Dobutamine Stress Myocardial Function versus Nuclear Perfusion Imaging

Dobutamine Stress Myocard Functie versus Nucleaire Perfusie Afbeelding

ISBN 90 73235 96 0

Optima Grafische Communicatie
P.O. Box 84118
3009 CC Rotterdam
The Netherlands

Dobutamine Stress Myocardial Function versus Nuclear Perfusion Imaging

Dobutamine Stress Myocard Functie versus Nucleaire Perfusie Afbeelding

Proefschrift

Ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam op gezag van de
Rector Magnificus Prof.dr. P.W.C. Akkermans M.A.
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
23 juni 1999 om 11.45 uur

door

Marcel Leonard Geleijnse

geboren te Delft

Promotiecommissie

Promotor	:	Prof.dr. J.R.T.C. Roelandt
Co-promotor	:	Dr. P.M. Fioretti
Overige leden	:	Prof.dr. M.L. Simoons
		Prof.dr. C.A. Visser
		Prof.dr. A. Distante

Financial support by the Netherlands Heart Foundation for the publication of this thesis is gratefully acknowledged.

Ter nagedachtenis aan oom Bart

CONTENTS

INTRODUCTION

Confirming or excluding coronary artery disease in patients with chest pain remains a challenge because this disease is still the leading cause of death in the Western world (1). Traditionally, exercise electrocardiography is performed as a first-line noninvasive diagnostic stress test (2). However, a substantial number of patients referred for evaluation of chest pain are unable to perform adequate exercise testing, mainly because of deconditioning or neurologic, respiratory, peripheral vascular, or orthopedic limitations (3). In these patients, dobutamine stress represents an alternative, exercise independent stress technique. Usually, this form of stress is combined with two-dimensional echocardiography, providing functional data on myocardial wall thickening (4), or nuclear perfusion imaging, providing data on myocardial perfusion (5). Despite the increasing number of dobutamine tests performed each year, little is known about the relative diagnostic and prognostic value of the two imaging modalities. In this thesis, a comparison between dobutamine stress echocardiography and technetium-99m single-photon emission computed tomographic imaging is presented.

Part A of the thesis deals with the methodology of dobutamine stress testing and the respective benefits of dobutamine stress echocardiography and technetium-99m perfusion imaging (chapters 1 to 3). In part B the diagnostic merits of the two stress modalities in patients with suspected coronary artery disease (chapter 4), prior myocardial infarction (chapter 5), left ventricular hypertrophy (chapter 6), and left bundle branch block (chapters 7 and 8) are discussed. Part C of the thesis discusses the prognostic merits of the stress modalities in patients with stable (chapters 9 to 11) and suspected unstable chest pain syndromes (chapter 12).

Most of the studies presented in this thesis would not have been possible without support by the Dutch Heart Foundation (Grant NHS 94.135)

References

1. National Heart, Lung, and Blood Institute: Morbidity from Coronary Heart Disease in the United States. National Heart, Lung, and Blood Institute Data Fact Sheet. Bethesda. MD. 1990.
2. Chaitman BR. The changing role of the exercise electrocardiogram as a diagnostic and prognostic test for chronic ischemic heart disease. *J Am Coll Cardiol* 1986; 8: 1195-1210.
3. Marwick T. Current status of non-invasive techniques for the diagnosis of myocardial ischemia. *Acta Clin Belg* 1992; 47: 1-5.
4. Berthe C, Piérard LA, Hiernaux M, Trotteur G, Lempereur P, Carlier J, Kulbertus HE. Predicting the extent and location of coronary artery disease in acute myocardial infarction by echocardiography during dobutamine infusion. *Am J Cardiol* 1986; 58: 1167-1172.
5. Mason JR, Palac RT, Freeman ML, Virupannavar S, Loeb HS, Kaplan E, Gunnar RM. Thallium scintigraphy during dobutamine infusion: nonexercise-dependent screening test for coronary disease. *Am Heart J* 1984; 107: 481-485

Part A – Test methodology

Chapter 1

Methodology, feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography

Geleijnse ML, Fioretti PM, Roelandt JRTC

J Am Coll Cardiol 1997; 30: 595-606

Methodology, Feasibility, Safety and Diagnostic Accuracy of Dobutamine Stress Echocardiography

MARCEL L. GELEIJNSE, MD, PAOLO M. FIORETTI, MD, PHD, FACC,
JOS R. T. C. ROELANDT, MD, PHD, FACC

Rotterdam, The Netherlands

Large numbers of patients referred for evaluation of chest pain are unable to perform adequate, diagnostic exercise testing. In these patients, dobutamine stress echocardiography (DSE) represents an alternative, exercise-independent stress modality. Apart from the ~5% of patients with an inadequate acoustic window, 10% of patients referred for this test have nondiagnostic (submaximal negative) test results. Serious side effects during or shortly after DSE are uncommon, with ventricular fibrillation or myocardial infarction occurring in ~1 of 2,000 studies. No deaths have been reported. On the basis of a total number of 2,246 patients, reported in 28 studies, the sensitivity, specificity and accuracy of the test for the detection of coronary artery disease (CAD) were 80%, 84% and 81%, respectively. Mean sensitivities for one-, two- and three-vessel disease were 74%, 86% and 92%, respectively. The sensitivity for detection of disease in the left circumflex coronary artery (55%) was lower, both compared with that for left anterior descending (72%) and right coronary artery disease (76%). The sensitivity of predicting multivessel disease by multiregion echocardiographic abnormalities varied widely, from 8% to 71%. In direct comparisons, DSE was superior to exercise electrocardiography and dipyridamole echocardiography and comparable to exercise echocardiography and radionuclide imaging. DSE is a useful, feasible and safe exercise-independent stress modality for assessing the presence, localization and extent of CAD.

(J Am Coll Cardiol 1997;30:595–606)

Confirming or excluding coronary artery disease (CAD) in patients with chest pain remains a challenge because this disease is still the leading cause of death in the Western world (1). Traditionally, exercise electrocardiography is performed as a first-line noninvasive diagnostic stress test (2). However, large numbers of patients referred for evaluation of chest pain are unable to perform adequate diagnostic exercise testing, mainly because of deconditioning or neurologic, respiratory, peripheral vascular or orthopedic limitations (3). In these patients, dobutamine stress echocardiography (DSE) represents an alternative, exercise-independent stress modality. Since its clinical introduction a decade ago (4), DSE has become an established method for the diagnosis of CAD (5–32). This review article deals with (1) methodologic aspects, and (2) clinical applications of DSE to assess the presence, localization and extent of CAD.

Methods and Statistical Analysis

We reviewed all DSE studies published in the major English language journals up to August 1996 that met defined criteria with respect to diagnostic accuracy for the detection of CAD. These criteria were 1) inclusion of patients both with and without angiographically defined CAD; and 2) statement of how many patients with and without CAD had negative and positive DSE results. Reports indicating that the patients included were subsets of larger published studies were excluded. Also excluded from the primary diagnostic analysis were studies solely involving patients with a myocardial infarction (MI) because the diagnosis of CAD is already established in these patients. When DSE was compared with other stress modalities, only those studies making direct comparisons in the same patients were included.

