Stress echocardiography *vs* nuclear stress imaging in clinical cardiology

Stress echocardiography and nuclear stress imaging are important non-invasive tools in clinical cardiology. This review discusses the uses, strengths and limitations of these imaging modalities and looks at whether stress echocardiography can actually replace nuclear stress imaging.

Stress echocardiography and nuclear stress imaging are well-validated non-invasive tools that are used for diagnosis of coronary artery disease in intermediate-risk patients, risk stratification and identification of viable myocardium. Stress echocardiography relies on ultrasound to detect regional wall motion abnormalities following increased workload induced by exercise or pharmacological agents (*Figure 1*). Nuclear stress imaging uses radiopharmaceuticals and cameras to identify abnormal myocardial perfusion secondary to stress, in segments supplied by diseased coronary arteries.

There is increasing awareness of the adverse effects of radiation attributed to diagnostic imaging techniques, including nuclear stress imaging. Also patients have become more conscious of radiation exposure with consequent ongoing effort to promote stress echocardiography. Nonetheless, both stress echocardiography and nuclear stress imaging have their advantages and limitations. In addition, availability, local expertise and patient preference play a major role in the chosen imaging modality. These issues will be discussed to elucidate whether stress echocardiography could ultimately replace nuclear stress imaging.

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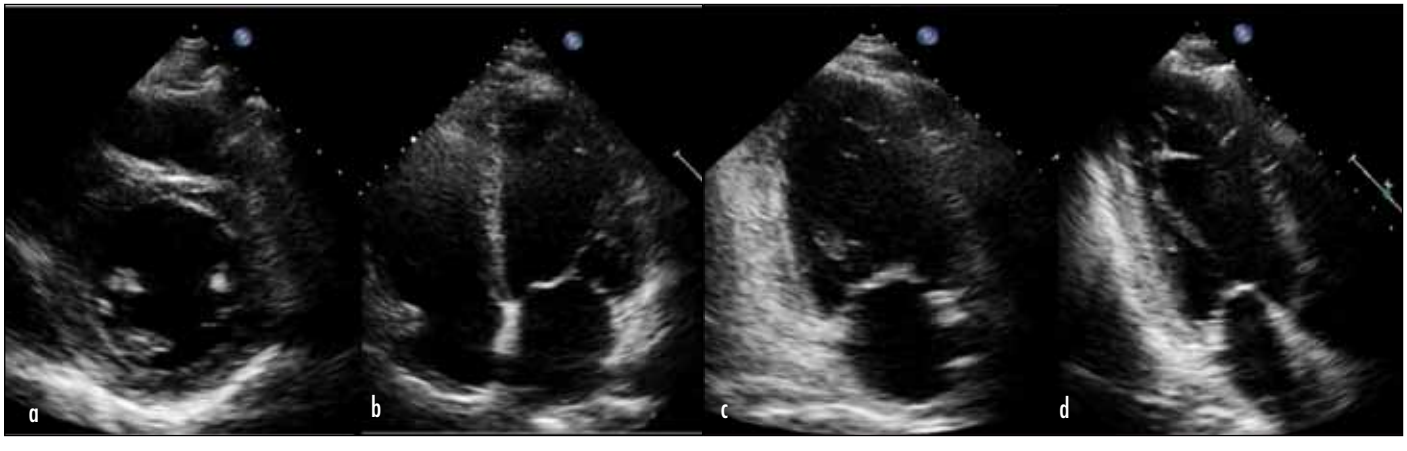
Techniques

To grasp the principles underlying stress imaging, it is crucial to understand the ischaemic cascade, i.e. the typical sequence of events when there is a mismatch between oxygen supply and demand secondary to coronary artery disease (*Figure 2*). Stress echocardiography and nuclear stress imaging target different aspects of the ischaemic cascade, and provide different information.

