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REVIEW ARTICLE

Can Stress Echocardiography Compete with Perfusion Scintigraphy in the Detection of Coronary Artery Disease and Cardiac Risk Assessment?

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Aims: The aim of this review was to define the place of stress echocardiography in the context of perfusion scintigraphy for the detection of coronary artery disease (CAD) and the assessment of cardiac risk. Stress echocardiography has the benefits of widespread availability, relatively low cost, portability, absence of radiation, and the determination of the ischaemic threshold. However, the echocardiographic windows are variable, sometimes with poor echogenicity, and interpretation is subjective and requires an adequate learning period.

Methods and Results: Diagnostic and prognostic comparisons were focused on studies comparing stress (exercise, dobutamine, adenosine or dipyridamole) echocardiography and perfusion scintigraphy in the same patients. These direct diagnostic comparisons (22 studies for a total of 1380 patients) show that stress echocardiography may be somewhat less sensitive in detecting and localizing mild CAD (in particular when vasodilators are used), but is more specific than perfusion scintigraphy. The direct prognostic comparisons (five studies for a total of 805 patients) show that stress echocardiography and perfusion scintigraphy have comparable prognostic value.

Conclusions: At this moment, stress echocardiography already seems very competitive with perfusion scintigraphy. In the near future, improvement in endocardial border detection and quantitation of wall motion analysis are expected to improve the value of stress echocardiography still further.
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Key Words: Coronary artery disease; Diagnosis; Perfusion scintigraphy; Stress echocardiography; Risk assessment.

Introduction

Stress echocardiography and myocardial perfusion scintigraphy are often used for the detection of coronary artery disease (CAD) and the assessment of cardiac risk [1–26]. This review attempts to define the place of stress echocardiography in the context of perfusion scintigraphy. As a number of variables (referral bias, extent and severity of CAD, definition of significant CAD, stress protocols, medications) may potentially influence the results of either test, the comparisons will focus on studies involving performance of both echocardiographic and scintigraphic imaging in the same patients for each of the most widely used stress techniques: exercise, dobutamine, and the direct vasodilators adenosine and dipyridamole. For these comparisons to be valid, we assume that the investigators in these studies are equally expert in either technique.

Methods and Statistical Analysis

A MedLine search on stress echocardiographic and perfusion scintigraphic studies published in the major English language journals was performed, using the

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search terms (adenosine or dipyridamole or dobutamine or exercise) and (echocardiography or thallium or technetium). Studies were only included in the main diagnostic and prognostic analysis if both stress echocardiography and perfusion scintigraphy was performed in all patients, using the same cardiac stressor. Studies were only included in the diagnostic analysis if these studies included patients both with and without angiographically defined CAD, and if it was stated how many patients with and without CAD had negative and positive test results. Studies describing special issues such as women and patients with left bundle branch block (LBBB) of left ventricular hypertrophy (LVH) were excluded from the primary diagnostic analysis. Special issues such as these were discussed separately.

Sensitivity was defined as the number of true positive tests divided by the total number of patients with angiographically significant CAD. Specificity was defined as the number of true negative tests divided by the total number of patients without angiographically significant CAD. Mean values for sensitivity and specificity were calculated by combining the results of individual patient data from multiple studies. Comparisons of sensitivity and specificity were performed using the standardized normal distribution test. Statistical significance was defined as $P<0{\cdot}05$.

Basic Principles of Stress Echocardiography Versus Perfusion Scintigraphy

In the presence of a flow-limiting coronary artery stenosis, exercise or pharmacological stress results in a sequence of functional events, known as the 'ischaemic cascade'[27]. According to this cascade, perfusion abnormalities (visualized at perfusion scintigraphy by relatively reduced tracer uptake) due to limited coronary flow reserve precede decreased myocardial contractility (visualized at echocardiography by abnormal regional systolic function).

The development of myocardial perfusion defects with either exercise or pharmacological stress depends on the induction of regional heterogeneity of myocardial blood flow. Coronary blood flow to the vascular bed of a normal artery dramatically increases during stress, whereas perfusion through a stenosed artery may change only minimally. Because the initial uptake of radiopharmaceuticals is flow-dependent within physiological ranges[28], the relative myocardial radionuclide concentration will be greater in vascular beds supplied by a normal artery relative to that in beds perfused by an artery with significant obstruction.

Regional malperfusion severe enough to cause metabolic consequences of ischaemia can be identified by echocardiography, based upon the response of the left ventricle. The normal response of the left ventricle to exercise or dobutamine stress is to increase endocardial excursion, the speed of contraction, and the degree of myocardial thickening. The most important indices pointing to the presence of myocardial ischaemia include stress-induced deterioration of regional endocardial excursion, and a reduction of myocardial thickening.

Strengths and Limitations of Stress Echocardiography

Clinical Considerations

Several aspects of stress echocardiography are attractive from the standpoint of clinical feasibility. In comparison with scintigraphic cameras, echocardiography machines are widely available at relatively low cost, are smaller in size and are more portable. The shorter time for performance and interpretation of a stress echocardiogram is attractive in the outpatient setting. Finally, the absence of ionizing radiation may be attractive to the public, for some of whom nuclear tests have a bad image.

Imaging Considerations

Two-dimensional echocardiography provides the ability to visualize the heart using a non-invasive, real-time approach. As ischaemia may be observed on-line, appropriate action can be taken during the test. Documentation of the ischaemic threshold can provide important information about the severity and extent of underlying CAD. Non-ischaemic explanations for the patient symptoms may be apparent from the visualization of valve anatomy and gradients or pericardial effusion. Finally, specificity lowering (breast) attenuation artifacts at perfusion scintigraphy are not problematic with echocardiography. The relative weaknesses of stress echocardiography are the sometimes poor echocardiographic windows (especially in obese or lung emphysema patients), making a correct interpretation difficult or impossible, and the visual (subjective) interpretation, which requires an important learning curve even for experienced echocardiographers[29–31].

