Stress Echocardiography Versus Stress Perfusion Scintigraphy

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38.1 Nuclear Cardiology, the Land of Our Fathers

Nuclear cardiology is the time-honored offspring of the marriage between nuclear technology and coronary physiology [1]. Several imaging paradigms later endorsed by stress echocardiography were first understood, proposed, and popularized by nuclear cardiology: the merit of imaging cardiac function during stress, in lieu of the simple electrocardiogram; the value of the pharmacological alternative to physical exercise for stressing the heart; the need to assess viability in segments with resting dysfunction; the advantage of routine use of digital handling for data acquisition, storage, and display; and the prognostic impact of extent and severity of stress-induced ischemia [2]. Although the comparison of nuclear cardiology and echocardiography previously involved a fundamental philosophical issue between the diagnosis of coronary disease based on perfusion (hence the possibility of influencing these data on the basis of small-vessel disease, hypertrophy, and other causes of abnormal coronary flow reserve) and evidence of ischemia (hence less sensitivity to mild disease that may engender submaximal attainment of flow without ischemia), recent advances have made it possible for both techniques to offer function and coronary flow reserve data [3]. Each technique is experiencing a “methodological drift” to incorporate information previously monopolized by the other – thus, gated single-photon emission computed tomography (SPECT), ventriculography, and attenuation correction have been added to SPECT, while harmonic imaging, pulsed Doppler coronary flow velocity imaging, myocardial contrast, and real-time three-dimensional (3D) imaging have been added to echocardiography. The benefits of these technical advances may render current comparisons somewhat obsolete.

38.2 SPECT, PET, and PET–CT Imaging: Advantages and Limitations

SPECT imaging in combination with 201 thallium or 99mTc-tracers is a powerful technique for the detection of perfusion abnormalities during hyperemia induced by pharmacological

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or physical stress and it also allows assessment of viability [4]. The mechanism of this test – based on the detection of relative hyperemia – is a fundamental distinction from stress echocardiography, which is dependent on the induction of ischemia in a functional and metabolic sense. Hyperemia may be induced directly (by coronary vasodilators) or indirectly (whereby endogenous vasodilators are produced in response to exercise or dobutamine). The presence of preexisting coronary vasodilation induced by antianginal therapy, or limitation of the vasodilator response due to drug therapy or submaximal exercise, may blunt the difference between rest and stress, impairing the detection of less severe stenoses and contributing to lower sensitivity [5]. Nonetheless, antianginal drug therapy has a greater effect on the results of echocardiography [6, 7] because it prevents the development of ischemia.

Advantages

SPECT and positron emission tomography (PET) have a high technical success rate and are relatively operator-independent. SPECT has excellent sensitivity (usually 85–90%) and good-to-moderate specificity (70–80%) for the detection of angiographically assessed coronary artery disease. The accuracy of PET is probably greater, especially in the posterior circulation and in obese subjects, where the inherent attenuation correction of PET is advantageous [8]. The extent and severity of stress-induced perfusion defects have important prognostic implications, now supported by a huge evidence base with SPECT [9, 10] and a smaller evidence base with PET [11].

Limitations

The major limitations of SPECT and PET are economic cost, environmental impact, and high radiation dose. For a cardiac imaging test, with the average cost (not charges) of an echocardiogram equal to 1 (as a cost comparator), the cost of a SPECT study is 3.27×, of PET 14×, and of PET–CT around 20× higher [12]. For stress imaging, compared with the treadmill exercise test equal to 1 (as a cost comparator), the cost of stress echocardio-graphy is 2.1×, of stress SPECT scintigraphy 5.7× [13], and of stress SPECT–CT around 20× higher. This cost assessment does not include the indirect additional costs of radiation-induced cancer and the environmental impact of radioactive tracer production and waste [14]. The older problem of limited availability of PET has been superseded by the problem of greater numbers of scanners but their heavy commitment to oncology work. In addition, PET perfusion imaging has been dependent on pharmacologic stress as PET tracers have a short half-life.

