <i>et al.</i> (RITED) 1994	3041	2 VF, 1 asystole
Beckmann <i>et al.</i> <sup>292</sup>	9354	324 (2 VF)
Varga <i>et al.</i> <sup>295</sup>	35 103	63 (5 deaths)
Total	64 542	461

<sup>a</sup>No life-threatening complications reported; however, minor and self-limiting adverse effects were documented.



**Table 8** Life-threatening complications in multicenter studies (EPIC) and multicenter registries for Dipyridamole stress echocardiography

Study	Patients	Complications
<i>Multicenter registry</i>		
Picano <i>et al.</i> <sup>281</sup>	10 451	1 cardiac death, 1 asystole, 2 AMI, 1 pulmonary oedema, 1 sustained VT
Varga <i>et al.</i> <sup>295</sup>	24 599	19 (1 death)
Total	35 050	25

**Table 9** Safety profile of pharmacologic stress echocardiography

	Dobutamine	Dipyridamole
% submaximal tests	10	5
Side effects	1/300 exams	1/1000
TV, FV	++	+
High grade AV block	+	++
Death	1/5000	1/10 000

physician present. Secondly, every test carries a definite, albeit minor risk. Thirdly, not all stress tests carry the same risk of major adverse reactions and dobutamine stress testing may be more dangerous than other forms of pharmacological stress, such as those produced by dipyridamole or adenosine. These conclusions come convergently from multicenter trials, meta-analyses of published literature and the Registry of Complications based on prospective data acquisition (German Registry) and retrospective data retrieval. Physical stress with exercise is probably safer than pharmacological testing.<sup>294,295</sup>

**Key point: Exercise is safer than pharmacological stress. Among pharmacological stresses, dipyridamole is safer than dobutamine. Both the doctor and the patient should be aware of the rate of complications—and the rate of complications (derived from literature and from the lab experience) should be spelled out in the informed consent.**

### Indication to stress echo

Indications for stress echocardiography can also be grouped in very broad categories, which could eventually encompass the overwhelming majority of patients:

- (i) coronary artery disease diagnosis;
- (ii) prognosis and risk stratification in patients with established diagnosis (e.g. after myocardial infarction);
- (iii) preoperative risk assessment;
- (iv) evaluation for cardiac aetiology of exertional dyspnoea;
- (v) evaluation after revascularization;
- (vi) ischaemia location,<sup>296</sup>
- (vii) evaluation of heart valve stenosis severity.

As a rule, the less informative the exercise ECG test is, the stricter the indication for stress echocardiography will be. The three main specific indications for stress echocardiography can be summarized as follows:

- (i) patients in whom the exercise stress test is contraindicated (e.g. patients with severe arterial hypertension);
- (ii) patients in whom the exercise stress test is not feasible (e.g. those with intermittent claudication);
- (iii) patients in whom the exercise stress test was non-diagnostic or yielded ambiguous results;
- (iv) left bundle branch block or significant resting ECG changes that makes any ECG interpretation during stress difficult;
- (v) submaximal stress ECG.

Stress echocardiography yields the greatest incremental diagnostic and prognostic value in patients in whom exercise electrocardiography is a non-diagnostic, ambiguous, or inconclusive. Pharmacological stress echocardiography is the choice for patients in whom exercise is unfeasible or contraindicated. The results of physical and pharmacological stress echo should be used in both in- and out-patients as 'a gatekeeper' to coronary angiography. In fact, for any given coronary anatomy, the prognostic benefit of recanalization is much higher with documented ischaemia on stress testing. Patients with stress echo positivity, especially those with a 'high-risk' positivity pattern (occurring at low dose or workload, with slow recovery and/or antidote resistance, with akinesis or dyskinesis of more than five segments of the left ventricle), should be referred to coronary angiography. In *Table 10*, several clinical targets of stress echocardiography are reported.