Diagnostic Accuracy of the Imaging Modalities

Exercise Stress Echocardiography Versus Perfusion Scintigraphy

Table 1 shows the sensitivity and specificity for the detection of CAD in seven studies[1–7], directly comparing exercise echocardiography and perfusion scintigraphy in the same 397 patients. The sensitivities of both tests for the identification of CAD were comparable (78% vs 83%, respectively), although there was a higher sensitivity for perfusion scintigraphy in the setting of single vessel CAD (78% vs 67%, respectively, $P<0{\cdot}05$).

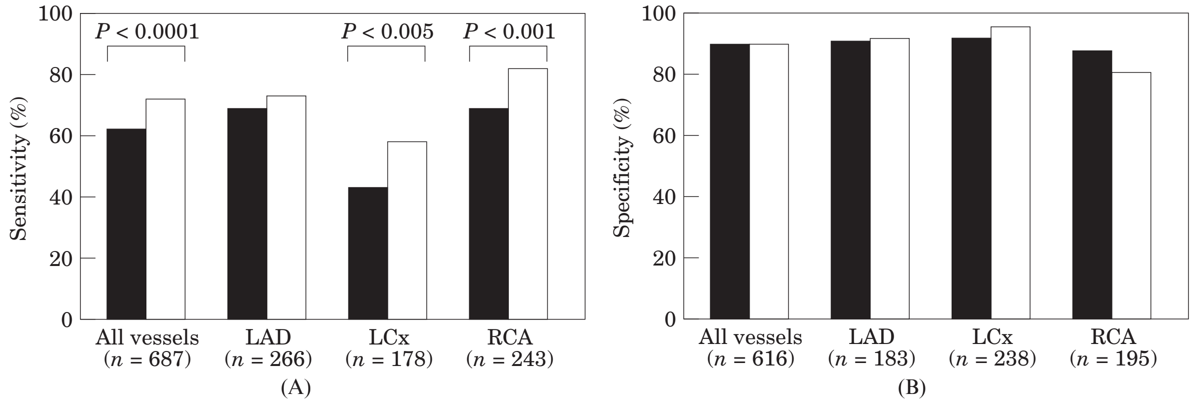

Figure 1. Sensitivity (A) and specificity (B) of stress echocardiography (black bars) and perfusion scintigraphy (white bars) for identification of disease in individual coronary arteries. LAD=left anterior descending coronary artery; LCx=left circumflex coronary artery; RCA=right coronary artery.

There was a trend towards a better specificity for stress echocardiography (91% vs 83%, P<0·10).

Dobutamine Stress Echocardiography Versus Perfusion Scintigraphy

Also shown in Table 1 are the sensitivity and specificity values reported in eight studies[8–15], comprising 593 patients who underwent simultaneous dobutamine stress echocardiography and perfusion scintigraphy. Dobutamine stress perfusion scintigraphy was the more sensitive test: 86% vs 80% (P<0·05). Dobutamine stress echocardiography, however, was the more specific test: 86% vs 73% (P<0·005). The finding that stress perfusion scintigraphy is more sensitive (especially in patients with single vessel CAD) is in line with the ischaemic cascade theory[27], which states that perfusion abnormalities due to limited coronary flow reserve precede wall motion abnormalities. That the difference in sensitivity between exercise or dobutamine stress echocardiography and perfusion scintigraphy is, in fact, only very small might be explained by two major factors: suboptimal inducement of blood flow heterogeneity by exercise or dobutamine[32] or inherent compensating strengths of echocardiography over perfusion scintigraphy, including improved spatial resolution, and the ability to categorize wall motion independently in each segment (contrasting with the relative blood flow comparisons used in myocardial perfusion imaging).

Vasodilator Stress Echocardiography Versus Perfusion Scintigraphy

As seen in Table 1, pooled data from six studies[15–21] directly comparing vasodilator (adenosine or dipyridamole) stress echocardiography and perfusion scintigraphy in the same 390 patients show that the sensitivity of vasodilator perfusion scintigraphy was superior to that of vasodilator echocardiography (85% vs 66%, P<0·0001), both for single-vessel CAD (78% vs 58%, P<0·01) and multivessel CAD (95% vs 74%, P<0·0001). These results are not surprising, since vasodilators primarily create blood flow heterogeneity (detected by perfusion scintigraphy and not echocardiography) and true myocardial ischaemic (detected by echocardiography) in only a limited number of patients. Of note, not all studies[20] used optimal doses of vasodilator to induce true myocardial ischaemia[33], and no single comparative study used the new, promising dipyridamole-atropine protocol[34].

The Optimal Pharmacological Stressor

The necessity of inducing myocardial ischaemia for the development of wall motion abnormalities suggests that dobutamine may be more effective than a direct vasodilator for stress echocardiography[35]. Indeed, pooled data[36] from seven studies directly comparing (high-dose) dobutamine vs (high-dose) dipyridamole or adenosine stress echocardiography showed that dobutamine stress echocardiography was the more sensitive test, while specificity was comparable. In contrast, direct vasodilators (adenosine or dipyridamole) are considered the most effective pharmacological drugs to create coronary blood flow heterogeneity[32,35,37]. The most appropriate means of comparing pharmacological stress echography and perfusion scintigraphy seems, therefore, to be to use dobutamine with the former and a direct vasodilator with the latter. Four studies have directly compared these two stress modalities[15, 18, 38, 39]. In only one study[15] was dipyridamole perfusion scintigraphy more sensitive than (high-dose) dobutamine stress echocardiography. Importantly, in all but one study[39], dobutamine stress echocardiography tended to be more specific for the detection of CAD.