38.3 MPI vs. Stress Echocardiography

Stress echocardiography and myocardial perfusion imaging (MPI) have a very similar pathophysiological rationale, methodological approach (with assessment of perfusion and function), and clinical results (Table 38.1).

Accuracy for Coronary Artery Disease

The sensitivity and specificity of both tests are in the 80–85% range, with greater sensitivity for SPECT (especially for single vessel and left circumflex disease) and greater

Table 38.1 Myocardial radionuclide perfusion imaging: advantages and limitations

	Advantages	Limitations
Operator-independent	++	
Radiation dose		−−−
Long-standing experience	+++	
Environment impact		−−−
Convincing display	++	
Low specificity (LBBB, HPT)		−−−
Extensive prognostic data base	+	
High cost, limited availability		−−−

Advantages are scored as + good; ++ very good; +++ excellent advantage. Limitations are scored as − mild; −− moderate; −−− severe limitation
LBBB left bundle branch block, *HPT* hypertension

specificity for stress echocardiography (especially in women, left ventricular hypertrophy, and left bundle branch block).

The equivalence between stress echocardiography and MPI is often considered surprising in light of the "ischemic cascade," which suggests that because perfusion disturbances precede ischemia, perfusion imaging should be more sensitive than wall motion imaging for the detection of ischemia. However, the results of these noninvasive tests are governed not only by the underlying physiology, but also by their imaging characteristics. The imaging strengths of echocardiography (spatial and temporal resolution, independent assessment of segmental wall motion) may therefore compensate for its current dependence on ischemia.

Beyond Sensitivity and Specificity

The modern application of functional testing has moved on from simply the diagnosis of coronary artery disease to assisting in decision-making, especially regarding the presence, location, and extent of ischemia. In these respects, the sensitivity and specificity for the diagnosis of coronary disease are of limited relevance – for example, in postinfarction patients, this analysis does not discriminate between the diagnoses of scar and ischemia.

The regional accuracy of stress echocardiography and perfusion scintigraphy may be important with respect to decision-making about revascularization. Breast and diaphragmatic attenuation are not the cause of artifacts with echocardiography, but should be readily recognized with nuclear imaging. The posterior wall poses a problem for perfusion scintigraphy (due to lower counts), and the lateral wall with echocardiography (due to overlying lung). Scintigraphy may be more accurate than echocardiography in these segments [15].

Although the assessment of the extent of ischemia appears to be broadly similar with echocardiography and nuclear techniques, stress echocardiography has a problem in defining the presence of multivessel coronary artery disease, with nuclear imaging being significantly more sensitive. Likewise, the detection of ischemia in combination with infarction is simpler with scintigraphy than echocardiography.

Prognostic Value for Coronary Artery Disease

The prognostic value of stress echocardiography has been well defined and comparison of the two techniques has shown them to be similar [16, 17]. Cardiac death is uncommon in individuals with stable chronic coronary disease. While ischemia and scar detected by either SPECT or stress echocardiography are predictive of cardiac events, the predictive value of a positive test result has generally been below 20%. For both echocardiography and nuclear tests, the next step in a patient with a positive test result is to substratify the level of risk. Clinical features such as age, diabetes, and symptoms of congestive heart failure are predictive of outcome in stable coronary artery disease, and may be used to select patients for more extensive testing combined with imaging assessment. Similarly, the results of stress testing – expressed, for example, as the Duke treadmill score – are of use in selecting patients for either test. Moreover, both stress echocardiography and myocardial perfusion SPECT [18] appear to be equally useful in substratifying patients at intermediate risk of events.

Interestingly, a cost-effectiveness study showed that outcomes of groups with comparable levels of risk were similar but the imaging and downstream costs of SPECT were greater in the low–intermediate-risk patients. Because of the higher sensitivity of SPECT, this technique was the most cost-effective strategy in intermediate–high-risk patients (e.g., those with known coronary artery disease) [19].