**Key point: Stress echocardiography should not be used as a first-line imaging technique for diagnostic and prognostic purposes in patients with known or suspected coronary artery disease but only when exercise ECG stress test is either non-diagnostic or non-interpretable (e.g. for left**

**Table 10** Clinical targets: CAD, DCM, valvular disease, and pulmonary hypertension

Clinical condition	Pathophysiologic target	Stress of choice	Echo variable
CAD	Myocardial ischaemia	Ex, dob, dip	WM
DC	Contractile reserve	Dob (ex, dip)	WM
Diabetes, hypertension, HCM	Coronary flow reserve	Dip (dob, ex)	PW LAD
Transmitral gradient	Increase in cardiac output	Ex, dob	PW mitral
Transaortic gradient	Increase in cardiac output	Ex, dob	CW aortic
Pulmonary hypertension	Pulmonary congestion/vasoconstriction	Ex	CW TR

CW, continuous wave Doppler; DC, dilated cardiomyopathy; DOB, dobutamine; DIP, dipyridamole; EX, exercise; HCM, hypertrophic cardiomyopathy; Hyperv, hyperventilation; LAD, left anterior descending coronary artery; PW, pulsed wave Doppler; TR, tricuspid regurgitation; WM, wall motion.

bundle branch block or pacemaker). The less informative and/or interpretable exercise electrocardiography is the higher is the level of appropriateness to stress echocardiography.

## Special subsets

### Valvular heart disease

The application of stress echocardiography to valvular heart disease is still a moving target and not all guidelines<sup>297,298</sup> recognize a specific role for this technique in the work-up of patients. In fact, the ESC document does not recognize any role for stress echocardiography in this set of patients, whereas the AHA/ACC document defines particular subsets in which stress echocardiographic parameters are used in surgical decision-making.

*Role of stress Doppler echocardiography in the evaluation of aortic stenosis severity in patients with low-transvalvular rates and gradients and left ventricular dysfunction and in asymptomatic patients with severe aortic stenosis*

In several specific cases, such as in patients with low-gradient aortic stenosis, the use of stress echocardiography in the decision-making process has significantly modified the outcome of patients. In selected patients with low-flow/low-gradient aortic stenosis and LV dysfunction, it may be useful to determine the transvalvular pressure gradient and to calculate valve area during a baseline state and again during exercise or low-dose pharmacological (i.e. dobutamine infusion) stress, with the goal of determining whether stenosis is severe or only moderate in severity.<sup>299–310</sup>

This approach is based on the notion that patients who do not have true anatomically severe stenosis will exhibit an increase in the valve area and little change in gradient during an increase in stroke volume.<sup>300–303</sup> Thus, if a dobutamine infusion produces an increase in stroke volume and an increase in valve area  $>0.2 \text{ cm}^2$  and little change in gradient, it is likely that baseline evaluation overestimated the severity of stenosis. In contrast, patients with severe aortic stenosis will have a fixed valve area with an increase in stroke volume and an increase in gradient. These patients are likely to respond favourably to surgery. Patients who fail to show an increase in stroke volume with dobutamine ( $<20\%$ ), referred to as 'lack of contractile reserve', appear to have a very poor prognosis with either medical or surgical therapy.<sup>305,309</sup> Although patients with low-output severe aortic stenosis have a poor prognosis, in those with contractile reserve, outcome is still better with aortic valve replacement than with medical therapy. The management decisions in patients with low-gradient aortic stenosis should therefore take into account the results of dobutamine echocardiograms (Table 11). The management of asymptomatic patients with aortic stenosis remains a source of debate. The wide variation in their individual outcome has recently raised the question of early elective surgery. In this respect, exercise testing is an interesting tool, and several studies have shown its prognostic value. When combined with pre-exercise imaging, it seems to provide incremental prognostic value when compared with either resting echo data or exercise ECG results. A reduced exercise tolerance, with development of dyspnoea or ST segment depression, is associated with a worse outcome. On top of this conventional, established information, a mean pressure gradient rise  $>20 \text{ mmHg}$  may contribute to a worse

**Table 11** Dobutamine stress echo in low gradient, low flow aortic stenosis

	Severe AS	Pseudostenosis	Indeterminate
Aortic valve area	No change	Increase $\geq 0.3 \text{ cm}^2$	No change
Mean pressure gradient	Markedly increased	No change	No change
Stroke volume $>20\%$	Yes	Yes	No

prognostic outcome and possibly favour early replacement in borderline cases.<sup>311</sup> More confirmatory, data are required to incorporate this parameter into the daily work-up of the asymptomatic aortic stenosis patients with high gradients.