Assessment of the Localization of CAD

In Figure 1, the sensitivities (Fig. 1A) and specificities (Fig. 1B) of stress echocardiography and perfusion

Table 1. Direct diagnostic comparisons between stress echocardiography and perfusion scintigraphy.

Author	Year	Patients	Protocol	Scan technique	Echocardiography				Perfusion scintigraphy			
					Sensitivity			Specificity %	Sensitivity			Specificity %
					Overall %	SVD %	MVD %		Overall %	SVD %	MVD %	
Exercise												
Wann[1]	1979	6	Supine-bike	Tl-201, Planar	33	0	50	100	67	0	100	100
Maurer[2]	1981	36	Treadmill	Tl-201, Planar	83	50	94	92	74	—	—	92
Pozzoli[3]	1991	75	Upright-bike	Tc-99m, SPECT	71	61	94	96	84	82	88	88
Galanti[4]	1991	53	Upright-bike	Tl-201, Planar	93	93	92	96	100	100	100	92
Quiñones[5]	1992	112	Treadmill	Tl-201, SPECT	74	58	89	88	76	61	89	81
Salustri[6]	1992	44	Upright-bike	Tc-99m, SPECT@	83	83	—	86	87	87	—	71
Hecht[7]	1993	71	Supine-bike	Tl-201, SPECT	90	77	100	80	92	95	90	65
Weighted mean		397			78	67	92	91	83	78	90	83
Dobutamine												
Günalp[8]	1993	27	30 µg/kg/min	Tc-99m, SPECT	83	78	89	89	94	89	100	89
Marwick[9]	1993	217	40 µg/kg/min	Tc-99m, SPECT	72	66	77	83	76	74	78	67
Forster[10]	1993	21	40 µg/kg/min+A	Tc-99m, SPECT	75	25	100	89	83	75	88	89
Senior[11]	1994	61	40 µg/kg/min	Tc-99m, SPECT	93	86	97	94	95	86	100	71
Di Bello[12]	1996	45	40 µg/kg/min+A	Tc-99m, SPECT	76	58	95	86	87	79	95	86
Kisacik[13]	1996	69	40 µg/kg/min+A	Tc-99m, SPECT	94	94	94	86	96	88	100	64
Huang[14]	1997	93	40 µg/kg/min+A	Tl-201, SPECT	93	74	100	77	90	74	96	81
Santoro[15]	1998	60	40 µg/kg/min+A	Tc-99m, SPECT	61	50	67	96	91	83	95	81
Weighted mean		593			80	69	88	86	86	78	91	73
Adenosine												
Nguyen[16]	1990	25	0·14 mg/kg/min	Tl-201, SPECT	60	—	—	100	90	—	—	100
Amanullah[17]	1993	40	0·14 mg/kg/min	Tc-99m, SPECT	74	—	—	100	94	—	—	100
Marwick[18]	1993	97	0·18 mg/kg/min	Tc-99m, SPECT	58	52	64	87	86	81	93	71
Weighted mean		162			63	52	64	90	89	81	93	78
Dipyridamole												
Ferrara[19]	1986	42	0·75 mg/kg	Tl-201, Planar	63	—	—	92	70	—	—	100
Perin[20]	1991	25	0·56 mg/kg	Tl-201, Planar	58	—	—	100	95	—	—	50
Santoro[15]	1998	60	0·84 mg/kg	Tc-99m, SPECT	55	50	57	96	97	92	100	89
Parodi[21]	1999	101	0·84 mg/kg	Tc-99m, Planar	78	65	88	76	79	70	93	90
Weighted mean		228			68	61	78	89	83	76	95	88
Grand total		1380			75	66	86	88	85	78	92	79

A=Atropine; MVD=multivessel disease; SVD=single vessel disease; Tl-201=Thallium-201; Tc-99m=Technetium-99m; SPECT=single-photon emission computed tomography; @=in some patients thallium-201 was used.

Table 2. Direct prognostic comparisons between stress echocardiography and perfusion scintigraphy.

Author	Year	Setting	Protocol	Scan technique	Patients	Echocardiography		Perfusion scintigraphy	
						RR + vs − test#	Normal study* %	RR + vs − test	Normal study %
Van Daele[22]	1994	Acute MI	Dipyridamole	Tc-99m, SPECT	89	1·4	—	1·1	—
Geleijnse[23]	1997	Chronic CAD	Dobutamine	Tc-99m, SPECT	220	4·5	0·4	4·0	0·5
Olmos[24]	1998	Chronic CAD	Exercise	Tc-99m, SPECT	225	2·2	0·9	2·3	0·9
Van Damme[25]	1997	Preoperative	Dobutamine	Tc-99m, SPECT	142	3·7	—	7·4	—
Pasquet[26]	1998	Preoperative	Dipyridamole	Tc-99m, SPECT@	129	3·0	—	11·5	—

#Univariate risk ratio positive test (for myocardial ischaemia) versus negative test for 'all' cardiac events. *Annual hard (death or nonfatal myocardial infarction) event rate. CAD=coronary artery disease; @=in some patients thallium-201 was used; RR=risk ratio.