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. *Accuracy* was defined by the total number of true positive and true negative tests divided by the total number of patients. *Normalcy rate*, a referral bias independent estimate of specificity (33), was defined as the proportion of patients with a low pretest likelihood of CAD (<10%) who had negative test results. Mean values for sensitivity, specificity and accuracy were calculated by combining the results of individual patient data from multiple studies. Comparisons of sensitivity, specificity and accuracy were performed using the standardized normal distribution test. Statistical significance was defined at $p < 0.05$.

From the Thoraxcentre, University Hospital Rotterdam-Dijkzigt and Erasmus University, Rotterdam, The Netherlands. This work was supported in part by Grant NHS 94.135 from the Dutch Heart Foundation, The Hague, The Netherlands.

Manuscript received September 7, 1996; revised manuscript received April 26, 1997, accepted May 16, 1997.

Address for correspondence: Dr. Marcel L. Geleijnse, Thoraxcentre, Ba 302, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

Abbreviations and Acronyms

CAD = coronary artery disease
CI = confidence interval
DSE = dobutamine stress echocardiography (echocardiographic)
ECG = electrocardiogram, electrocardiographic
LBBB = left bundle branch block
LVH = left ventricular hypertrophy
MI = myocardial infarction
Tc = technetium

Test Methodology

Dobutamine: pharmacology and mechanism of action. Dobutamine is a synthetic catecholamine with a relatively short plasma half-life of ~2 min due to rapid metabolization in the liver to inactive metabolites (34,35). It has strong $beta_1$-receptor and mild $alpha_1$- and $beta_2$-receptor agonist activity. When used at low dose (up to 10 μg/kg body weight per min), marked inotropic effects (mediated by both $alpha_1$- and $beta_1$-receptor stimulation) are encountered. These effects are extensively used for treatment of heart failure. When used at high dose (20 to 40 μg/kg per min), heart rate is progressively increased (mediated by $beta_1$-receptor stimulation). Systemic blood pressure increases only minimally because of an increase in cardiac output and a decrease in systemic vascular resistance because of peripheral vasoconstrictive effects (mediated by $alpha_1$-receptor stimulation) overwhelmed by vasodilative effects (mediated by $beta_2$-receptor stimulation). In patients without a sufficient increase in heart rate, the addition of atropine has been proposed to further increase heart rate by its vagolytic effects (14). As a result of the hemodynamic changes there is an increase in oxygen demand. However, in myocardial regions supplied by a coronary artery with a critical stenosis, the increase in oxygen demand cannot be met by an adequate increase in blood flow (36). Hence, regional ischemia develops and causes regional wall motion abnormalities that can be detected by two-dimensional echocardiography (5–32).

Protocol. Protocols for DSE vary from institution to institution, particularly with regard to dobutamine dose (range 20 to 40 μg/kg per min), atropine addition (range 0 to 2 mg) and stage duration (range 2 to 8 min) (5–32,37). Usually, centers that use lower peak doses of dobutamine use longer stage durations and stop beta-adrenergic blocking agent treatment more often before the test. To date, the most widely used protocol uses dobutamine up to 40 μg/kg per min, with the addition of atropine up to 1 mg (14).

According to this protocol, a rest electrocardiogram (ECG) and two-dimensional echocardiogram are acquired, intravenous access is secured, and dobutamine is then administered intravenously by an infusion pump, starting at 5 or 10 μg/kg per min for 3 min, increasing by 10 μg/kg per min every 3 min up to a maximum of 40 μg/kg per min. In patients not achieving 85% of their theoretic maximal heart rate (220 beats/min minus age for men, beats/min 200 minus age for women) and without symptoms or signs of myocardial ischemia, atropine is administered on top of the maximal dose of dobutamine, starting with 0.25 mg intravenously and repeated up to a maximum of 1.0 mg within 4 min, with continuation of dobutamine infusion. Throughout dobutamine infusion, the ECG (three leads) is continuously monitored and recorded (12 leads) at 1-min intervals. Blood pressure is measured and recorded by sphygmanometry or automatic device every 3 min. The echocardiogram is continuously monitored and recorded on video or quad screen during the final minute of each dobutamine (or atropine) stage and recovery. Reasons for interruption of the test are severe or extensive new wall motion abnormalities; horizontal or downsloping ST segment depression >0.2 mV at an interval of 80 ms after the J point compared with baseline; ST segment elevation >0.1 mV in patients without a previous MI; severe angina; a symptomatic reduction in systolic blood pressure ≥40 mm Hg from baseline; hypertension (blood pressure ≥240/120 mm Hg); significant tachyarrhythmias; and any serious side effect regarded as due to dobutamine. A beta-blocker that can be injected intravenously must be available to reverse the effects of dobutamine if they do not revert spontaneously and quickly. Contraindications to DSE include critical aortic stenosis, hypertrophic cardiomyopathy, uncontrolled hypertension, uncontrolled atrial fibrillation, known severe ventricular arrhythmias and electrolyte abnormalities (mainly hypokalemia) (38,39). The addition of atropine is contraindicated in patients with narrow-angle glaucoma, myasthenia gravis, obstructive uropathy or obstructive gastrointestinal disorders.

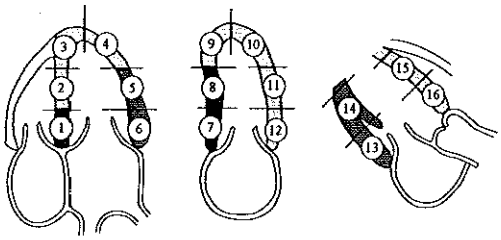


Figure 1. Diagrams showing the 16 regional wall segments and distribution of coronary perfusion. **Left,** Apical four-chamber view; **middle,** apical two-chamber view; **right,** long-axis view. **Dotted areas** = left anterior descending coronary artery; **crosshatched areas** = left circumflex coronary artery; **solid areas** = right coronary artery.

Echocardiographic interpretation. For purposes of analysis, the left ventricle is usually divided into the 16-segment model recommended by the American Society of Echocardiography (Fig. 1) (40). Although the quad screen format (with rest, low and high dose and recovery images next to each other in one screen) facilitates wall motion analysis, it is not a prerequisite because videotape analysis seems to be as reliable (41). *Wall motion or thickening* is reported according to an arbitrary numerical classification: 1 = *normal*, characterized by

a uniform increase in wall excursion and thickening; 2 = *hypokinesia*, denoted by reduced (<5 mm) inward systolic wall motion; 3 = *akinesia*, is marked by an absence of inward motion and thickening; 4 = *dyskinesia*, indicated by systolic thinning and outward systolic wall motion. Hypokinetic segments can be further classified as *mild* (2A) or *severe* (2B) hypokinetic segments to refine the analysis. A *normal stress echocardiogram* is defined by a uniform increase in wall motion and systolic wall thickening, with a reduction in end-systolic cavity area. A *positive test* is denoted by development of new wall motion dyssynergy or by worsening of regional dyssynergy in one or more segments. In patients with rest wall motion abnormalities, use of the "biphasic" response (i.e., initial improvement of dyssynergy at low dose followed by worsening of dyssynergy at high dose) has improved detection of CAD (42). More subtle criteria for positive test are tardokinesia (delayed excursions) and relative failure to augment wall thickening. These more subtle criteria should be used with caution by unexperienced interpreters because too strict application could lead to substantial loss in specificity (43). Moreover, isolated mild wall motion deterioration in mid- or basal inferoposterior segments needs to be interpreted with caution because these segments are known to be less specific for CAD (43,44). Several investigators have reported (8,12,13,25) that the inclusion of rest wall motion abnormalities in addition to new or worsening wall motion abnormalities as a criteria for positive test results in a gain in sensitivity without a loss in specificity for the detection of CAD. However, the inclusion of rest wall motion abnormalities as a criterion for CAD is appropriate only in patients without a previous MI because in patients with a previous MI, this diagnosis is nearly certain and does not require further testing for this purpose.