**Key point:** In the presence of LV dysfunction and low-gradient aortic stenosis, low-dose dobutamine stress echocardiography is recommended to assess stenosis severity. In asymptomatic patients with severe aortic stenosis, exercise echo may play a role in decision-making.

*Role of stress Doppler echocardiography in the evaluation of patients with mitral stenosis and discordant symptoms and stenosis severity.*

A baseline resting transthoracic echocardiography examination usually suffices for dictating management in asymptomatic patients with mild stenosis (who are left on medical therapy) and in symptomatic patients with moderate-to-severe stenosis, who are candidates for either percutaneous or surgical mitral valve repair. In a few patients, there may nonetheless be a need for a more detailed evaluation of the haemodynamic consequences of the stenosis, whenever the symptomatic status does not fit with stenosis severity. In asymptomatic patients with severe stenosis (mean gradient  $>10 \text{ mmHg}$  and mitral valve area below  $1.0 \text{ cm}^2$ ), or symptomatic patients with moderate stenosis (with mean gradient between 5 and  $10 \text{ mmHg}$  and mitral valve area between  $1.0$  and  $1.5 \text{ cm}^2$ ), the measurement of pulmonary pressures during exercise (or dobutamine) may help distinguish those who could benefit from surgery from those who should continue on medical treatment.<sup>312–314</sup> In these patients, measurement of systolic pulmonary pressure (from the tricuspid regurgitant flow velocity) and transmitral pressure gradient during exercise may be used as surrogates to the invasive measurements, thus avoiding cardiac catheterization.

**Key point:** Exercise (or dobutamine) echocardiography with focus on transmitral pressure gradient and pulmonary pressure is useful in assessing the nature of symptoms in patients with mitral stenosis still in the grey zone between valve repair and medical treatment after rest evaluation.

*Stress Doppler echocardiography for the evaluation of patients with regurgitant lesions.*

In very selected cases, when symptoms are discrepant with the severity of the regurgitant lesion, stress echocardiography may prove to be a useful tool for identifying patients with a worse prognosis. Indeed the lack of contractile reserve—failure to increase LV ejection fraction during exercise—unmasks patients with latent LV dysfunction who might be referred for surgery.<sup>315–320</sup> The lack of contractile

reserve and a rise in pulmonary artery systolic pressure during exercise >60 mmHg unmasks patients with latent LV dysfunction who might be referred for surgery.<sup>298</sup> Exercise echocardiography has been used to reveal the presence of severe mitral regurgitation with exercise in patients with rheumatic mitral valve disease and only mild mitral stenosis and regurgitation at rest.<sup>315</sup> Similarly, exercise echocardiography is of value in identifying haemodynamically significant dynamic mitral regurgitation in patients with LV systolic dysfunction. In some patients, dynamic mitral regurgitation can account for acute pulmonary oedema and predicts poor outcome. Patients who presented an increase in the effective regurgitant orifice or systolic pulmonary pressure at peak exercise had a higher incidence of morbidity and mortality.<sup>317</sup> As in patients with chronic mitral regurgitation, the development of irreversible LV dysfunction is a major concern in the management of asymptomatic patients with severe aortic regurgitation. In patients with normal function at rest, a stress-induced increase in contractile reserve, following exercise or dobutamine, before surgery predicts improvement in LV function after valve replacement surgery. The usefulness of contractile reserve can be extended to the evaluation of aortic regurgitation patients who have developed LV dysfunction. Any increase in ejection fraction during dobutamine stress echocardiography predicted favourable outcome after surgery and a return to systolic function. Despite these data, the role of stress testing is less well established in patients with aortic regurgitation than in those with mitral regurgitation.