scintigraphy for individual vessels are shown as reported in eight studies (one report assessed two different stressors), for a total of 1,303 vessels (3, 6, 7, 11, 14, 15, 21). The respective sensitivities were, respectively: 62% vs 72% ($P<0{\cdot}0001$) for overall detection of individual CAD; 69% vs 73% for left anterior descending coronary disease; 43% vs 58% ($P<0{\cdot}005$) for the left circumflex coronary disease, and 69% vs 82% ($P<0{\cdot}001$) for right coronary disease. Specificities were, respectively, 90% vs 90%, 91% vs 92%, 92% vs 96%, and 88% vs 81%. For both stress echocardiography and perfusion scintigraphy, the sensitivity for detection of left circumflex coronary disease was (independent of the stressor) significantly less compared to detection of CAD in other coronary arteries. In addition to variation in coronary anatomy (with a small circumflex territory in some patients), perfusion scintigraphy suffers from a less reliable assessment of the posterior regions of the heart due to problems of photon attenuation, and echocardiography suffers from problems with resolution of the lateral wall endocardium because of the parallel orientation of this wall and the ultrasound beam. Overall differences in sensitivity for detection of individual vessel CAD between stress cardiography and perfusion scintigraphy were mainly caused by the included dipyridamole studies[15,21]. When these studies were excluded from the analysis, overall sensitivity for detection of individual vessel, CAD was, respectively for stress echocardiography and perfusion scintigraphy, 69% vs 72%, and overall specificity was 90% for both imaging modalities.

Assessment of the Extent of CAD

An important goal of stress testing is the identification of patients with multivessel CAD, who could benefit from revascularization from a prognostic point of view[40]. Patients with multivessel CAD can be differentiated from patients with single vessel CAD by detection of wall motion or perfusion abnormalities in two or more coronary territories. The relative ability of stress echocardiography and perfusion scintigraphy to predict the extent of CAD has been investigated in four studies (one report assessed two different stressors) for a total of 220 patients[7,11,15]. The mean reported sensitivity for stress echocardiography (50%, range 14–70%) did not differ significantly from that reported for perfusion scintigraphy (58%, range 48–77%). However, analogous to the prior section, in one study[15] the sensitivity of dipyridamole echocardiography for multivessel CAD was clearly less than that of dipyridamole perfusion scintigraphy (14% vs 57%). The mean reported specificity for stress echocardiography (97%, range 90%–100%) was comparable to that reported for perfusion scintigraphy (95%, range 92%–100%). The relative underestimation of multivessel CAD by both imaging modalities can be explained by the premature cessation of stress because of the development of limiting ischaemia (angina, ST-segment deviation, or new wall motion abnormalities in one region as a test end-point during stress echocardiography), imperfect assignment of myocardial regions to coronary arteries, collateral circulations, anatomically significant but functionally non-significant lesions, and (for perfusion scintigraphy) diffuse hypoperfusion.

Special Subgroups

Left Bundle Branch Block

In LBBB patients, exercise perfusion scintigraphic studies often suffer from false positive perfusion defects in the interventricular septum in the absence of left anterior descending coronary stenosis[41]. Several mechanisms have been proposed to explain these perfusion defects. In LBBB patients, septal contraction occurs at the very end of systole. The regional myocardial compressive effect may restrict coronary blood flow during early diastole, when most perfusion normally occurs[42]. As the heart rate increases and diastole shortens, the relative septal hypoperfusion may become even more apparent. Alternatively, with markedly delayed septal contraction, the myocardium in this region encounters a decreased afterload to that of other left ventricular segments. This may result in a relative reduction in coronary septal blood flow as a result of coronary autoregulatory mechanisms[43]. Because of the suspected major role of heart rate increase in the development of septal defects, vasodilator (dipyridamole, adenosine) perfusion scintigraphy, which causes only a moderate increase in heart rate, is advocated as the stress test of choice[44]. Some promising reports on the value of stress echocardiography in LBBB patients have been published[45,46]. In particular, in patients with preserved interventricular septal contraction (despite LBBB) dobutamine stress echocardiography may be a very accurate test to detect CAD in the left anterior descending coronary[46]. However, currently there are no studies directly comparing stress echocardiography with vasodilator perfusion scintigraphy.

Hypertension and/or Left Ventricular Hypertrophy

Hypertension is a major risk factor for CAD, and a frequent finding in patients undergoing stress testing. Several reports have suggested that the specificity of perfusion scintigraphy in patients with hypertension and/or LVH to detect CAD is suboptimal[47–49]. Perfusion defects despite the absence of obstructive epicardial CAD may be caused by a relative reduction in the microvascular bed size and a reduction in resistance vessels diameter secondary to vascular hypertrophy[50]. Although severely impaired perfusion may be expected to influence stress echocardiographic results also, several stress echocardiographic studies have shown excellent specificity values in patients with hypertension and/or

LVH[51–53], comparable to values for patients without hypertension, studied in the same study[54]. Furthermore, the presence of LVH consistently did not affect the diagnostic accuracy of stress echocardiography in patients with hypertension[55–57]. Direct comparative studies with perfusion scintigraphy were mainly performed with dobutamine stress echocardiography[9,53,56]. In retrospective studies, variable results were reported concerning the value of this latter stress modality relative to dobutamine stress scintigraphy[9,56]. In a large, prospective study, both dobutamine and dipyridamole stress echocardiography were more specific than exercise perfusion scintigraphy for the detection of CAD in patients with a history of hypertension[53].

Women

The diagnosis of CAD in women may be troublesome, because they have (certainly until the seventh decade of life) a relatively low pre-test probability of CAD and a lower exercise capacity[58]. Perfusion scintigraphy may suffer from additional problems, such as anterolateral breast attenuation artifacts in rest or during stress in case of breast movement[59], and the relatively small size of the female heart, given that the spatial resolution of perfusion scintigraphy is approximately 1 cm[60]. Several stress echocardiographic studies have shown excellent sensitivity and specificity values in women[61–63], comparable to values for men, studied in the same study[63]. Comparative studies with perfusion scintigraphy were only performed for dobutamine stress echocardiography[64–66]. In the studies using a high-dose dobutamine-atropine protocol, stress echocardiography was more accurate than dobutamine[65] and more specific than exercise/dipyridamole[64] perfusion scintigraphy.