Other possible dobutamine-induced markers of ischemia. *Abnormal left ventricular diastolic filling.* Changes in diastolic indexes are known to precede systolic changes and therefore may be a more sensitive indicator of myocardial ischemia (45). Despite the finding (46) that left ventricular filling is predominantly mediated by a complex interaction of active myocardial relaxation, passive filling properties and left atrial pressure, one study clearly demonstrated (47) that during dobutamine stress testing, an abnormal response of Doppler indexes of left ventricular early filling (E velocity) is a more sensitive marker for the detection of significant single-vessel disease than are wall motion abnormalities. Other, confirmative publications are needed to firmly establish the clinical utility of left ventricular filling indexes.

Sinus node deceleration. Dobutamine stress-induced sinus node deceleration, defined as an initial increase and subsequent decrease in heart rate with progressive dobutamine infusion, occurs more often during dobutamine infusion than during exercise (48). In a small group of patients, it was reported (49) to be a specific marker of inferior wall ischemia, as assessed by dobutamine perfusion scintigraphy. Currently, there are no stress echocardiographic data reporting the pathophysiology of isolated sinus node deceleration. Cardiac slowing, in particular in combination with hypotension (see later), may also result from a neurally mediated cardiovascular vasodepressor reflex (50).

Mitral regurgitation. Low dose dobutamine is known to have a beneficial effect on chronic mitral regurgitation, especially in patients with left ventricular dysfunction (51,52). Although the mechanism of this beneficial effect remains unclear, it may be related to a decrease in afterload or mitral orifice size that results from the vasodilatory and inotropic effects of dobutamine (53). It has been suggested (12) that the development of new or worsening mitral regurgitation with stress doses of dobutamine is related to ischemia and improves the sensitivity of DSE for the detection of CAD. However, a study specifically addressed to this subject reported (51) that in fact very few patients developed new or worsening mitral regurgitation during high dose dobutamine infusion, and there was no association with stress-induced wall motion abnormalities.

Hypotension. Generally, dobutamine stress causes an increase in cardiac output and a small reduction in systemic vascular resistance (53,54), with a small increase in systolic blood pressure as a net result (5–32). Although the pathophysiology of dobutamine stress-induced hypotension has not been completely defined, theoretically, it may result from 1) an inadequate increase in cardiac output to compensate for an expected decrease in systemic vascular resistance; and 2) a disproportionate decrease in systemic vascular resistance in the presence of a normal increase in cardiac output. An inadequate increase in cardiac output may be due to inadequate contractile reserve, severe ischemic left ventricular dysfunction or left-sided obstructive heart disease. Dynamic left ventricular cavity obliteration due to strong inotropic stimulation was proposed as an important cause for reduced cardiac output and hypotension (55), especially in patients with dehydration. Later studies could not confirm this mechanism (56), and the proposed bolus of saline before dobutamine (55,57) did not prevent cavity obliteration in a canine model (58). The second mechanism, a disproportionate decrease in systemic vascular resistance, may be due to excessive sensitivity of the peripheral circulation to $beta_2$-receptor stimulation, increased $beta_2$-receptor density (deconditioned patients) or a neurally mediated mechanism in which vigorous myocardial contraction stimulates the intramyocardial mechanoreceptors, resulting in sympathetic withdrawal and enhanced parasympathetic activity (the Bezold-Jarisch reflex) (59). In contrast to exercise stress-induced hypotension (60), all presently available data indicate that there is no relation between ischemic left ventricular systolic dysfunction (54,56,61,62) or angiographically detected CAD (61) and dobutamine stress-induced hypotension.

ECG changes. Whereas ST segment changes are the hallmark of ischemia in exercise tests (2), they seem to have less value during dobutamine stress. In an early study in patients with mainly unstable angina and severe coronary lesions, dobutamine stress-induced ST segment depression was described as a highly accurate diagnostic test (63). However, subsequent reports in stable patients with less severe lesions could never confirm these data (7,12,29,64). Whether this is due to misplacement of electrodes (because of the apical

acoustic window), less stress (lower rate–pressure product than for exercise tests) or other factors still needs to be established. In contrast, as in exercise testing (65), dobutamine stress-induced ST segment elevation in patients without a previous MI was consistently reported to be associated with (severe) coronary artery disease (63,64,66,67).

Feasibility and safety. In ~5% of patients, an inadequate acoustic window precludes the performance of successful DSE (37,68), although this proportion may underestimate the actual number of patients with an inadequate acoustic window in an unselected population. Furthermore, 10% of tests are nondiagnostic (absence of ischemic markers in submaximal tests) (68,69) because of an insufficient hemodynamic response to dobutamine–atropine administration or limiting side effects. Noncardiac side effects (nausea, headache, chills, urgency and anxiety) are usually well tolerated, without the need for test termination. The most common cardiovascular side effects are angina, hypotension and cardiac arrhythmias. Although angina occurs in ~20% of patients (68,70), severe angina as a test end point without accompanying new or worsening wall motion abnormalities is rare. Dobutamine stress-induced hypotension occurs, depending on its definition, in 5% to 37% of patients (54,56,61,62,68,71): A ≥20-mm Hg decrease in systolic blood pressure occurs in ~20% (54,61,71); severe, symptomatic hypotension necessitating test termination occurs only rarely (71). Arrhythmias are not uncommon (68,70), with frequent premature atrial or ventricular contractions occurring in ~10% of patients and supraventricular or ventricular tachycardias each occurring in ~4% of patients. Ventricular tachycardias are usually nonsustained and have been attributed to $beta_1$-receptor stimulation and dobutamine-induced reduction in plasma potassium concentrations (39). These arrhythmias are more frequently encountered in patients with a history of previous ventricular arrhythmias or baseline wall motion abnormalities (68). No study has reported an association between the addition of atropine or new wall motion abnormalities and ventricular tachycardias (68,70). On the basis of combined diagnostic and safety reports on DSE (5–32,68–70), it can be roughly estimated that ventricular fibrillation or MI occurs in 1 of 2,000 studies. These severe complications can occur up to 20 min after dobutamine withdrawal (69), and it has been suggested (69) that in these patients, $alpha_1$-mediated coronary and systemic vasoconstriction might be paradoxically exacerbated, not reversed, by beta-blocker administration. Atropine intoxication, although generally requiring a dose of atropine of at least 5 mg (72), has been reported in a few patients receiving ≤1 mg of atropine (69). Fatal events were not reported (5–32,68–70).