**Key point: Stress echocardiography has been shown to be useful for the assessment of regurgitant valve lesions when symptoms do not fit with severity at rest echocardiography.**

#### Non-cardiac surgery

Patients undergoing non-cardiac surgery are at significant risk of cardiovascular morbidity and mortality. Perioperative myocardial infarction is the most frequent complication in this respect. Evidence exists that coronary plaque rupture, leading to thrombus formation and subsequent vessel occlusion, is the dominant causative mechanism behind such an event, similar to myocardial infarctions occurring in non-surgical settings. The incidence of plaque rupture is triggered by the perioperative stress response, which includes a cytokine response, catecholamine surge with associated haemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation, and consequent hypercoagulability. This mechanism is responsible for half of all adverse perioperative cardiac events. In patients with established coronary artery disease, perioperative infarction may also be caused by a sustained myocardial supply/demand imbalance due to prolonged tachycardia and increased myocardial contractility. From the epidemiological viewpoint, coronary disease is known to be the leading cause of perioperative mortality and morbidity following vascular and general surgery.<sup>321</sup> The diagnostic/therapeutic corollary of these considerations is that coronary artery disease—and therefore the perioperative risk—in these patients has to be effectively identified preoperatively. In low and intermediate risk patients, with an estimated perioperative cardiac risk of <5%, this can be accurately done with clinical scores (such as Detsky's or Goldman's score), electrocardiography, and rest echocardiography. However,

in patients with an estimated cardiac risk of more than 5% additional ischaemic-provocative tests are recommended. Pharmacological stress echocardiography appears to be the first choice as it combines information on valve abnormalities and myocardial ischaemia. Exercise stress has limitations, due to the limited exercise capacity, mainly related to the indication of surgery such as arthritis and vascular disease. Nuclear scintigraphy has comparable prognostic value with pharmacological stress echocardiography for the identification of stress-induced ischaemia.<sup>322</sup> Experience either with dipyridamole<sup>201–206</sup> or dobutamine<sup>154,160,323–326</sup> unequivocally indicates that these tests have a very high negative predictive value (between 90 and 100%); a negative test is associated with a very low incidence of cardiac events and permits a safe surgical procedure. Usefulness in the risk stratification is high for perioperative events and remains excellent also for long-term follow-up.<sup>156,327</sup> To date, it does not appear reasonable to perform coronary revascularization prior to peripheral vascular surgery in patients with a positive stress echocardiography result, with the exception of those with test results suggestive of left main disease or an equivalent such as two-vessel disease with proximal stenosis in the LAD.<sup>328–330</sup> A more conservative approach—with watchful cardiological surveillance coupled with pharmacological cardioprotection with cardioselective  $\beta$ -blockers and statins—can be adopted in patients with less severe ischaemic responses during stress.<sup>331,332</sup> Risk stratification with pharmacological stress echocardiography should probably be targeted at patients over 70 years of age, with current or previous angina pectoris, and previous myocardial infarction and heart failure. In other patients, the event rate using  $\beta$ -blocker therapy is so low that an indiscriminate risk stratification policy with stress echocardiography is probably untenable.<sup>333</sup>

**Key point: Stress echocardiography is recommended in high-risk patients with a previous history of CAD scheduled for elective high-risk surgical procedures. The test is not recommended in low-to-medium-risk patients.**

#### Stress echocardiography in the emergency department

Stress echo has been performed in the ED with several forms of testing,<sup>172,221,334–341</sup> including exercise,<sup>338–340</sup> dobutamine,<sup>172</sup> and dipyridamole.<sup>221</sup> Studies unanimously show a very high feasibility of stress echo, higher with pharmacologic means than with exercise, with an excellent safety profile, and with very high negative predictive value of stress echo results. One study reported the similar prognostic accuracy of stress echo and stress SPECT scintigraphy performed simultaneously in the same patient.<sup>339</sup> It is important to note that the rate of positivity in the screened population varied considerably, from 3 to 45%. When the selection criterion is any form of 'chest pain', typical or atypical, a very low positivity rate may be expected. If only patients with high-to-intermediate clinical risk are screened, the rate of positivity may be substantially higher.<sup>340</sup> Patients with positive stress echo have underlying coronary artery disease and should be admitted to the CCU. The efficacy of this algorithm has been shown not only in single-center experiences but also in large-scale, multicentre validation of the SPEED trial, which analysed more than 500 patients recruited from six centres from three different countries.<sup>221</sup> The negative predictive value of a negative algorithm is very high (99%). However, there are

occasional patients with a negative stress test and early readmission for acute coronary syndromes. The used algorithms currently in the ED certainly minimize the causes of error, but cannot unmask every substrate of myocardial ischaemia. The quest for the 'optimal' algorithm in the ED will certainly continue in the coming years, but rest and stress echo in the ED are here to stay.