Prognostic Accuracy of the Imaging Modalities

Although numerous studies have described the prognostic value of stress echocardiography[67], only five prognostic studies[22–26] have directly compared the predictive value of this stress modality relative to perfusion scintigraphy. As seen in Table 2, one study focused on patients after acute myocardial infarction[22], two studies focused on patients with known or suspected stable CAD[23,24], and another two studies[25,26] focused on patients assessed before undergoing major surgery, describing the prediction of perioperative events. In none of these studies was a significant difference found between stress echocardiography and perfusion scintigraphy, as measured by the risk ratio of a positive test over a negative test for the occurrence of cardiac events, although in the preoperative era perfusion scintigraphy tended to perform somewhat better. In both studies in patients with known or suspected stable CAD[23,24], a positive echocardiographic or scintigraphic study not only increased subsequent cardiac risk in absolute terms, but the extent of wall motion abnormalities was at least as discriminative as the extent of perfusion abnormalities to further stratify patients into intermediate and high-risk subsets. Most importantly, patients with a normal stress echocardiogram or perfusion scintigram had a comparable annual hard (cardiac death or non-fatal myocardial infarction) event rate of less than 1%. Thus, both stress echocardiography and stress perfusion scintigraphy may identify a group of patients at low risk for future cardiac events in whom no further (more invasive) tests are required.

Conclusions and Recommendations

This review has concentrated on direct comparisons of stress echocardiography and perfusion scintigraphy for the diagnosis of CAD and the assessment of cardiac risk. As described, stress echocardiography has some relative strengths and limitations For the moment stress echocardiography (in particular when vasodilators are used) seems somewhat less sensitive to detecting and localizing (mild) CAD, but seems the more specific test. These findings may partly be explained by the relative low stressor dose used in some studies[8,20], since it is well known that stress echocardiography is more vulnerable to submaximal stress[33,68,69]. However, it should also be noted that many scintigraphic studies were not performed with the newest technetium-99m SPECT technology. For prognostic purposes, more related to severe forms of CAD, stress echocardiography and perfusion scintigraphy seem to have comparable strength. At this moment we recommend the following guidelines for the use of the two imaging modalities (disregarding costs and assuming equal available expertise for both modalities).

Perfusion scintigraphy is more useful in:
- patients with a poor echocardiographic window (obese, airway disease);
- patients with a high pre-test probability of CAD;
- patients requiring vasodilator stress;
- patients with LBBB (in combination with a direct vasodilator);
- detection of (anatomically defined) mild CAD.

Echocardiography is more useful in:
- patients in whom safety is a major concern;
- assessment of the functional significance of a known stenosis;
- patients with a low pre-test probability of CAD;
- patients with a suspicion of significant valvular, myocardial or pericardial disease.

Echocardiography may be more useful in:
- patients with hypertension and/or left ventricular hypertrophy;
- women.

In the near future, many technical improvements are expected to improve the value of stress echocardiography further. In particular, changes in stress protocols, such as the addition of atropine to dobutamine[70] or dipyridamole[34], improvement in endocardial border detection with second harmonic imaging[71] and contrast echocardiography[72], and quantitation of wall motion analysis to provide objective data with colour kinesis[73] or tissue Doppler imaging[74] are expected to improve the value of stress echocardiography still further.

References

[1] Wann LS, Faris JV, Childress RH, Dillon JC, Weyman AE, Feigenbaum H. Exercise cross-sectional echocardiography in ischemic heart disease. *Circulation* 1979; **60:** 1300–1308.

[2] Maurer G, Nanda NC. Two dimensional echocardiographic evaluation of exercise-induced left and right ventricular asynergy: correlation with thallium scanning. *Am J Cardiol* 1981; **48:** 720–727.

[3] Pozzoli MMA, Fioretti PM, Salustri A, Reijs AE, Roelandt JRTC. Exercise echocardiography and technetium-99m MIBI single-photon emission computed tomography in the detection of coronary artery disease. *Am J Cardiol* 1991; **67:** 350–355.

[4] Galanti G, Sciagrà R, Comeglio M *et al.* Diagnostic accuracy of peak exercise echocardiography in coronary artery disease: Comparison with thallium-201 myocardial scintigraphy. *Am Heart J* 1991; **122:** 1609–1616.

[5] Quiñones MA, Verani MS, Haichin RM, Mahmarian JJ, Suarez J, Zoghbi WA. Exercise echocardiography versus Thallium-201 single-photon emission computed tomography in evaluation of coronary artery disease. Analysis of 292 patients. *Circulation* 1992; **85:** 1026–1031.

[6] Salustri A, Pozzoli MMA, Hermans W *et al.* Relation between exercise echocardiography and perfusion single-photon emission computed tomography in patients with single-vessel coronary artery disease. *Am Heart J* 1992; **124:** 75–83.

[7] Hecht HS, Debord L, Shaw R, Chin H, Dunlap R, Ryan C, Myler RK. Supine bicycle stress echocardiography versus tomographic thallium-201 exercise imaging for the detection of coronary artery disease. *J Am Soc Echocardiogr* 1993; **6:** 177–185.

[8] Günalp B, Dokumaci B, Uyan C *et al.* Value of dobutamine Technetium-99m-Sestamibi SPECT and echocardiography in the detection of coronary artery disease compared with coronary angiography. *J Nucl Med* 1993; **34:** 889–894.

[9] Marwick T, D'Hondt A, Baudhuin T, Willemart B, Wijns W, Detry JM, Melin J. Optimal use of dobutamine stress for the detection and evaluation of coronary artery disease: combination with echocardiography or scintigraphy, or both. *J Am Coll Cardiol* 1993; **22:** 159–167.