Intraobserver and interobserver agreement. Intraobserver and interobserver agreement for ischemia within institutes as reported in individual studies (6,7,20,23,25,31) ranged from 95% to 98% and from 92% to 96%, respectively. However, a study specifically addressing interinstitutional agreement in DSE between five centers (73) reported that abnormal or normal results of DSE were agreed on by four or five of the five centers in only 73% of patients. Agreement on the left anterior descending territory (78%) was similar to that for the combined right coronary and left circumflex territories (74%). For specific segments, agreement ranged from 84% to 97% and was highest for the basal anterior segment and lowest for the basal inferior segment. Agreement was clearly higher in patients without CAD or with extensive CAD and was lower in patients with limited echocardiographic image quality.

Diagnostic Accuracy

Detection of CAD. As with other tests for detection of CAD, the diagnostic accuracy of DSE is expressed by its sensitivity, specificity and accuracy. These indexes depend on several technical factors, such as the definition of a positive test and the threshold for defining significant CAD. In addition, several characteristics of the patients studied may affect these indexes, such as the presence or absence of MI, the number of male patients, referral bias, the level of stress and the severity (percent stenosis) and extent (number of diseased vessels) of CAD in the referred cohort.

The reported sensitivity, specificity and accuracy for each of 28 published studies (5–32) are shown in Table 1. The overall (weighted mean) sensitivity, specificity and accuracy of DSE for a total of 2,246 patients was 80% (95% confidence interval [CI] 78% to 82%), 84% (95% CI 82% to 86%) and 81% (95% CI 79% to 83%), respectively (Fig. 2). When only the 17 largest series from single centers were included (7,9–12,14,16,18–21,26–28,30–32) (thus avoiding potential double counting of previously included patients from the same center in an earlier report), these respective numbers were, for a total of 1,454 patients, 81% (95% CI 79% to 84%), 85% (95% CI 82% to 87%) and 82% (95% CI 80% to 85%). The normalcy rate was reported to be 92% (74).

From the results of the individual studies in Table 1 it cannot be concluded that the addition of atropine improves the diagnostic accuracy of DSE. However, in those studies in which atropine was used, relatively many patients were taking a beta-blocker and had mild CAD. Indeed, all studies directly comparing DSE with versus without atropine (14,32) showed an increase in sensitivity without a loss in specificity. These results were recently confirmed by a study from the Mayo Clinic (75) showing that the addition of atropine significantly increased sensitivity, especially in patients taking a beta-blocker and with milder forms of CAD.

The effect of the number of diseased coronary arteries was assessed in 15 studies (5–8,12,16,20–23,25,26,28,31,32), for a total of 897 patients. Mean sensitivity increased significantly from 74% for single-vessel disease to 86% for double-vessel disease and to 92% for triple-vessel disease (Fig. 3).

Different reports from center to center are most likely due to the aforementioned factors. One of the most important avoidable factors influencing test sensitivity is the use of beta-blockers. These medications lower peak cardiac work load and inotropic response during DSE (5,76) and thus have the potential to lower the sensitivity of the test, especially when atropine is not added to dobutamine (77). Investigators who

Table 1. Diagnostic Accuracy of Dobutamine Stress Echocardiography As Reported in 28 Studies

Year and First Author (ref no.)	Protocol		No. of Pts	Men (%)	MI (%)	No CAD (%)	MVD (%)	Beta-Blocker	Cor Angio		WMA	Sens (%)	Spec (%)	Accuracy (%)
	Dobutamine (μg/kg per min)	Stage Duration (min)							% Diam Stenosis	Anal				
1991														
Sawada (5)	30	3	55	62	0	36	26	+	≥ 50	Q	New	89	85	87
Previtali (6)	40	5	35	86	3	20	34	−	≥ 70	V	New	68	100	74
Cohen (7)	40	3	70	100	27	27	50	−	≥ 70	V	New	86	95	89
1992														
Salustri (8)	40*	3	52	73	27	29	33	+	≥ 50	Q	New	54	80	62
Martin (9)	40	3	40	95	35	38	NA	+	≥ 50	V	New	76	60	70
Segar (10)	30	3	85	61	NA	26	NA	NA	≥ 50	Q	New	95	82	92
Marcovitz (11)	30	3	141	60	29	23	33	+	≥ 50	Q	Any	96	66	89
Mazeika (12)	20	8	50	88	26	28	48	−	≥ 70	V	New	64	93	72
Salustri (13)	40	3	46	70	33	39	39	+	≥ 50	Q	New	57	78	65
McNeill (14)	40*	3	80	74	35	41	NA	+	≥ 50	V	New	70	88	78
1993														
Marwick (15)	40	3	97	71	0	39	29	−	≥ 50	Q	Any	85	82	84
Günalp (16)	30	5	27	85	0	33	33	−	≥ 50	V	New	83	89	85
Forster (17)	40*	3	21	55	0	43	38	+	≥ 50	V	New	75	89	81
Marwick (18)	40	3	217	72	0	35	34	+	≥ 50	Q	Any	72	83	76
Hoffmann (19)	40*	2	60	77	0	20	35	−	≥ 70	Q	New	79	83	80
Previtali (20)	40	5	80	78	19	29	41	−	≥ 50	V	New	79	83	80
Takeuchi (21)	30	5	120	74	52	38	31	+	≥ 50	Q	Any	85	93	88
Baudhuin (22)	40	3	136	61	0	30	29	−	≥ 50	Q	Any	79	83	80
Cohen (23)	40	3	52	98	25	29	40	−	≥ 70	V	New	86	87	87
1994														
Marwick (24)	40	3	86	70	0	35	40	+	≥ 50	Q	Any	54	83	64
Beleslin (25)	40	3	136	85	57	13	8	+	≥ 50	Q	New	82	76	82
Senior (26)	40	3	61	72	21	28	49	−	≥ 50	V	Any	93	94	93
Sochowski (27)	40	3	46	67	0	46	28	+	≥ 50	V	New	68	81	74
Ostojic (28)	40	3	150	83	51	13	11	+	≥ 50	Q	New	75	79	75
1995														
Daoud (29)	30	3	76	58	37	15	55	+	≥ 50	V	Any	92	73	89
Dagianti (30)	40	5	60	79	0	58	25	−	≥ 70	Q	New	72	97	87
Ho (31)	40	3	54	85	41	21	67	NA	≥ 50	V	New	93	73	89
1996														
Pingitore (32)	40*	3	110	83	27	16	46	+	≥ 50	Q	New	84	89	85

*Atropine addition. Anal = analysis; CAD = coronary artery disease; Cor Angio = coronary angiography; Diam = diameter; MI = myocardial infarction; MVD = multivessel disease; NA = not available; Pts = patients; Q = (semi)quantitative; ref = reference; Sens = sensitivity; Spec = specificity; V = visual; WMA = wall motion abnormality.

compared study patients with versus without beta-blocker therapy (13,18,25) consistently found that sensitivity was lower in patients with beta-blocker therapy despite the finding that patients taking beta-blockers generally have a higher prevalence of (extensive) CAD (13).