**Key point: Stress echocardiography is recommended in patients with chest pain admitted to the ER for risk stratification purposes—especially when ECG stress test is submaximal, not feasible, or non-diagnostic.**

## Contraindications

A poor acoustic window makes any form of stress echocardiography unfeasible to perform. However, a difficult resting echocardiography greatly increases the probability of obtaining no interpretable study results during exercise and should be an indication for the less technically demanding pharmacological stress echocardiography. However, this limitation of stress echocardiography today should not exceed 5% of all referrals. With new transducer technology using harmonic imaging and the use of intravenous contrast agents for LV opacification (discussed later), optimal endocardial border delineation is achievable in the vast majority of patients and should be available in every stress echo laboratory. Specific contraindications to dipyridamole (or adenosine) echocardiography include the presence of severe conduction disturbances, since adenosine can cause transient block at the atrio-ventricular node and severe bronchopneumopathic disease requiring chronic xantine therapy, since adenosine is a powerful bronchoconstrictor. Patients with resting systolic blood pressure under 100 mmHg generally should not receive dipyridamole and caution should be taken with dobutamine. In fact, dobutamine causes an increase in systolic blood pressure in the majority of patients but can also cause a decrease in systolic blood pressure in some patients. Dipyridamole usually causes a modest decrease in systolic blood pressure of 10–20 mmHg, but occasionally causes more severe decrease. Adenosine is the preferred option because of its rapid half-life (<10 s) in patients with unstable carotid artery disease. Significant hypertension and prolonged hypotension should be avoided in these patients, rendering adenosine the agent of choice. Patients who do not achieve the target heart rate with dobutamine alone or inducible ischaemia with dipyridamole alone are commonly administered atropine. Atropine in this setting is a risk only for closed-angle glaucoma patients, a minority of those with glaucoma. Severe prostatic disease is also a contraindication to atropine use.

## New technologies applied to stress echocardiography

The state-of-the art diagnosis of ischaemia in stress echocardiography remains the eyeballing interpretation of regional wall motion in black and white cine-loops. Many new signs have been proposed but not fully validated in their clinical meaning: reduced coronary regional perfusion defect by contrast echo, reduced coronary flow reserve, increased echodensity and reduced regional cyclic variation by tissue

characterization, altered tissue Doppler imaging and its derivatives and colour-kinesis, and anatomical M-Mode and 3D echo. These techniques have exciting potential to clinically describe pathophysiological parameters located upstream in the ischaemic cascade when compared with regional wall motion abnormalities and to establish the diagnosis of myocardial ischaemia in a more quantitative basis.

At present, there is no easy solution to the need to quantify regional function as the problem is complicated by issues of translational motion, tethering, torsional movement, image quality, and so on.<sup>342</sup> With new technologies, like new drugs, large-scale experience should be gathered before accepting a catchy description promoted by the marketing offices as proven. Like new tests, new technologies should be viewed critically in the present era of cost-effectiveness.

## Contrast-enhanced echocardiography

The development of contrast media in echocardiography has been slow. In the past decade, transpulmonary contrast agents have become commercially available for clinical use. The approved indication for the use of contrast echocardiography currently lies in improving endocardial border delineation in patients in whom adequate imaging is difficult or suboptimal.<sup>343</sup> In coronary artery disease patients, in whom particular attention should be focused on regional myocardial contraction, clear endocardial definition is crucial. Intravenous contrast agents can improve endocardial delineation at rest<sup>343</sup> and with stress.<sup>344</sup> Training is needed to ensure accurate interpretation of the contrast-enhanced images. When ultrasound contrast agents are used, contrast-specific imaging modalities should be used. The ability of contrast echocardiography to supplement wall motion information by providing information on perfusion can add additional diagnostic value to stress echocardiography.

## Real-time three-dimensional imaging

Technological advances in transducer and computer technology have led to the recent introduction of real-time 3D echocardiography. Similar to 2D echocardiography, contrast echocardiography can be used for enhancement of endocardial border definition and possibly for myocardial perfusion. Initial studies with 3D echocardiography during stress echocardiography have been encouraging;<sup>345,346</sup> however, no data are available on the additional value of this technique over conventional wall motion interpretation. Matrix probes used for real-time 3D echocardiography offer the unique feature of recording all LV segments simultaneously, which may be advantageous for stress studies.