A number of common principles govern stress echocardiography and nuclear stress imaging. Both require a stressor which is either exercise (using treadmill or bicycle) or pharmacological. Treadmill stress echocardiography is limited by the inability to obtain images during exercise, possibly decreasing its sensitivity since ischaemic wall motion abnormality is usually short-lasting unless the stenosis is very severe. Bicycle ergometry enables imaging during exercise and is probably more sensitive and safer since it enables early detection of ischaemia. Exercise nuclear stress imaging detects perfusion abnormalities (*Figure 3*).

Pharmacological stress is usually reserved for patients who cannot exercise. Pharmacological stressors include the vasodilators, dipyridamole or adenosine, or the ino-

Figure 1. Standard imaging planes used in stress echocardiography. a. Parasternal short axis view showing the left ventricle in cross section at the level of the papillary muscles. b. Apical four-chamber view showing the anterolateral and inferoseptal walls of the left ventricle. c. Apical two-chamber view showing the anterior and inferior walls of the left ventricle. d. Apical long axis view showing the anteroseptal and inferolateral walls of the left ventricle.



trope, dobutamine. Dobutamine is commonly used in stress echocardiography since it is more likely to create wall motion abnormalities by increasing left ventricular contractility. Dipyridamole and adenosine preferentially vasodilate non-diseased vessels because territories supplied by diseased vessels use some of their flow reserve by dilating the microvascular bed to maintain normal perfusion in the face of reduced coronary flow. There is therefore impaired flow reserve to increase perfusion in the face of stress (or pharmacological dilatation by adenosine), reducing delivery of tracer to affected areas. This leads to a perfusion mismatch that is detected by nuclear stress imaging; they are thus the preferred stressors in nuclear stress imaging (Anthony, 2005). However, this perfusion abnormality might not result in wall motion abnormality detectable by stress echocardiography, making this less sensitive. Furthermore, nuclear stress imaging is performed with gated single photon emission computed tomography that enables concomitant assessment of left ventricular global function (Schuijf et al, 2006) (*Figure 4*).

A major difference is that stress echocardiography uses ultrasound, i.e. non-ionizing radiation, which is considered safe, while nuclear stress imaging uses radioisotopes which emit ionizing radiation, enabling their distribution within the myocardium to be determined. The commonly used tracers are thallium(Tl)-201 and two technetium-99m labeled radiopharmaceuticals. Radiation is a major issue with nuclear stress imaging since high doses are used (2.2–31.5 mSv), comparable with or higher than the values obtained with computed tomography coronary angiography (4.0–21.4 mSv) and with coronary angiography (2.3–22.7 mSv) (Einstein et al, 2007). Ionizing radiation has various adverse effects, mainly deterministic, e.g. skin erythema and cataracts (relatively rare), and stochastic effects, i.e. cancer development and germ cell mutations, depending on the organ or tissue being irradiated. In view of increasing awareness of the adverse effects of radiation, new techniques are being developed to minimize radiation dose (discussed later).

Advantages and limitations of stress echocardiography and nuclear stress imaging are highlighted in *Tables 1* and *2*. The major limitation of stress echocardiography is suboptimal image quality, seen in up to 30% of patients; this can be partly overcome using of contrast echocardiography to improve delineation of the endocardium. The efficacy of stress echocardiography *vs* nuclear stress imaging in different scenarios is discussed below.

Diagnosis of coronary artery disease

Sensitivity and specificity

The diagnostic accuracy of nuclear stress imaging and stress echocardiography in detecting coronary artery disease is expressed by its sensitivity and specificity, with coronary angiography being the gold standard. Various studies have shown nuclear stress imaging to have slightly better sensitivity while stress echocardiography is more specific, in keeping with the ischaemic cascade. In a pooled analysis of 79 studies, single photon emission computed tomography nuclear stress imaging had 86%

Figure 2. The ischaemic cascade. *In theory, gated single photon emission computed tomography analysis can give an indication of diastolic dysfunction but, in practice, it is more accurately assessed using stress echocardiography. ECG = electrocardiogram.