Bayesian analysis. Although values for sensitivity and specificity have a useful role, the use of DSE in diagnostic practice is to assist in the clinical recognition of CAD. In this sense, tests are used to reclassify the initial clinical impression of the probability of CAD into high, low and intermediate risk subgroups. According to the Bayes theorem, the likelihood of a positive test result is determined by the probability of CAD in the patient studied, as well as the accuracy of the test (78). In one report (79) that included 223 patients without a previous MI, the study cohort was grouped into those with a high (>80%), intermediate (10% to 80%) and low probability (<10%) of CAD before and after DSE, and the ability of DSE to restratify patients was analyzed. According to the pretest likelihood of CAD, 68 patients (30%) were regarded as having a "diagnostic" low or high probability of CAD. By application of the Bayes theorem, DSE defined 121 patients (54%) as being in the high or low posttest probability groups. Importantly, the accuracy of predicting CAD in the high probability group and the absence of CAD in the low probability group after DSE was excellent (87%).

Detection of disease in individual coronary arteries. The coronary arteries and their branches supply different regions of the left ventricular myocardium. Based on the known anatomic relations between coronary arteries and various myocardial regions, general guidelines have been developed for the assign-

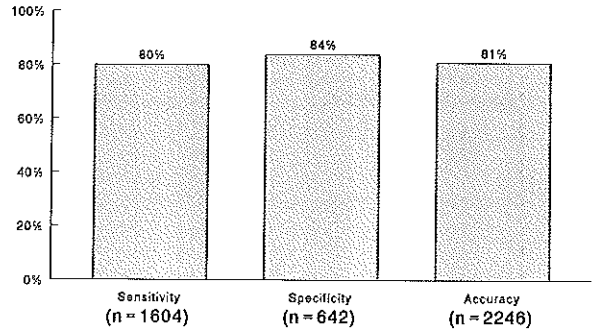


Figure 2. Sensitivity, specificity and accuracy of DSE for detection of CAD.

ment of these myocardial regions to specific coronary arteries (Fig. 1). It is therefore possible to infer disease of a given coronary artery by noting the location of a wall motion abnormality on echocardiography. Figure 4 summarizes the sensitivity and specificity for the identification of disease in the left anterior descending, left circumflex and right coronary arteries. The mean reported (12,21,26,31) sensitivities were 72%, 55% and 76%, respectively, and the mean specificities were 88%, 93% and 89%, respectively. The sensitivity for detection of left circumflex disease was lower than that for left anterior descending ($p < 0.02$) and right coronary disease ($p < 0.005$). The lower sensitivity for detection of disease in the left circumflex artery can be explained by the variation in coronary anatomy (with a small circumflex territory in some patients) and problems with resolution of the lateral wall endocardium because of the parallel orientation of the wall and the ultrasound beam. To compensate for the variation in blood supply of the posterior wall (by either the left circumflex or right coronary artery, depending on their relative size) others (6,11,12) divided the blood supply of the heart into two systems: an anterior (left anterior descending coronary artery) system and a posterior (left circumflex and right coronary arteries) system. For these circulations, the mean reported sensitivities were 75% and 73%, respectively, and the mean specificities were 86% and 80%, respectively.

Identification of extensive CAD. An important goal of noninvasive stress testing is the identification of patients with left main or three-vessel CAD. Such patients could benefit from revascularization from a prognostic point of view (80). Patients with multivessel disease can be differentiated from patients with single-vessel disease by detection of echocardiographic abnormalities in two or more coronary territories. Investigators who examined the prediction of multivessel disease by this method (5,7,12,15,18,26) consistently reported a high specificity (range 90% to 100%). However, the sensitivity of DSE for the prediction of multivessel disease varied markedly from 8% to 71%. Several factors contribute to the underestimation of multivessel disease: inadequate stress protocols, the premature cessation of stress because of the development of limiting ischemia in one region, imperfect assignment of myocardial regions to coronary arteries, collateral circulations and anatomically significant but functionally nonsignificant lesions. Recent reports have shown that DSE provides other, unique features to identify multivessel disease, by measuring the ischemic threshold (10,81) and left ventricular volume changes (82). Eventually, an algorithm based on patient clinical characteristics, combined with the aforementioned indicators of multivessel disease may lead to improved identification of multivessel disease.

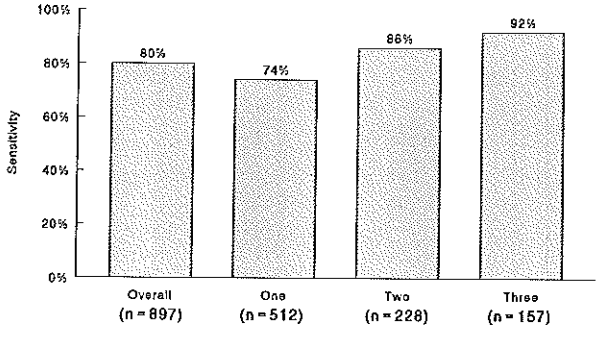


Figure 3. Sensitivity of DSE for detection of CAD by number of diseased vessels.

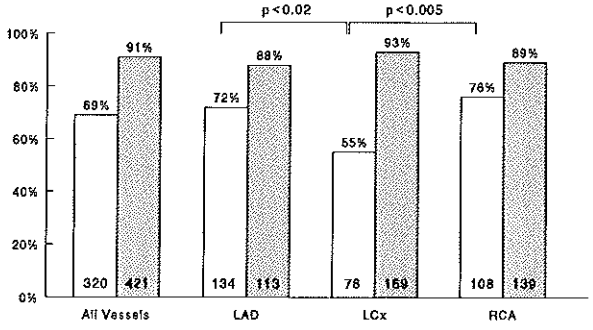


Figure 4. Sensitivity (open bars) and specificity (hatched bars) of DSE for detection of CAD in individual coronary arteries. Numbers within bars indicate number of vessels. Included in the analysis were patients with single-vessel and multivessel CAD. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

Patients with left bundle branch block or left ventricular hypertrophy. The ability of noninvasive tests to diagnose or localize CAD in patients with left bundle branch block (LBBB) or left ventricular hypertrophy (LVH) has been disappointing. Exercise-induced changes on the ECG are nondiagnostic in the presence of LBBB (83) and lack specificity in the presence of LVH, even in the absence of baseline ECG abnormalities (84). Moreover, several scintigraphic studies (85,86) have reported false positive results for detecting CAD in the presence of LBBB (especially when exercise stress is used) and LVH, resulting in a low specificity. Reports on the use of DSE in patients with LBBB or LVH are scarce. One study (87) in 13 patients without a previous MI and LBBB reported a sensitivity of 80%, a specificity of 87% and an accuracy of 85%. A study (84) in 28 patients with a history of hypertension and (echocardiographically defined) LVH reported a sensitivity of 89%, a specificity of 100% and an accuracy of 93%. The latter study reported that DSE was more specific (100% vs. 22%, $p < 0.0001$) and accurate (93% vs. 54%, $p < 0.0001$) compared with exercise electrocardiography. Although both DSE studies reported excellent accuracies for the detection of CAD, these small studies require confirmation from larger series to firmly establish the diagnostic value of DSE in patients with LBBB or LVH.