[10] Forster T, McNeill AJ, Salustri A, Reijs AE, El-Said ES, Roelandt JRTC, Fioretti PM. Simultaneous dobutamine stress echocardiography and 99m-technetium isonitrile single photon emission computed tomography in patients with suspected coronary artery disease. *J Am Coll Cardiol* 1993; **21:** 1591–1596.

[11] Senior R, Sridhara BS, Anagnostou E, Handler C, Raftery EB, Lahiri A. Synergistic value of simultaneous stress dobutamine sestamibi single-photon emission computerized tomography and echocardiography in the detection of coronary artery disease. *Am Heart J* 1994; **128:** 713–718.

[12] Di Bello V, Bellina CR, Gori E *et al.* Incremental diagnostic value of dobutamine stress echocardiography and dobutamine scintigraphy (technetium 99m-labeled sestamibi single-photon emission computed tomography) for assessment of presence and extent of coronary artery disease. *J Nucl Cardiol* 1996; **3:** 212–220.

[13] Kisacik HL, Özdemir K, Altinyay E *et al.* Comparison of exercise stress testing with simultaneous dobutamine stress echocardiography and technetium-99M isonitrile single-photon emission computerized tomography for the diagnosis of coronary artery disease. *Eur Heart J* 1996; **17:** 113–119.

[14] Huang PJ, Ho YL, Wu CC *et al.* Simultaneous dobutamine stress echocardiography and thallium perfusion imaging for the detection of coronary artery disease. *Cardiology* 1997; **88:** 556–562.

[15] Santoro GM, Sciagrà R, Buonamici P *et al.* Head-to-head comparison of exercise stress testing, pharmacologic stress echocardiography, and perfusion tomography as first-line examination for chest pain in patients without a history of coronary artery disease. *J Nucl Cardiol* 1998; **5:** 19–27.

[16] Nguyen T, Heo J, Ogilby JD, Iskandrian AS. Single photon emission computed tomography with thallium-201 during adenosine-induced coronary hyperemie: correlation with coronary arteriography, exercise thallium imaging and two-dimensional echocardiography. *J Am Coll Cardiol* 1990; **16:** 1375–1383.

[17] Amanullah AM, Bevegard S, Lindvall K, Aasat M. Assessment of left ventricular wall motion in angina pectoris by two dimensional echocardiography and myocardial perfusion by technetium-99m sestamibi tomography during adenosine-induced coronary vasodilation and comparison with coronary angiography. *Am J Cardiol* 1993; **72:** 983–989.

[18] Marwick T, Willemart B, D'Hondt AM *et al.* Selection of the optimal nonexercise stress for the evaluation of ischemic regional myocardial dysfunction and malperfusion. Comparison of dobutamine and adenosine using echocardiography and 99m Tc-MIBI single photon emission computed tomography. *Circulation* 1993; **87:** 345–354.

[19] Ferrara N, Bonaduce D, Leosco D *et al.* Two-dimensional echocardiographic evaluation of ventricular asynergy induced by dipyridamole: correlation with thallium scanning. *Clin Cardiol* 1986; **9:** 437–442.

[20] Perin EC, Moore W, Blume M, Hernandez G, Dhekne R, DeCastro M. Comparison of dipyridamole echocardiography with dipyridamole thallium scintigraphy for the diagnosis of myocardial ischemia. *Clin Nucl Med* 1991; **16:** 417–420.

[21] Parodi G, Picano E, Marcassa C *et al.* High dose dipyridamole myocardial imaging: simultaneous scintigraphy and two-dimensional echocardiography in the detection and evaluation of coronary artery disease. *Coron Art Dis* 1999; **10:** 177–184.

[22] Van Daele M, McNeill AJ, Fioretti PM *et al.* Prognostic value of dipyridamole sestamibi single-photon emission computed tomography and dipyridamole stress echocardiography for new cardiac events after an uncomplicated myocardial infarction. *J Am Soc Echocardiogr* 1994; **7:** 370–380.

[23] Geleijnse ML, Elhendy A, Cornel JH *et al.* Cardiac imaging for risk stratification with dobutamine-atropine stress testing in patients with chest pain. Echocardiography, perfusion scintigraphy, or both? *Circulation* 1997; **96:** 137–147.

[24] Olmos LI, Dakik H, Gordon R *et al.* Long-term prognostic value of exercise echocardiography compared with exercise 201T1, ECG, and clinical variables in patients evaluated for coronary artery disease. *Circulation* 1998; **98:** 2679–2686.

[25] Van Damme H, Piérard L, Gillain D, Benoit TH, Rigo P, Limet R. Cardiac risk assessment before vascular surgery: a prospective study comparing clinical evaluation, dobutamine stress echocardiography, and dobutamine Tc-99m sestamibi tomoscintigraphy. *Cardiovasc Surg* 1997; **5:** 54–64.

[26] Pasquet A, D'Hondt AM, Verhelst R, Vanoverschelde JL, Melin J, Marwick TH. Comparison of dipyridamole stress echocardiography and perfusion scintigraphy for cardiac risk stratification in vascular surgery patients. *Am J Cardiol* 1998; **82:** 1468–1474.