Merits of SPECT and Stress Echocardiography

The advantages of stress perfusion imaging include less operator-dependence, higher technical success rate, higher sensitivity, and better accuracy when multiple resting left ventricular wall motion abnormalities are present [13]. The advantages listed in guidelines for stress echocardiography over stress perfusion scintigraphy include a higher specificity and a greater availability, versatility, and greater convenience [13]. The lower specificity of SPECT may reflect problems of posttest referral bias with an established test technique and false-positive rates related to image artifacts. It should be recognized that recent technical advances, including gated SPECT and attenuation correction, have improved the specificity of SPECT.

Finally, echocardiography provides important anatomic and functional information that is either not provided or is provided poorly by scintigraphy. Valve diseases such as aortic stenosis or ischemic mitral regurgitation are important comorbidities of coronary artery disease, and may merit dynamic evaluation in some circumstances [20]. Likewise, exertional dyspnea may be an important presenting symptom of coronary artery disease [21], but may also be due to diastolic dysfunction. The ability to measure left ventricular filling pressure with exercise may be a useful adjunct to exercise echocardiography [22].

38.4 Current Clinical Indications

The current indications to MPI substantially overlap with stress echocardiography [4, 23]. The technique is especially indicated in patients with nonfeasible, nondiagnostic, or ambiguous exercise ECG stress test results. The use of MPI as a first-line imaging technique (whenever resources permit) is allowed [24] but not recommended by the guidelines. Stress imaging can be used as a first-line test in patients with uninterpretable ECG for baseline left bundle branch block, Wolff–Parkinson–White syndrome, paced rhythms, or alterations on resting ECG. In clinical environments where stress echocardiography expertise is available, MPI should be restricted to patients in whom stress echocardiography is not feasible or has yielded ambiguous results. The performance of both stress imaging tests is of dubious efficiency. A concordantly positive result is highly predictive of a critical coronary artery stenosis and clears the pathway toward an ischemia-driven revascularization. More often, a discordant result is found with stress echocardiography negativity (typical of a high specificity technique) and perfusion imaging positivity (typical of a high sensitivity technique). This patient has the same probability of having normal coronary arteries or mild-to-moderate coronary artery disease. Proceeding to coronary angiography, with unavoidable escalation of costs, risks, and revascularization, has a very questionable prognostic benefit. In these patients we currently perform stress cardiovascular magnetic resonance (CMR) [25, 26], which has at least the same accuracy as scintigraphy for viability and ischemia detection [12, 27], with no radiation burden and no ecological stress. Appropriate indications to MPI as stipulated by recent specialty European guidelines [23] are listed in Table 38.4.

38.5 The Elephant in the Room – Radiation Safety

The radiation burden of stress SPECT and PET ranges from the dose equivalent of 500–1,600 chest X-rays [3, 28] (Table 38.2). In light of dose optimization, which in Europe is also reinforced by the EURATOM law [29] and medical imaging guidelines [30],

Table 38.2 The radiation dose for common nuclear cardiology examinations (from [31])

Procedures	Effective radiation dose (mSv)	Equivalent no. of chest radiographs
Perfusion cardiac rest–stress technetium 99m sestamibi scan	10	500
Perfusion cardiac rest–stress thallium scan	21	1,050
Thallium-201 stress and reinjection (3.0 mCi + 1.0 mCi)	25	1,250
Dual isotope (3.0 mCi Th-201 + 30 mCi Tc-99m) stress	27	1,600
Cardiac PET ^{18}F–FDG	3.5	175
Cardiac PET ^{13}N-ammonium	2.0	100
Cardiac PET ^{15}O-water	4.0	200
CT–PET	25	1,500

it is especially disorienting that in the USA – generally expected to be a reliable site of best medical practice – 35% of the 9.3 million stress scintigraphies in 2002 were performed used 201Tl with 86% of these being dual isotope studies, perhaps because of the relatively fast patient throughput [28]. Thallium is still proposed by authorities as the best tracer for cardiac studies in the USA [28], and yet it has been officially dismissed for its obviously unfavorable radioprotection profile in many European laboratories including the Institute of Clinical Physiology of Pisa.