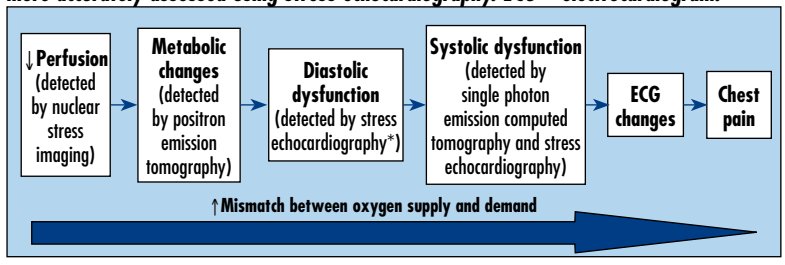


Figure 3. Myocardial perfusion scintigraphy images obtained following administration of technetium-99m. a. Images obtained after exercise and at rest show homogenous tracer uptake in all segments and thus no evidence of myocardial necrosis or ischaemia. b. Images obtained after exercise stress testing show absent tracer uptake in the apex and anteroseptal segment and reduced tracer uptake in the inferior wall, with increased tracer uptake of the inferior wall only at rest. These findings are in keeping with anteroseptal and apical myocardial infarction with ischaemia of the inferior wall.

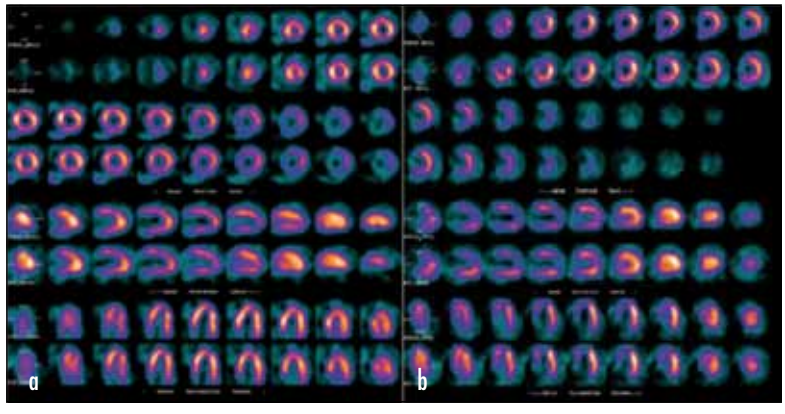
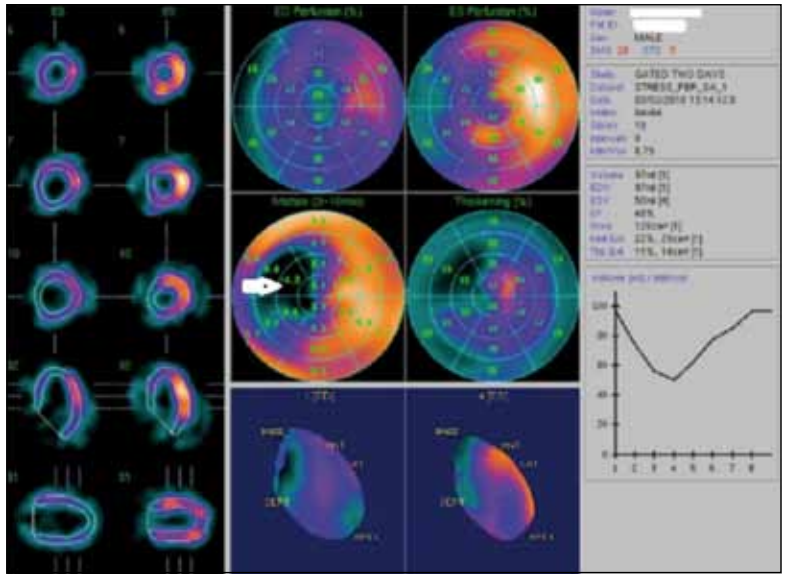


Figure 4. Gated single photon emission computed tomography acquisition and standard three plane reconstruction revealing an ejection fraction of 48% and septal akinesia (white arrow).



sensitivity and 74% specificity (Underwood et al, 2004) while pooled analysis of 43 studies showed that exercise and dobutamine echocardiographies had mean sensitivities of 84% and 80% respectively, and mean specificities of 82% and 84% respectively (Bax et al, 2005). The systematic review by O'Keefe et al (1995) and the meta-analysis of Fleischmann et al (1998) showed similar results (*Figure 5*). Some argue that referral bias contributes to the low specificity of nuclear stress imaging, but this also overestimates the sensitivity of the test (Anthony, 2005).