Comparison with other stress modalities in patients able to exercise adequately. *Exercise electrocardiography.* Apart from the special issues, discussed in the previous section of this review, several studies directly compared DSE with exercise electrocardiography in more heterogeneous patient groups. As seen in Figure 5, pooled data from eight studies (8,12,20,23–26,30) directly comparing DSE and exercise electrocardiography in the same 560 patients show that the sensitivity (76% vs. 63%, $p < 0.0001$), specificity (88% vs. 64%, $p < 0.0001$) and accuracy (79% vs. 63%, $p < 0.0001$) of DSE was clearly superior. However, since most studies did not specify how many patients were able to exercise adequately, were using digoxin or had abnormal rest ECG results, these results do not indicate that the routine exercise test should be replaced by DSE. Especially in patients with a low pretest likelihood of CAD and in men with normal results on the rest ECG it can be anticipated that DSE will provide little incremental diagnostic information in a cost-effective manner.

Exercise echocardiography. The diagnostic accuracy of DSE has led to enthusiasm for its general use rather than its particular use in patients unable to exercise adequately. However, exercise echocardiography can be performed as well in these patients. As seen in Figure 6, pooled data from four studies (23–25,30) directly comparing DSE and exercise echo-

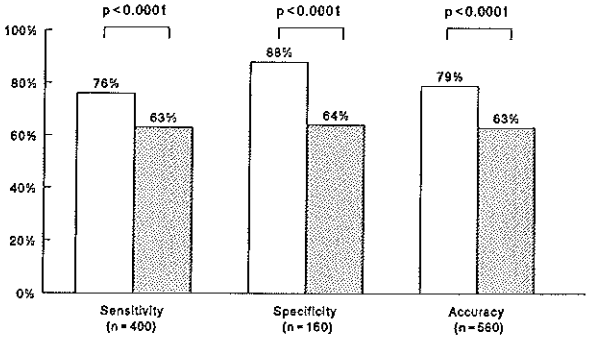


Figure 5. Sensitivity, specificity and accuracy of DSE (open bars) versus exercise electrocardiography (hatched bars) for detection of CAD.

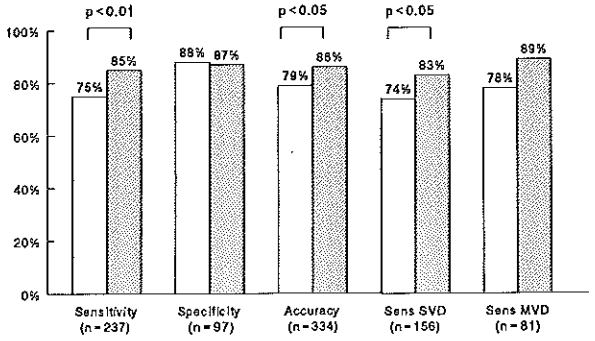


Figure 6. Sensitivity (Sens), specificity and accuracy of DSE (open bars) versus exercise echocardiography (hatched bars) for detection of CAD. MVD = multivessel disease; SVD = single-vessel disease.

cardiography in the same 334 patients show that the sensitivity (75% vs. 85%, $p < 0.01$) and accuracy (79% vs. 86%, $p < 0.05$) of exercise echocardiography were significantly higher. It should be emphasized that these differences were caused by one particular study in which DSE showed low accuracy (24). In that study a large number of DSE tests were submaximal because a modest decline in systolic blood pressure was used as a, not uncommon, end point, and a substantial number of the study patients were using beta-blockers while atropine was not added to dobutamine. It seems likely that in this patient cohort, the previously described dobutamine–atropine protocol would have resulted in better diagnostic accuracy, probably comparable to exercise echocardiography. However, the choice for the latter in patients who are expected to exercise adequately can be justified by better patient acceptance, fewer unpleasant side effects and the complementary functional information provided by exercise, such as duration of exercise, increase in heart rate, blood pressure response and reproduction of symptoms.

Comparison with other stress modalities in patients unable to exercise adequately. *Dipyridamole echocardiography.* In patients unable to perform adequate exercise, echocardiographic imaging can also be performed with dipyridamole as a pharmacologic stressor (36). In normal arteries dipyridamole, an indirect coronary vasodilator (88), causes a three- to fivefold increase in both subendocardial and subepicardial coronary flow (89). However, in stenosed arteries this augmentation is limited (depending on stenosis severity), creating flow heterogeneity. Echocardiographically detected functional evidence of ischemia is not caused by marked changes in blood pressure or heart rate (which change only minimally to moderately) but by coronary steal—either "vertical" (subepicardium from subendocardium) (90) or "horizontal" (nonstenotic from stenotic vessel territory) (91). As seen in Figure 7, pooled data from six studies (9,13,20,27,28,30) directly comparing DSE and dipyridamole echocardiography in the same 422 patients show that DSE is more sensitive for the detection of CAD (73% vs. 65%, $p < 0.05$), mainly because of a higher sensitivity in patients with single-vessel disease. The specificity (82% vs. 89%) and accuracy (76% vs. 72%) of the respective tests were not significantly different. These results are not surprising because dipyridamole creates primarily blood flow heterogeneity (not detected by echocardiography) and "true" ischemia only in a limited number of patients. Moreover, the detection of ischemia with dobutamine stress is facilitated by the improved thickening of normal segments as opposed to decreased thickening of ischemic segments, whereas dipyridamole has a lesser effect on normal segments. However, recent reports (32,92) have suggested that the addition of atropine to dipyridamole increases the sensitivity of the dipyridamole test for the

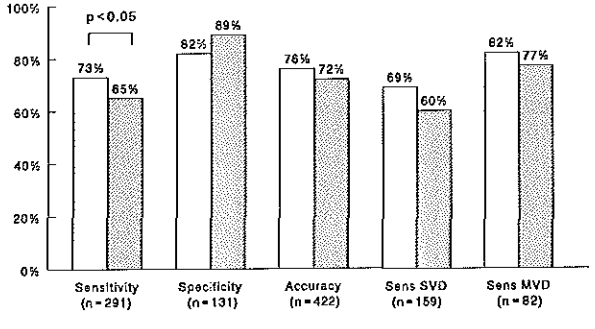


Figure 7. Sensitivity, specificity and accuracy of DSE (open bars) versus dipyridamole echocardiography (hatched bars) for detection of CAD. Abbreviations as in Figure 6.

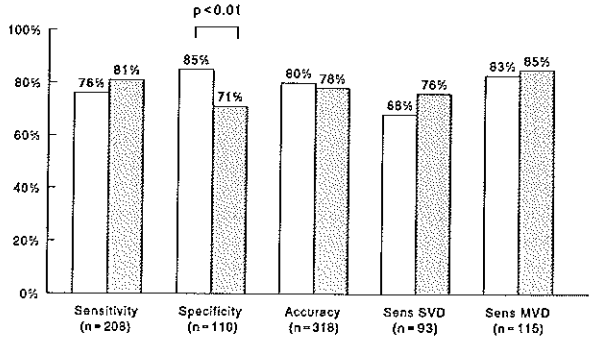


Figure 8. Sensitivity, specificity and accuracy of DSE versus dobutamine technetium-99m perfusion imaging (hatched bars) for detection of CAD. Abbreviations as in Figure 6.

detection of CAD to a level comparable with dobutamine–atropine stress echocardiography.