In addition to the issue of economic cost, discussed above, the main differences between the tests from a societal perspective are the ecological impact and the radiation burden for the patients and the doctors. The additional extra-risk of a cancer is around 1 in 1,000 (for a middle-aged man performing a sestamibi scan) but can be as high as 1 in 300 for a 35-year-old woman undergoing a thallium scan [29, 30]. In terms of population burden, the 10 million scans performed each year in the USA translate into a population risk of 20,000 new cancers per lifetime [4, 27, 28]. With the confidence intervals of the current risk estimates, the risk may be two- to threefold higher (60,000 new cancers) or two- to threefold lower (7,000 new cancers). One must be sure that there is no better way to make an accurate diagnosis of coronary artery disease. The great number (>30%) of inappropriate examinations [31], the frequent unawareness of dose and risks by the referring physician and the practitioner [32], and the provision of limited radiation safety information to the patient [33] set the stage for a perfect medicolegal storm [34, 35], especially in presence of tight regulations existing in the European law and strongly discouraging unjustified use of ionizing testing [30].

PET and SPECT scanners have been linked to computed tomographic (CT) scanners, which are digital radiological systems that acquire data in the axial plane, producing images of internal organs of high spatial and contrast resolution. The combination of PET or SPECT and CT as a single unit provides spatial and pathological correlation of the abnormal metabolic or flow activity, allowing images from both systems to be obtained from a single instrument in one examination procedure with optimal coregistration of images [4]. The resulting fusion images facilitate the most accurate interpretation of both PET and SPECT and CT studies (Fig. 38.1). The recent White Paper on Multimodality Imaging of the European Society of Radiology and the European Association of Nuclear Medicine put forward two indications on multimodality imaging [8]: (1) Diagnosis of coronary artery disease: the major advantage of the integrated approach to the diagnosis of coronary artery disease is the added sensitivity of PET and SPECT and CT angiography. With integrated PET/SPECT–CT systems, the limitations of both techniques can be overcome, leading to improved diagnostic capability. (2) Guiding management of coronary artery disease: Not all coronary artery stenoses are flow limiting, and PET or SPECT stress perfusion imaging complements the anatomical CT data by providing functional information on the hemodynamic significance of such stenoses, thus allowing more appropriate selection of patients who may benefit from revascularization procedures. However, while there are no questions about the diagnostic accuracy and the beauty of SPECT and, even more staggering, of combined PET–CT scans, it is very counterintuitive to accept an extensive use of these techniques in light of their exorbitant costs, high radiation burden, environmental impact, and availability of several nonionizing imaging techniques (such as ultrasound and magnetic resonance imaging) offering comparable information.