Table 1. Advantages and disadvantages of stress echocardiography

Advantages	Radiation-free
	Real-time examination
	Low cost
	Easily portable
	One-time procedure
	Additional information about valvular heart disease, pericardium
Disadvantages	Suboptimal image quality*
	Operator-dependent
	Interobserver variability
	Short time frame for imaging
	Respiratory motion artefacts*
	Artefacts secondary to translation and rotational movements of the heart

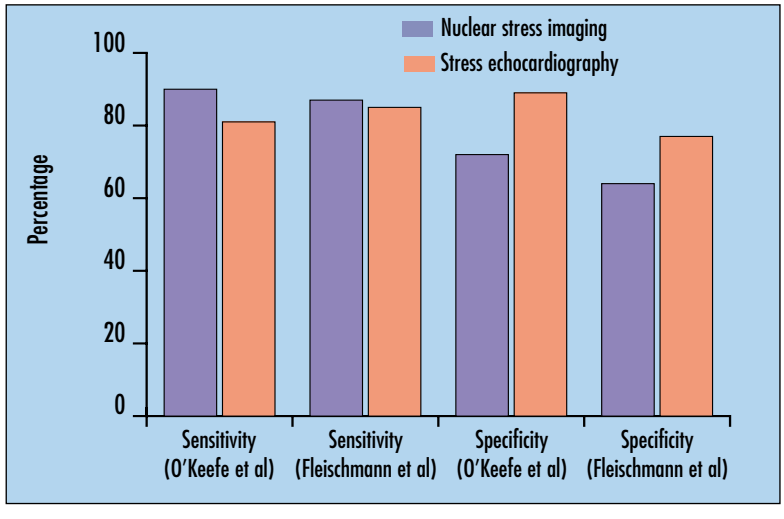
*Potential problems with nuclear stress imaging but more commonly encountered with stress echocardiography

Table 2. Advantages and disadvantages of nuclear stress imaging

Advantages	Technically easy
	Reproducible image acquisition*
	Assessment of both perfusion and left ventricular contractility with single photon emission computed tomography
Disadvantages	Radiation exposure
	Requires gamma or computed tomography equipment

*Although image acquisition is reproducible, image reporting carries reasonable variability, especially for inexperienced reporters, or those who report a limited number per year.

Figure 5. Sensitivity and specificity of nuclear stress imaging and stress echocardiography derived from O'Keefe et al (1995) and Fleishmann et al (1998).



Factors that decrease the sensitivity of nuclear stress imaging include insufficient exercise, use of β-blockade and obesity. Furthermore, sensitivity varies with the number of diseased coronary vessels, increasing from 84% in single-vessel disease to 100% in triple-vessel disease. Nonetheless, nuclear stress imaging is more sensitive than stress echocardiography in detecting single-vessel disease. Sensitivity also varies with the diseased vessel; dobutamine nuclear stress imaging has low sensitivity for detection of left circumflex coronary artery disease and low specificity for right coronary artery disease. Thus, a well-trained reporter is crucial for accurate assessment of nuclear stress imaging.

Sensitivity of stress echocardiography also diminishes with inadequate exercise and β-blockers. Limitations of stress echocardiography in diagnosis of coronary artery disease are outlined in *Table 3*. A well-trained experienced echocardiographer is crucial for adequate assessment of regional systolic wall thickening; this is a stronger indicator of wall motion abnormality than endocardial excursion. Scrupulous attention is also needed to diagnose ischaemia with dobutamine stress echocardiography as well as to identify tethering effects of ischaemic segments. Regular quality control is also necessary to ensure accurate and consistent results with stress echocardiography.