Radionuclide imaging. During dobutamine stress, coronary blood flow to the vascular bed of a normal artery increases dramatically, whereas perfusion through a stenosed artery may change minimally. On the basis of this induction in regional flow heterogeneity, the dobutamine stress test can also be performed in conjunction with radionuclide perfusion imaging. In four studies comparing DSE with dobutamine technetium-99m (Tc-99m) imaging in 318 patients, sensitivity was 76% versus 81%, specificity 85% versus 71% ($p < 0.01$) and accuracy 80% versus 78% (Fig. 8). The finding that DSE is more specific but may be less sensitive (especially in patients with single-vessel disease) is in line with the "ischemic cascade" theory (93), which states that perfusion abnormalities due to limited coronary flow reserve precede echocardiographic and ECG changes. Only two studies (with available angiographic data) reported the diagnostic accuracy of DSE versus vasodilator perfusion imaging. In one study (15) comparing DSE with adenosine Tc-99m imaging in 97 patients, sensitivity was 85% versus 86%, specificity 82% versus 71% and accuracy 84% versus 80%. In another study (31) comparing DSE with dipyridamole thallium-201 imaging in 54 patients, sensitivity was 93% versus 98%, specificity 73% versus 73% and accuracy 89% versus 93%. Therefore, DSE and radionuclide perfusion imaging seem to have comparable diagnostic accuracy, and the choice of one test over the other can be based on patient characteristics and the competence of the laboratory performing the test.

Patients after MI. The major goals of DSE in patients with a previous MI are to assess infarct-related coronary artery patency and to identify patients with multivessel CAD. Although the first report on DSE was in patients after MI (4), few studies have been specifically addressed to such patients. Infarct-related coronary artery stenosis was assessed in four studies (94–97) without use of the "biphasic" response (42,98). Sensitivities, specificities and accuracies in these studies ranged between 56% and 93%, 82% and 91% and 63% and 93%, respectively (Table 2). The higher sensitivity found in the study of Takeuchi et al. (94) might be explained by their definition of a positive (ischemic) test. DSE was defined as positive if peak wall motion score index was equal to or higher than that at the rest study. In the other studies, DSE was defined as positive if new or worsening wall motion abnormalities occurred. The detection of significant coronary artery stenosis in patients with rest wall motion abnormalities should be based on new or worsening wall motion abnormalities occurring at any stage, with use of the "biphasic" response (42,98). Thus, Takeuchi et al. probably overestimated, and the other studies probably underestimated, true sensitivity. Smart et al. (99) recently reported in a large series of patients, with use of the "biphasic" response, a sensitivity of 82%, a specificity of 80% and a diagnostic accuracy of 82% for the detection of infarct-related coronary artery stenosis. The presence of multivessel CAD in

Table 2. Diagnostic Dobutamine Stress Echocardiographic Studies in Patients With Myocardial Infarction

Year	First Author (ref no.)	No. of Pts	IRA		Prediction of MVD: Remote Ischemia		Prediction of MVD: ≥2 Coronary Territories	
			Sens	Spec	Sens	Spec	Sens	Spec
1986	Berthe (4)	30	NA	NA	85%	88%	NA	NA
1994	Takeuchi (94)	40	93%	91%	NA	NA	NA	NA
1995	Bigi (95)	121	70%	NA	84%	93%	NA	NA
1996	Elhendy (96)	132	76%	85%	73%	88%	47%	89%
1997	Elhendy (97)	72	56%	82%	68%	93%	40%	96%
1997	Smart (99)	206	82%	80%	68%	97%	NA	NA

IRA = infarct-related artery; other abbreviations as in Table 1.

patients with a previous MI should ideally be based on an ischemic response in two coronary vascular territories. However, an approach in which remote ischemia (ischemia detected outside the infarct-related coronary artery territory) is considered diagnostic for multivessel CAD also seems valid because in most of these patients the infarct-related coronary artery is also significantly narrowed. Several studies (4,95–97, 99) assessed the value of DSE for the identification of multivessel CAD by this latter criterion. Sensitivities, specificities and accuracies in these studies ranged between 68% and 85%, 88% and 97% and 81% and 87%, respectively (Table 2). Importantly, in two of the cited studies (94,97) a direct comparison was made between DSE and radionuclide imaging. In both studies DSE was found to be as accurate as radionuclide imaging and even showed a trend toward greater sensitivity.

Future Developments

At present, the major limitations of DSE are endocardial border definition and subjective interpretation of stress-induced wall motion abnormalities. Enhancement of border definition (and thus interpretation) is currently under investigation with gray-scale B-mode color encoding (100), intravenous contrast agents (101), tissue Doppler interrogation (102), tissue characterization techniques and backscatter analysis (103). Eventually, the results of these investigations should lead to improved automatic border detection and objective (computerized), realistic criteria for wall motion abnormalities diagnostic of CAD (43).

Conclusions

DSE is a feasible, safe and useful exercise-independent stress modality for assessing the presence, localization and extent of CAD. The diagnostic accuracy of DSE seems at least comparable to other, competitive noninvasive stress modalities used in patients with limited exercise capacity. New technical developments are expected to further increase its strengths and should make the interpretation of stress echocardiograms more uniform and less subjective.