## TDI and derivatives

Tissue Doppler imaging permits the quantitative and reproducible assessment of myocardial velocity and deformation. Limited signal quality and a learning curve require special expertise from the user. Although velocity measurements need regional normal values or complex models for interpretation, it could be shown that the newly occurring post-systolic shortening—a known sign of regional ischaemia—can be recognizable with deformation imaging and used for diagnosing ischaemia. No data currently demonstrate the superiority of quantitative techniques over



conventional wall motion analysis for the assessment of viable and ischaemic myocardium.<sup>347–351</sup>

**Key point: No new technology application to stress echocardiography is routinely recommended except for contrast for endocardial border enhancement, which should be used whenever there are suboptimal resting or peak stress images. Intravenous contrast for LV opacification improves endocardial border definition and may salvage an otherwise suboptimal study.**

### Comparison with competing techniques: cost and risk assessment

Given the many factors affecting the value of diagnostic accuracy, reliable information on the relative value of different tests can only be gained by studying an adequate number of patients in head-to-head comparison under the same conditions. When compared with standard exercise electrocardiography testing, stress echocardiography has an advantage in terms of sensitivity and a particularly impressive advantage in terms of specificity.

In recent guidelines, the advantages of stress echocardiography over perfusion scintigraphy include higher specificity, greater versatility, greater convenience, and lower cost.<sup>352</sup> The advantages of stress perfusion imaging include a higher technical success rate, higher sensitivity (especially for single-vessel disease involving the left circumflex), better accuracy when multiple resting LV wall motion abnormalities are present, and a more extensive database for the evaluation of prognosis.<sup>352,353</sup> The ESC Guidelines on stable angina conclude that 'On the whole, stress echo and stress perfusion scintigraphy, whether using exercise or pharmacological stress (inotropic or vasodilator), have very similar applications. The choice as to which is employed depends largely on local facilities and expertise'.<sup>296</sup> Cardiac magnetic resonance (CMR) is the latest technique to enter the field of cardiac imaging.<sup>354–358</sup> The advantages of the technique are related to the absence of ionizing radiation, at the price of higher costs and lower availability when compared with echocardiography. Despite the high costs, the time of image acquisition, safety profile, and low availability makes CMR an excellent option only when stress echocardiography is inconclusive or not feasible.<sup>359</sup>

The high cost of stress imaging procedures warrants some financial justification, and three arguments have been proposed. First, a negative stress imaging test implies such a low risk of an event that revascularization could not be justified on prognostic grounds. Secondly, compared with simple stress testing, the use of imaging tests in particular situations has been shown to reduce downstream costs (both diagnostic and therapeutic). Thirdly, several studies have shown that in comparison with coronary angiography (where the detection of coronary stenoses seems to lead inexorably to coronary intervention), decision-making based on functional testing is associated with similar outcomes at lower levels of downstream cost. On the basis of this large body of evidence assessing the comparable accuracy of stress echo and perfusion scintigraphy, the choice of one test over the other will depend on the overall biological risk related to the use of radiations. This is recommended by the executive European Law (1997) and the European Commission Medical Imaging Guidelines (2001).

EU Medical Imaging Guidelines and the European law (Euratom directive 97/43) state that a radiological (and medico-nuclear) examination can be performed only 'when it cannot be replaced by other techniques that do not employ ionising radiation' and it should always be justified (article 3: 'if an exposure cannot be justified it should be prohibited'). At patient level, the effective dose of a single nuclear cardiology stress imaging scan ranges from 10 to 27 mSv (with dual isotope imaging protocol). The corresponding equivalent dose exposure is 500 chest X-rays (sestamibi), 1200 chest X-rays (Thallium), and 1300 chest X-rays (dual isotope protocol). According to the latest and most authoritative estimates of BEIR VII, the estimated risk of cancer for a middle-aged patient ranges from 1 in 1000 (for a sestamibi) to 1 in 400 (for a dual isotope scan). Therefore, in an integrated risk-benefit balance, stress echo has shown advantages when compared with imaging techniques such as scintigraphy.<sup>360–363</sup>