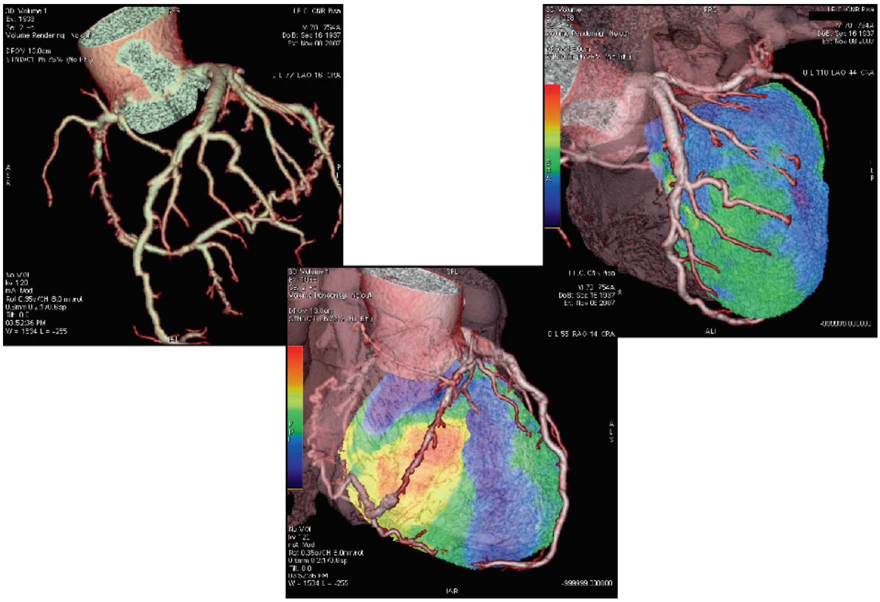

Fig. 38.1 An example of hybrid PET–CT imaging, with simultaneous representation of coronary anatomy (*left*) and perfusion (*right and middle panels*). (Courtesy of Dr. Danilo Neglia, Head of Cardiac PET Lab, Institute of Clinical Physiology, Pisa, Italy)

The long-standing comparison and competition between echocardiography and SPECT has radically changed in the last 5 years, as we have entered the "age of sustainability," i.e., the need to consider economic cost, biological hazards, long-term radiation risks, and environmental impact in our diagnostic flow-charts. (3). In light of this new perspective, the previous attractions of the polychrome, 3D, quantitative, operator-independent approach of nuclear imaging may come to appear a little jaded. Specifically, in centers having the requisite expertise for stress echocardiography, there are limited reasons to add nuclear perfusion imaging for diagnostic and prognostic purposes, and there may be social and ecological reasons why the nuclear alternative is less desirable [36]. If contrast-enhanced stress echocardiography does not salvage the technically difficult stress echocardiography, stress CMR provides an excellent, quantitative and reproducible, alternative for a nonionizing assessment of wall motion, and perfusion reserve, with accuracy at least comparable to MPI for ischemia and viability detection.

Perhaps in part related to competing technologies, the number of perfusion scans in the USA has begun to decline. The approach of ignoring [13], negating [38], or minimizing [23] the risks linked to radiation exposure is changing in a time of increased cultural, regulatory, and legal pressure towards the prescribers to minimize the biological burdens of inappropriate prescriptions. There is also an increasing attention to awareness regarding doses and risks of nuclear cardiology procedures in prescribers, practitioners, and patients [39] (Table 38.3).

Table 38.3 Head-to-head comparison between myocardial perfusion imaging (*MPI*) and stress echocardiography

	MPI	Stress echocardiography
Diagnostic parameter	Perfusion (WM)	WM (CFR)
Relative cost	3	1
Sensitivity	Higher	High
Specificity	Moderate	High
Radiation burden (CXr)	500–1500	0
Patient friendliness	Low	High
Operator friendly	Low	High
Environment friendly	Low	High

WM wall motion, *CFR* coronary flow reserve, *CXr* X-ray

38.6 Conclusion

Nuclear perfusion imaging and stress echocardiography show common pathophysiological roots and produce similar clinical fruits. They share a bipartisan imaging strategy to replace an anatomy-driven with a more physiologically oriented approach, referring for coronary angiography for ischemia-driven revascularization only patients with uncontrolled symptoms or a high-risk pattern of stress imaging. They are, more or less, equally reliable "gatekeepers" for more invasive, risky, and costly procedures, and have a recognized similar diagnostic and prognostic accuracy [40–43]. On the basis of these well-established findings, ACC/AHA guidelines concluded that "the choice of which test to perform depends on issues of local expertise, available facilities and considerations of cost-effectiveness" [13]. However, the societal climate surrounding medical practice has become more sensitive to the environmental costs of testing, and recent European guidelines have added that the advantages of stress echocardiography include its "being free of radiation" [24]. However, if we put the choice of cardiac stress imaging in the wider context of medical imaging, the European Commission recommendations clearly state that a nonionizing test should always be preferred when the information is grossly comparable to an ionizing test and both are available [36]. Applying guidelines, whenever a stress imaging test is clinically indicated, stress echocardiography is the first line test; when stress echocardiography is not feasible or yields ambiguous response, stress CMR is an excellent radiation-free option. If stress CMR technology and expertise are not available, stress MPI can be considered (Table 38.4). Although very different practice patterns are today present in high-volume centers, MPI and stress echocardiography are better used as alternative rather than redundant techniques. A good MPI is better than a bad stress echocardiography study, and a good stress echocardiography study is better than a poor MPI – but it is equally obvious that the capability to perform good echocardiography is one of the indicators of the quality of a cardiology division, and that the choice between stress echocardiography and MPI should be made in the context of the environmental, biological, and economic effects (Tables 38.5 and 38.6).