[27] Nesto RW, Kowalchuck GJ. The ischemic cascade: Temporal sequence of hemodynamic, electrocardiographic and

symptomatic expressions of ischemia. *Am J Cardiol* 1987; **57:** 23C–27C.
[28] Leppo JA, Meerdink DA. Comparison of the myocardial uptake of a technetium-labeled isonitrile analogue and thallium. *Circ Res* 1989; **64:** 632–639.
[29] Picano E, Lattanzi F, Orlandini A, Marini C, L'Abbate A. Stress echocardiography and the human factor: the importance of being expert. *J Am Coll Cardiol* 1991; **24:** 928–933.
[30] Varga A, Picano E, Dodi C, Barbieri L, Pratali L, Gaddi O. Madness and method in stress echo reading. *Eur Heart J* 1999; **20:** 1271–1275.
[31] Hoffmann R, Lethen H, Marwick T *et al*. Analysis of interinstitutional observer agreement in the interpretation of dobutamine stress echocardiogram. *J Am Coll Cardiol* 1996; **27:** 330–336.
[32] Pennel DJ, Ell PJ. Whole-body imaging of thallium-201 after six different stress regimens. *J Nucl Med* 1994; **35:** 425–428.
[33] Casanova R, Petroncini A, Guidotti PL, Capacci PF, Jacopi F, Fabbri M, Maresta A. Dose and test for dipyridamole infusion and cardiac imaging early after uncomplicated acute myocardial infarction. *Am J Cardiol* 1992; **70:** 1402–1406.
[34] Picano E, Pingitore A, Conti U *et al*. Enhanced sensitivity for detection of coronary artery disease by addition of atropine to dipyridamole echocardiography. *Eur Heart J* 1993; **14:** 1216–1222.
[35] Fung AY, Gallagher KP, Buda AJ. The physiologic basis of dobutamine as compared with dipyridamole stress interventions in the assessment of critical coronary stenosis. *Circulation* 1987; **76:** 943–951.
[36] Geleijnse ML, Marwick TH, Boersma E, Deckers JW, Melin JA, Fioretti PM. Optimal pharmacological stress testing for the diagnosis of coronary artery disease: a probabilistic approach. *Eur Heart J* 1995; **16 (Suppl M):** 3–10.
[37] Lee J, Chae SC, Lee K, Heo J, Iskandrian AS. Biokinetics of thallium-201 in normal subjects: comparison between adenosine, dipyridamole, dobutamine and exercise. *J Nucl Med* 1994; **35:** 535–541.
[38] Smart SC, Bhatia N, Stoiber T. Dobutamine-atropine stress echocardiography and dipyridamole sestamibi scintigraphy for the detection of coronary artery disease: limitations and concordance. *J Am Coll Cardiol* (in press).
[39] Ho FM, Huang PJ, Liau CS, Lee FK, Chieng PU, Su CT, Lee YT. Dobutamine stress echocardiography compared with dipyridamole thallium-201 single-photon emission computed tomography in detecting coronary artery disease. *Eur Heart J* 1995; **16:** 570–575.
[40] Califf RM, Harrell FE Jr, Lee KL *et al*. The evolution of medical and surgical therapy for coronary artery disease: a 15-year perspective. *JAMA* 1989; **67:** 302–309.
[41] Hirzel HO, Senn M, Nuessch K, Bettner C, Pfeiffer A, Hess OM, Krayenbuehl HP. Thallium-201 scintigraphy in complete left bundle branch block. *Am J Cardiol* 1984; **53:** 764–769.
[42] Ono S, Nohara R, Kambara H, Okuda K, Kawai C. Regional myocardial perfusion and glucose metabolism in experimental left bundle branch block. *Circulation* 1995; **85:** 1125–1131.
[43] Olsson RA, Bunger R. Metabolic control of coronary flow. *Prog Cardiovasc Dis* 1987; **29:** 369–387.
[44] O'Keefe J, Bateman TM, Barnhart CS. Adenosine thallium-201 is superior to exercise thallium-201 for detecting coronary artery disease in patients with left bundle branch block. *J Am Coll Cardiol* 1993; **21:** 1332–1338.
[45] Mairesse GH, Marwick TH, Arnese M *et al*. Improved identification of coronary artery disease in patients with left bundle branch block by use of dobutamine stress echocardiography and comparison with myocardial perfusion tomography. *Am J Cardiol* 1995; **76:** 321–325.
[46] Geleijnse ML, Vigna C, Kasprzak JD *et al*. Usefulness and limitations of dobutamine-atropine stress echocardiography for the diagnosis of coronary artery disease in patients with left bundle branch block. A multicenter study. *Eur Heart J* 2000; (in press).
[47] Schulman DS, Francis CK, Black HR, Wackers FJT. Thallium-201 stress imaging in hypertensive patients. *Hypertension* 1987; **10:** 16–21.
[48] DePuey EG, Guertler-Krawczynska E, Perkins JV, Robbins WL, Whelchel JD, Clements SD. Alterations in myocardial thallium-201 distribution in patients with chronic systemic hypertension undergoing 201 single-photon emission computed tomography. *Am J Cardiol* 1988; **62:** 234–238.
[49] Houghton JL, Frank MJ, Car AA, Von Dohlen TW, Prisant LM. Relations among impaired coronary flow reserve, left ventricular hypertrophy and thallium perfusion defects in hypertensive patients without obstructive coronary artery disease. *J Am Coll Cardiol* 1990; **15:** 43–51.
[50] Tomanek RJ. Response of the coronary vasculature to myocardial hypertrophy. *J Am Coll Cardiol* 1990; **15:** 528–533.
[51] Picano E, Lucarini AR, Lattanzi F, Distante A, Legge VD, Salvetti A, L'Abbate A. Dipyridamole echocardiography in essential hypertension patients with chest pain. *Hypertension* 1988; **12:** 238–243.
[52] Marwick TH, Torelli J, Harjai K, Haluska B, Pashkow F, Stewart WJ, Thomas JD. Influence of left ventricular hypertrophy on detection of coronary artery disease using exercise echocardiography. *J Am Coll Cardiol* 1995; **26:** 1180–1186.
[53] Fragasso G, Lu C, Dabrowski P, Pagnotta P, Sheiban I, Chierchia SL. Comparison of stress/rest myocardial perfusion tomography, dipyridamole and dobutamine stress echocardiography for the detection of coronary disease in hypertensive patients with chest pain and positive exercise test. *J Am Coll Cardiol* 1999; **34:** 441–447.
[54] Elhendy A, Van Domburg RT, Roelandt JRTC, Geleijnse ML, Mohsen Ibrahim M, Fioretti PM. Safety and feasibility of dobutamine-atropine stress testing in hypertensive patients. *Hypertension* 1997; **29:** 1232–1239.
[55] Senior R, Basu S, Handler C, Raftery EB, Lahiri A. Diagnostic accuracy of dobutamine stress echocardiography for detection of coronary heart disease in hypertensive patients. *Eur Heart J* 1996; **17:** 289–295.
[56] Elhendy A, Geleijnse ML, Van Domburg RT *et al*. Comparison of dobutamine stress echocardiography and technetium-99m sestamibi single-photon emission tomography for the diagnosis of coronary artery disease in hypertensive patients with and without left ventricular hypertrophy. *Eur J Nucl Med* 1998; **25:** 69–78.
[57] Ho YL, Wu CC, Lin LC *et al*. Assessment of the coronary artery disease and systolic dysfunction in hypertensive patients with dobutamine-atropine stress echocardiography: effect of the left ventricular hypertrophy. *Cardiology* 1998; **89:** 52–58.
[58] Chaitman BR, Bourassa MG, Davis K *et al*. Angiographic prevalence of high risk coronary artery disease in patients subsets (CASS). *Circulation* 1981; **64:** 360–367.
[59] Gordon DePuey G, Garcia EV. Optimal specificity of thallium-201 SPECT through recognition of imaging artifacts. *J Nucl Med* 1989; **30:** 441–449.
[60] Hansen CL, Crabbe D, Rubin S. Lower diagnostic accuracy of thallium-201 SPECT myocardial perfusion imaging in women: an effect of smaller chamber size. *J Am Coll Cardiol* 1996; **28:** 1214–1219.
[61] Masini M, Picano E, Lattanzi F, Distante A, L'Abbate A. High dose dipyridamole-echocardiography test in women: correlation with exercise-echocardiography test and coronary arteriography. *J Am Coll Cardiol* 1988; **12:** 682–685.
[62] Marwick TH, Anderson T, Williams MJ *et al*. Exercise echocardiography is an accurate and cost-efficient technique for detection of coronary artery disease in women. *J Am Coll Cardiol* 1995; **26:** 335–341.
[63] Elhendy A, Geleijnse ML, Van Domburg RT *et al*. Gender differences in the accuracy of dobutamine stress echocardiography for the diagnosis of coronary artery disease. *Am J Cardio.* 1997; **80:** 1414–1418.
[64] Takeuchi M, Sonoda S, Miura Y, Kuroiwa A. Comparative diagnostic value of dobutamine stress echocardiography and stress thallium-201 single-photon emission computed