Assessment of special populations

Female gender

Women tend to have a higher false positive rate than men in exercise stress testing, resulting in further investigation. Breast attenuation and smaller left ventricular chamber decrease the accuracy of single photon emission computed tomography nuclear stress imaging. A meta-analysis by Geleijnse et al (2007) showed that dobutamine stress echocardiography and nuclear stress imaging had comparable sensitivity (77% *vs* 73% respectively) but dobutamine stress echocardiography was more specific (90% *vs* 70%, $P<0.0001$). Although the authors concluded that stress echocardiography is the best diagnostic tool for coronary artery disease in women, the

Table 3. Limitations of stress echocardiography

Identification of multivessel disease with normal left ventricular function
Single vessel disease
Identification of ischaemia in areas with resting wall motion abnormalities
Estimation of left ventricular end-systolic volume and thickness with dobutamine stress echocardiography

studies analysed were small (~63 subjects in each study) and were performed over 10 years ago. In view of evolving expertise and techniques, further studies are warranted.

Diabetes mellitus

Diabetic patients are at increased risk of cardiovascular disease and silent ischaemia, so require adequate assessment for coronary artery disease, first with non-invasive techniques. Abnormal nuclear stress imaging is an indicator of cardiac events in both asymptomatic and symptomatic diabetic patients. There is no significant difference in sensitivity, specificity and normalcy rates of single photon emission computed tomography nuclear stress imaging between diabetic and non-diabetic patients, although diabetic patients show a much higher cardiac event rate than non-diabetic subjects with similar nuclear stress imaging results. An abnormal stress echocardiography result is an independent predictor of cardiovascular disease in diabetic patients. However, it is still unclear which of the two techniques is better in these patients. Penfornis et al (2001) showed that dobutamine stress echocardiography and Tl-201 single photon emission computed tomography had comparable positive predictive value (69% *vs* 75%), but their study only involved 56 patients. More studies are thus needed.

Left bundle–branch block

False positive results have been shown with Tl-201 scintigraphy as regards disease in the left anterior descending artery in the presence of left bundle–branch block (Hirzel et al, 1984). Although this may have improved with newer techniques, it remains problematic and operator expertise is required to detect artefacts associated with left bundle–branch block. Dobutamine stress echocardiography is both specific and accurate in diagnosing left anterior descending disease in patients with left bundle–branch block (Mairesse et al, 1995), making it the preferred imaging modality in this patient population; however, no head-to-head study has been performed to identify the better imaging modality.

Left ventricular hypertrophy

Stress echocardiography is also a better imaging technique in subjects with left ventricular hypertrophy. Fragasso et al (1999) showed that the sensitivity, specificity, accuracy, positive and negative predictive values for dobutamine stress echocardiography were 88%, 80%, 84%, 85% and 83% respectively while those for 99mTc-sestamibi single photon emission computed tomography were 98%, 36%, 71%, 67% and 94%. The low specificity of nuclear stress imaging is probably secondary to microvascular disease not visible on coronary angiography.

Cardiac transplant recipients

Cardiac transplant patients need to be screened for coronary artery disease since they undergo accelerated coronary vasculopathy. The best imaging modality for diagnosis of coronary artery disease is intravascular ultrasound, but this is invasive and has associated complications. A suitable non-invasive imaging technique is stress echocardiography since it has reasonably good sensitivity and specificity compared to nuclear stress imaging (Kass and Haddad, 2006). Dobutamine stress echocardiography is also useful following cardiac transplantation in children. The findings of dobutamine stress echocardiography correlate well with intravascular ultrasound findings (Spes et al, 1999).

Prognostic value

Prognostic value of a normal test

In a meta-analysis, exercise nuclear stress imaging and stress echocardiography had comparable negative predictive value for myocardial infarction and cardiac death (98.8% *vs* 98.4%), and annualized event rates (0.45%/year *vs* 0.54%/year) (Metz et al, 2007). However, this meta-analysis included 17 studies assessing nuclear stress imaging but only four analysing stress echocardiography, reflecting the wealth of data available with nuclear stress imaging compared to stress echocardiography.