Table 38.4 Appropriate indications to MPI

	Appropriate	Uncertain	Inappropriate
Symptomatic, intermediate pretest probability, unable to exercise, abnormal ECG	√		
Acute chest pain, uncertain diagnosis	√		
Evaluation post-PCI or CABG		√	
Patients capable to exercise, interpretable ECG			√

Appropriate indications to MPI in a cardiological environment without access to stress echocardiography and/or stress CMR
CABG coronary artery bypass graft, *PCI* percutaneous coronary intervention

Table 38.5 The comparable diagnostic and prognostic information of cardiac stress imaging techniques (modified from [2])

	References	Population	Techniques	Results
Diagnostic accuracy for CAD	O'Keefe et al. (1995) [17]	11 studies (808 pts)	Stress echocardiography Perfusion imaging	Sensitivity = 78% Specificity = 86% Sensitivity = 83% (p = ns vs. echocardiography) Specificity = 77% (p = ns vs. echocardiography)
	Fleischmann et al. (1998) [18]	44 studies (5,974 pts)	Exercise echocardiography vs. exercise SPECT	Sensitivity = 85% Specificity = 77% Sensitivity = 87% (p = ns vs. echocardiography) Specificity = 64%
Prognostic value	Gibbons et al. (1999) [21]	9 studies (3,497 pts)	Stress echocardiography	PPV: 14%-66% NPV: 81%-98%
		12 studies (12,589 pts)	Stress myocardial imaging	PPV = 3.8%-41% NPV = 81.2%-100%
Diagnostic value of viability	Bax et al. (1997) [19]	37 studies (1,341 pts)	F-18 fluorodeoxyglucose metabolic imaging	Specificity higher ($p < 0.001$) for low-dose dobutamine
			Thallium perfusion imaging Dobutamine echocardiography	
Prognostic value of viability	Allman et al. (2002) [20]	24 studies (3,089 pts)	F-18 fluorodeoxyglucose metabolic imaging	No measurable performance difference for predicting revascularization benefit between the three testing techniques
			Thallium perfusion imaging Dobutamine echocardiography	

CAD coronary artery disease, *NPV* negative predictive value, *PPV* positive predicted value, *pts* patients, *ns* not significant

Table 38.6 Broad levels of risk for common X-ray examinations and isotope scans

X-ray examination or nuclear medicine isotope scan	Effective doses (mSv) clustering around a value of:	Equivalent period of natural background radiation	Lifetime additional risk of cancer per examination[a]
Chest X-ray	0.01	A few days	Negligible risk
Skull X-ray	0.1	A few weeks	Minimal risk
			1 in 1,000,000 to 1 in 100,000
Breast (mammography) Lung isotope scan	1.0	A few months to a year	Very low risk 1 in 100,000 to 1 in 10,000
Cardiac gated study Cardiac thallium scan	10	A few years	Low risk 1 in 10,000 to 1 in 1,000

[a] These risk levels represent very small additions to the 1-in-3 chance we all have of getting cancer. The table is summarized from Table 38.2 of "Radiation and your patient: a web module produced by Committee 3 of the International Commission on Radiological Protection (ICRP)".
Typically, environmental radiation amounts to approximately 2–3 mSv per year

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