tomography for detecting coronary artery disease in women. *Coron Art Dis* 1996; **7:** 831–835.
[65] Elhendy A, Van Domburg RT, Bax JJ, Nierop PR, Geleignse ML, Ibrahim MM, Roelandt JRTC. Noninvasive diagnosis of coronary artery stenosis in women with limited exercise capacity. Comparison of dobutamine stress echocardiography and ^{99m}Tc sestamibi single-photon emission CT. *Chest* 1998; **114:** 1097–1104.
[66] Ho YL, Wu CC, Huang PJ *et al*. Assessment of coronary artery disease in women by dobutamine stress echocardiography: comparison with stress thallium-201 single-photon emission computed tomography and exercise electrocardiography. *Am Heart J* 1998; **135:** 655–662.
[67] Marwick TH. Current status of stress echocardiography for diagnosis and prognostic assessment of coronary artery disease. *Coron Art Dis* 1998; **9:** 411–426.
[68] Marwick TH, D'Hondt AM, Mairesse GH, Baudhuin T, Wijns W, Detry JM, Melin JA. Comparative ability of dobutamine and exercise stress in inducing myocardial ischemia in active patients. *Br Heart J* 1994; **72:** 31–38.
[69] Hutchinson SJ, Shen A, Soldo S, Hla A, Kawanishi DT, Chandraratna AN. Transesophageal assessment of coronary flow velocity reserve during 'regular' and 'high'-dose dipyridamole stress testing. *Am J Cardiol* 1996; **77:** 1164–1168.
[70] McNeill AJ, Fioretti PM, El-Said EM, Salustri A, Forster R, Roelandt JRTC. Enhanced sensitivity for detection of coronary artery disease by addition of atropine to dobutamine stress echocardiography. *Am J Cardiol* 1992; **70:** 41–46.
[71] Spencer KY, Bednarz J, Rafter PG, Korcarz C, Lang RM. Use of harmonic imaging without echocardiographic contrast to improve two-dimensional image quality. *Am J Cardiol* 1998; **82:** 794–799.
[72] Porter TR, Xie F, Kricsfeld A, Chiou A, Dabestani A. Improved endocardial border resolution during dobutamine stress echocardiography with intravenous sonicated dextrose albumin. *J Am Coll Cardiol* 1994; **23:** 1440–1443.
[73] Koch R, Lang RM, Garcia MJ *et al*. Objective evaluation of regional left ventricular wall motion during dobutamine stress echocardiographic studies using segmental analysis of color kinesis images. *J Am Coll Cardiol* 1999; **34:** 409–419.
[74] Sutherland GR, Stewart MJ, Groundstroem KWE *et al*. Color Doppler myocardial imaging: A new technique for the assessment of myocardial function. *J Am Soc Echocardiogr* 1994; **7:** 441–458.