In addition, there is conflicting evidence regarding the prognostic value of a negative stress echocardiography. Whereas some studies have shown that a negative stress echocardiography identifies patients at very low risk of cardiac events (≤1%) (McCully et al, 1998; Marwick et al, 2001), analysis of 13 studies showed significantly high annualized death or myocardial infarction rate (3.4%/year) with an even higher rate in subjects with known coronary artery disease (6%) (Brown et al, 2000). On the other hand, normal nuclear stress imaging predicts a good prognosis even in subjects with strongly positive exercise electrocardiograms (Krishnan et al, 1994) or with known significant coronary artery disease (Pavin et al, 1997).

Prognostic value of an abnormal test

Abnormal nuclear stress imaging is a strong prognostic indicator of adverse cardiovascular events, not only in patients with stable angina but also in unstable angina, and following myocardial infarction, percutaneous coronary intervention and coronary artery bypass grafting. A meta-analysis of >12 000 subjects showed an annualized myocardial infarction or death rate of 0.6% for a normal single photon emission computed tomography nuclear stress imaging result *vs* 7.4% for an abnormal result (Iskander and Iskandrian, 1998). Various adverse prognostic factors have been identified (*Table 4*). Furthermore, abnormal nuclear stress imaging provides additional incremental value independent of the Duke treadmill score. Nuclear stress imaging also provides significantly more prognostic information than catheterization results.

An abnormal stress echocardiogram is also a significant predictor of cardiac events. Pooled analysis of 13 studies showed an annualized myocardial infarction or death rate

of 1.2% for a normal study *vs* 7.05% for an abnormal one (Schuijf et al, 2006). Stress echocardiography also provides additional incremental prognostic information to the Duke treadmill score, especially in intermediate-risk patients. Poor prognostic markers of stress echocardiography include significant extent of wall motion abnormality, visible scar tissue and a low ischaemic threshold.

Few studies have directly compared the two imaging modalities as regards prognosis. Geleijnse et al (1997) showed that stress echocardiography and Tc-99m single photon emission computed tomography had similar prognostic value for myocardial infarction or cardiac death during follow up of 31±15 months. Olmos et al (1998) showed similar results. Hoque et al (2002) followed up patients for 5 and 10 years and demonstrated significant heterogeneity in prediction of cardiac events by these two modalities. Ischaemia extent by stress echocardiography was a better predictor of total and cardiac deaths, sudden death and congestive heart failure whereas extent of fixed defect by Tl-201 single photon emission computed tomography was a better predictor of myocardial infarction or unstable angina. This is interesting since one would expect scar to predict heart failure and arrhythmic deaths and ischaemia to predict myocardial infarction or acute coronary syndrome deaths. Further studies are needed to compare the prognostic benefit of stress echocardiography and nuclear stress imaging, especially on a long-term basis.

Assessment of myocardial viability

Myocardial hibernation and myocardial stunning are the main pathophysiological processes leading to viable dysfunctional myocardium. Hibernation is a chronic state of abnormal contractility secondary to underperfusion caused by coronary artery disease; recovery of contractility is achieved on revascularization. Myocardial stunning refers to reversible abnormal myocardial contractility despite resolution of ischaemia. Revascularization improves the prognosis in subjects with dysfunctional viable myocardium, as evidenced by two meta-analyses (Allmann et al, 2002; Camici et al, 2008) showing improved survival with revascularization in subjects with coronary artery disease, left ventricular dysfunction and myocardial viability as assessed using non-invasive techniques. This prognostic benefit has been questioned by the results of the STICH trial. Some claim that it has numerous limitations with regard to study design, myocardial viability assessment and criteria, and indication to viability testing; however, this is outside the scope of this review. Nonetheless, current practice is early identification of viable myocardium which requires reliable non-invasive diagnostic tools.