**Key point: Stress echocardiography should be preferred due to its lower cost, wider availability and—most importantly—for the radiation-free nature. Stress scintigraphy offers similar information to stress echocardiography, but with a radiation burden between 600 and 1300 chest X-rays for every single stress scintigraphy. This poses a significant biological risk both for the individual and for the society, since small individual risks multiplied by millions stress tests per year become a significant population burden.**

### The training issue

It is not reasonable to begin using stress echocardiography without a complete training in transthoracic echocardiography, and the EAE accreditation exam is highly recommended. The basic skills required for imaging the heart under resting conditions do not differ substantially from those required for imaging the same heart from the same projections during stress. The diagnostic accuracy of an experienced echocardiographer who is an absolute beginner in stress echocardiography is more or less equivalent to that achieved by tossing a coin. However, 100 stress echocardiographic studies are more than adequate to build the individual learning curve and reach the plateau of diagnostic accuracy.<sup>364</sup> It is wise to do the following: start with low-dose tests for viability and later progress to tests for ischaemia; start with safer and easier vasodilator tests and later progress to adrenergic stresses; and start with pharmacological, and then progress to physical exercise stress echocardiography. In the case of a patient with a known or suspected infarction, no echocardiographer would make the diagnosis of presence, site, and extension of dyssynergy on the basis of a single cardiac cycle in one view from only one approach: the dyssynergy can be highly localized, and some regions can be adequately visualized only in some projections. An important general rule of stress echocardiography stems from an obvious fact: all views that can be obtained should be obtained both in resting conditions and during stress. It is also evident that the temporal sampling must be continuous so that the exact ischaemia-free stress time can be determined and the stress immediately stopped as soon as an obvious dyssynergy develops. Today, the interpretation of stress echocardiography is by necessity qualitative and subjective. Diagnostic accuracy is not only a function of experience; for a given diagnostic

accuracy, every observer has his/her own sensitivity–specificity curve: there are ‘over-readers’ (high sensitivity, low specificity) and ‘under-readers’ (low sensitivity, high specificity), depending on whether images are aggressively or conservatively interpreted as abnormal. Many studies are unquestionably negative or positive; still, there is a ‘grey zone’ of interpretable tests in which the visualization of some regions can be suboptimal and the cardiologist’s level of experience in interpreting the test is critical for a correct reading. Interobserver variability is certainly a common problem in medicine, and in cardiology variability can be substantial with almost all diagnostic methods, including resting electrocardiography,<sup>365</sup> exercise electrocardiography,<sup>366</sup> perfusion scintigraphy,<sup>367</sup> and coronary angiography.<sup>368</sup> There are many precautions that may minimize variability, providing not only high accuracy but also better reproducibility. These parameters are related to the physician interpreting the study, the technology used, the stress employed, and the patient under study. Variability will be substantially reduced if one agrees in advance not to consider minor degrees of hypokinesia, since mild hypokinesia is a normal variant under most stresses and a finding widely overlapping between a normal and a diseased population.<sup>369–372</sup> The inclusion among positivity criteria of isolated asynergy of basal-infero-lateral or basal-infero-septal segments will also inflate variability. Obviously, the inclusion of patients with resting images of borderline quality or the use of stresses degrading image quality will also dilate variability, which is tightly linked to the quality of the images. Other factors, including new technologies such as tissue Doppler have a potential to reduce variability.<sup>373</sup> Digital acquisition may improve reproducibility.<sup>371</sup> In patients with a difficult acoustic window, native second harmonic imaging and the use of contrast agents help to improve accuracy and reduce variability.<sup>375,376</sup> Finally, the single most important factor deflating variability is a specific course of training in a large-volume stress echocardiography lab with exposure to joint reading<sup>376</sup> and *a priori* development of standardized<sup>377</sup> and conservative<sup>378</sup> reading criteria.

**Key point:** It is recommended to perform at least 100 exams under the supervision of an expert reader in a high-volume laboratory, and ideally with the possibility of angiographic verification, before starting stress echocardiography on a routine basis. Maintenance of competence requires at least 100 stress echo exams per year.

**Conflict of interest:** none declared

## Funding

Funding has been provided by the European Association of Echocardiography.

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