Stress echocardiography and nuclear stress imaging assess different aspects of myocardial viability. Dobutamine stress echocardiography assesses contractility: improved contractility on low-dose dobutamine indicates contractile reserve, while improved left ventricular function on low-dose dobutamine with worsening left ventricular function on higher doses (biphasic response) indicates viability with superimposed ischaemia. Viability assessment by Tl-201 single photon emission computed tomography depends on perfusion and cell membrane integrity while assessment with Tc-99m single photon emission computed tomography depends on perfusion, cell membrane integrity and mitochondrial function. In the meta-analysis of 563 patients, nuclear imaging had higher sensitivity compared to dobutamine stress echocardiography (90% *vs* 74%) while dobutamine stress echocardiography showed higher specificity (78% *vs* 57%) (Bax et al, 2001). Panza et al (1995) showed that Tl-201 imaging identified many more viable segments than dobutamine stress echocardiography; it has been suggested that this is because it cannot distinguish between viable myocardium and subendocardial myocardial infarction. In support of this, histological analysis of cardiac biopsies revealed that damage and fibrosis results in loss of viability as detected by dobutamine stress echocardiography but possibly not by nuclear stress imaging (Pagano et al, 2000).

There are conflicting results regarding which imaging technique best predicts improvement in wall motion abnormalities following revascularization. Sequential stress echocardiography and nuclear stress imaging improve the predictive value but this is costly. Nonetheless, current guidelines do not indicate which is the best imaging modality for diagnosing myocardial viability.

Table 4. Markers of adverse cardiovascular outcomes obtained using nuclear stress imaging

Significant extent of stress defect†
Significant number of reversible defects
Transient ↑201-thallium lung uptake
Transient left ventricular dilation
Delayed tracer redistribution
Ejection fraction <45%*
End-systolic volume >70 ml*
End-diastolic volume >120 ml*

* refers to factors derived from gated single photon emission computed tomography studies. †Summed stress score using 20-segment, 5-point scoring system can indicate the extent of stress defect. The myocardial tomogram is divided into 20 segments and each segment is scored using a 5-point scoring system (0=normal, 1=equivocal, 2=moderate, 3=severe reduction of radioisotope uptake, and 4=absence of detectable tracer uptake in a segment). Summed stress score <4 is normal, 4–8 is mildly abnormal, and >8 is severely abnormal.

Preoperative evaluation

It is estimated that 900 000–5 000 000 patients undergoing non-cardiac surgery worldwide sustain a major cardiac event yearly. To reduce the perioperative cardiac event rate to <2%, one needs to identify high-risk patients using non-invasive tools. In a meta-analysis by Shaw et al (1996), both perfusion defects identified with nuclear stress imaging and wall motion abnormalities noted on

stress echocardiography were predictive of adverse perioperative cardiac events in patients undergoing vascular surgery although there were wider confidence intervals with stress echocardiography because of the smaller number of patients being studied (1994 *vs* 446).

A more recent and extensive meta-analysis by Beattie et al (2006) showed that, in subjects listed for elective non-cardiac surgery, stress echocardiography is a better tool than Tl-201 to identify postoperative cardiac events (likelihood ratio = 4.09, 95% confidence interval=3.21–6.56; *vs* likelihood ratio = 1.83, 95% confidence interval=1.59–2.10, p<0.001) because there were less false-negative results. Furthermore, the likelihood ratio for a negative stress echocardiography was less (0.23, 95% confidence interval=0.17–0.32; *vs* 0.44, 95% confidence interval=0.36–0.54). This meta-analysis also demonstrated that postoperative adverse events were predicted by a moderately large defect identified by either modality. Thus, it is reasonable to say that only patients with significant abnormalities in imaging should be investigated before elective non-cardiac surgery. Even though there are currently no guidelines for this, the authors believe that stress echocardiography is the best option as it has the highest specificity.

Additional uses of stress echocardiography

Unlike nuclear stress imaging, stress echocardiography is also useful in assessing the severity of valvular heart disease, particularly aortic stenosis and mitral stenosis (Gottdiener, 2001). Stress echocardiography is useful in identifying subjects with functional aortic stenosis secondary to low cardiac output resulting in incomplete opening of the valve leaflets. Aortic valve replacement is not beneficial in these patients. During dobutamine stress echocardiography, they exhibit increased left ventricular contraction accompanied by an increase in the aortic valve area, unlike patients with structural aortic stenosis in whom increased left ventricular contractility occurs without an increase in the estimated valve area. Nonetheless, some patients do not increase left ventricular contractility and the test is thus indeterminate. Furthermore, dobutamine stress echocardiography should be performed cautiously in patients suspected of having aortic stenosis since the vasodilator response with a fixed left ventricular outflow tract may result in haemodynamic collapse.

The functional severity of mitral stenosis can also be assessed by stress echocardiography. Some patients presenting with dyspnoea have only mild mitral stenosis on resting echocardiography. However, during exercise, the increased preload reveals the underlying severity of mitral stenosis, as estimated using the pressure gradient across the valve.

Resting images can also indicate important underlying comorbidities that cannot be assessed with nuclear stress imaging, including pericardial effusion, left ventricular hypertrophy and diastolic dysfunction.

Cost effectiveness

Cost-effectiveness analysis involves comparison of the economic value of two different methods. Both techniques are effective in decreasing referral to coronary angiography, but whereas numerous studies showed the cost effectiveness of nuclear stress imaging without adverse patient outcomes, including the END and EMPIRE studies, data with regards to stress echocardiography are scarce. Since both techniques are evolving fast, more studies are needed to assess this.

Novel techniques

New techniques are constantly being developed to assess as many factors in the ischaemic cascade as possible, thus increasing sensitivity of both tests. Developments in single photon emission computed tomography will enable assessment of metabolic imaging. Dynamic single photon emission computed tomography and resolution recovery techniques are two major areas of development in nuclear stress imaging. Dynamic single photon emission computed tomography is expected to improve image quality, clinical throughput and the patient's imaging experience, as well as possibly improving diagnosis of multivessel coronary artery disease, global ischaemia and detection of myocardial microvascular dysfunction. Besides decreasing imaging time, resolution recovery software may also be used to reduce administered radioactivity while keeping scan times the same. On the other hand, contrast echocardiography may prove a useful adjunct to stress echocardiography, enabling assessment of myocardial perfusion as well as improved endocardial delineation.

Conclusions

The clinician's goal should be diagnosis of coronary artery disease and accurate risk stratification without harming the patient. Furthermore, the diagnostic tool used should enable appropriate decision making regarding referral to invasive investigations that entail more complications and increasing cost. Studies the diagnostic and prognostic capabilities of the two imaging techniques have been discussed and, despite differences in individual studies and in particular patient populations, stress echocardiography and nuclear stress imaging are generally comparable. One would tend to favour stress echocardiography as it does not expose the patient to radiation. However, there are no guidelines recommending that stress echocardiography should replace nuclear stress imaging because comparisons between the two studies are usually made in laboratories specialized in that particular technique. Consequently, optimized results might not be achieved in all institutions. This is particularly relevant with stress echocardiography where there is significant inter-reader variability. Thus, both local expertise and available facilities are crucial in deciding which stress modality to use.

The choice also depends on the clinical information needed as well as the individual being investigated. Thus,

a 30-year-old woman with atypical chest pain should ideally be investigated with stress echocardiography to reduce radiation exposure, while this is less of a concern when assessing older subjects. Finally, implementation of novel techniques both in nuclear stress imaging and stress echocardiography, including use of tissue Doppler and contrast echocardiography, as well as improved training will determine the future of these imaging modalities and whether stress echocardiography might ultimately replace nuclear imaging. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Stress echocardiography and nuclear stress imaging are generally comparable for the diagnosis of coronary artery disease, with nuclear imaging being slightly more sensitive and stress echocardiography more specific.
- Stress echocardiography is probably better for assessing myocardial viability although there are currently no guidelines addressing this issue. It is also the preferred non-invasive imaging technique to assess for coronary artery disease in subjects with left ventricular hypertrophy and cardiac transplant recipients.
- As stress echocardiography is radiation-free, one would tend to favour its use rather than nuclear imaging. However, accurate interpretation of stress echocardiography requires skill, so the choice of technique depends on local expertise and availability, as well as on the individual being investigated.

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