References

1. Morbidity from Coronary Heart Disease in the United States: National Heart, Lung, and Blood Institute Data Fact Sheet. Bethesda (MD): National Heart, Lung, and Blood Institute, 1990.
2. Chaitman BR. The changing role of the exercise electrocardiogram as a diagnostic and prognostic test for chronic ischemic heart disease. J Am Coll Cardiol 1986;8:1195–210.
3. Marwick T. Current status of non-invasive techniques for the diagnosis of myocardial ischemia. Acta Clin Belg 1992;47:1–5.
4. Berthe C, Piérard LA, Hiernaux M, et al. Predicting the extent and location of coronary artery disease in acute myocardial infarction by echocardiography during dobutamine infusion. Am J Cardiol 1986;58:1167–72.
5. Sawada SG, Segar DS, Ryan T, et al. Echocardiographic detection of coronary artery disease during dobutamine infusion. Circulation 1991;83: 1605–14.
6. Previtali M, Lanzarini L, Ferrario M, Tortorici M, Mussini A, Montemartini C. Dobutamine versus dipyridamole in coronary artery disease. Circulation 1991 Suppl III:III-27–31.
7. Cohen JL, Greene TO, Ottenweller J, Binenbaum SZ, Wilchfort SD, Kim CS. Dobutamine digital echocardiography for detecting coronary artery disease. Am J Cardiol 1991;67:1311–8.
8. Salustri A, Fioretti PM, Pozzoli MMA, McNeill AJ, Roelandt JRTC. Dobutamine stress echocardiography: its role in the diagnosis of coronary artery disease. Eur Heart J 1992;13:70–7.
9. Martin TW, Seaworth JF, Johns JP, Pupa LE, Condos WR. Comparison of adenosine, dipyridamole, and dobutamine in stress echocardiography. Ann Intern Med 1992;116:190–6.
10. Segar DS, Brown SE, Sawada SG, Ryan T, Feigenbaum H. Dobutamine stress echocardiography: correlation with coronary lesion severity as determined by quantitative angiography. J Am Coll Cardiol 1992;19:1197–202.
11. Marcovitz PA, Armstrong WF. Accuracy of dobutamine stress echocardiography in detecting coronary artery disease. Am J Cardiol 1992;69:1269–73.
12. Mazeika PK, Nadazdin A, Oakley CM. Dobutamine stress echocardiography for detection and assessment of coronary artery disease. J Am Coll Cardiol 1992;19:1203–11.
13. Salustri A, Fioretti PM, McNeill AJ, Pozzoli MMA, Roelandt JRTC. Pharmacological stress echocardiography in the diagnosis of coronary artery disease and myocardial ischemia: a comparison between dobutamine and dipyridamole. Eur Heart J 1992;13:1356–62.
14. McNeill AJ, Fioretti PM, El-Said EM, Salustri A, Forster T, Roelandt JRTC. Enhanced sensitivity for detection of coronary artery disease by addition of atropine to dobutamine stress echocardiography. Am J Cardiol 1992;70:41–6.
15. 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;87:345–54.
16. 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: 889–94.
17. Forster T, McNeill AJ, Salustri A, et al. 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;21:1591–6.
18. Marwick T, D'Hondt AM, Baudhuin T, et al. 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;22:159–67.
19. Hoffmann R, Lethen H, Kleinhans E, Weiss M, Flachskampf FA, Hanrath P. Comparative evaluation of bicycle and dobutamine stress echocardiography with perfusion scintigraphy and bicycle electrocardiogram for identification of coronary artery disease. Am J Cardiol 1993;72:555–9.
20. Previtali M, Lanzarini L, Fetiveau R, et al. Comparison of dobutamine stress echocardiography, dipyridamole stress echocardiography and exercise stress testing for diagnosis of coronary artery disease. Am J Cardiol 1993;72:865–70.
21. Takeuchi M, Araki M, Nakashima Y, Kuroiwa A. Comparison of dobutamine stress echocardiography and stress thallium-201 single-photon emission computed tomography for detecting coronary artery disease. J Am Soc Echocardiogr 1993;6:593–602.
22. Baudhuin T, Marwick T, Melin J, Wijns W, D'Hondt AM, Detry JM. Diagnosis of coronary artery disease in elderly patients: safety and efficacy of dobutamine echocardiography. Eur Heart J 1993;14:799–803.
23. Cohen JL, Ottenweller JE, George AK, Duvvuri S. Comparison of dobutamine and exercise echocardiography for detecting coronary artery disease. Am J Cardiol 1993;72:1226–31.
24. Marwick TH, D'Hondt AM, Mairesse GH, et al. Comparative ability of dobutamine and exercise stress in inducing myocardial ischemia in active patients. Br Heart J 1994;72:31–8.
25. Beleslin BD, Ostojic M, Stepanovic J, et al. Stress echocardiography in the detection of myocardial ischemia: head-to-head comparison of exercise, dobutamine, and dipyridamole tests. Circulation 1994;90:1168–76.
26. 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;128:713–8.
27. Sochowski RA, Yvorchuk KJ, Yang YY, Rattes MF, Chan KL. Dobut-

amine and dipyridamole stress echocardiography in patients with a low incidence of severe coronary artery disease. J Am Soc Echocardiogr 1995;8:482–7.
28. Ostojic M, Picano E, Belesiin B, et al. Dipyridamole-dobutamine echocardiography: a novel test for the detection of milder forms of coronary artery disease. J Am Coll Cardiol 1994;23:1115–22.
29. Daoud EG, Pitt A, Armstrong WF. Electrocardiographic response during dobutamine stress echocardiography. Am Heart J 1995;129:672–7.
30. Dagianti A, Penco M, Agati L, et al. Stress echocardiography: comparison of exercise, dipyridamole and dobutamine in detecting and predicting the extent of coronary artery disease. J Am Coll Cardiol 1995;26:18–25.
31. Ho FM, Huang PJ, Liau CS, et al. Dobutamine stress echocardiography compared with dipyridamole thallium-201 single-photon emission computed tomography in detecting coronary artery disease. Eur Heart J 1995;16:570–5.
32. Pingitore A, Picano E, Quarta Colosso M, et al. The atropine factor in pharmacologic stress echocardiography. J Am Coll Cardiol 1996;27:1164–70.
33. Rozanski A. Assessment of the information boondoggle resulting from the evaluation of noninvasive tests in cardiology. J Nucl Med 1995;36:1009–13.
34. Ruffolo RR. The pharmacology of dobutamine. Am J Med 1987;294:244–8.
35. Meyer SL, Curry GC, Donsey MS, Twieg DB, Parkey RW, Willerson JT. Influence of dobutamine on hemodynamics and coronary blood flow in patients with and without coronary artery disease. Am J Cardiol 1976;38: 103–8.
36. 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;76:943–51.
37. Pellikka PA, Roger VL, Oh JK, Miller FA, Seward JB, Tajik J. Stress echocardiography part II. Dobutamine stress echocardiography: techniques, implementation, clinical applications, and correlations. Mayo Clin Proc 1995;70:16–27.
38. Williams ME, Gervino EV, Rosa RM, et al. Catecholamine modulation of rapid potassium shifts during exercise. N Engl J Med 1985;312:823–7.
39. Coma-Canella I. Changes in plasma potassium during the dobutamine stress test. Int J Cardiol 1991;33:55–60.
40. American Society of Echocardiography Committee on Standards (Subcommittee on Quantitation of Two-Dimensional Echocardiograms). Recommendations of quantification of the left ventricle by two-dimensional echocardiography. J Am Soc Echocardiogr 1989;2:358–67.
41. Castini D, Gentile F, Omaghi M, et al. Dobutamine echocardiography: usefulness of digital image processing. Eur Heart J 1995;16:1420–4.
42. Senior R, Lahiri A. Enhanced detection of myocardial ischemia by stress dobutamine echocardiography utilizing the "biphasic" response of wall thickening during low and high dose dobutamine infusion. J Am Coll Cardiol 1995;26:26–32.
43. Carstensen S, Ali SM, Stensgaard-Hansen FV, et al. Dobutamine-atropine stress echocardiography in asymptomatic healthy individuals: the relativity of stress-induced hyperkinesia. Circulation 1995;92:3453–63.
44. Bach DS, Muller DWM, Gros BJ, Armstrong WF. False positive dobutamine stress echocardiograms: characterization of clinical, echocardiographic and angiographic findings. J Am Coll Cardiol 1994;24:928–33.
45. Labovitz AJ, Lewen MK, Kern M, Vandormael M, Deligonal U, Kennedy HL. Evaluation of left ventricular systolic and diastolic dysfunction during transient myocardial ischemia produced by angioplasty. J Am Coll Cardiol 1987;10:748–55.
46. Nishimura RA, Abel MD, Hatle LK, Tajik AJ. Assessment of diastolic function of the heart: background and current applications of Doppler echocardiography. Part II. Clinical studies. Mayo Clin Proc 1989;64:181–204.
47. El-Said EM, Roelandt JRTC, Fioretti PM, et al. Abnormal left ventricular early diastolic filling during dobutamine stress Doppler echocardiography is a sensitive indicator of significant coronary artery disease. J Am Coll Cardiol 1994;24:1618–24.
48. Hopfenspirger MR, Miller TD, Christian TF, Gibbons RJ. Sinus node deceleration during dobutamine perfusion scintigraphy as a marker of inferior ischemia. Am J Cardiol 1994;74:817–9.
49. Miller TD, Gibbons RJ, Squires RW, Allison TG, Gau GT. Sinus node deceleration during exercise as a marker of significant narrowing of the right coronary artery. Am J Cardiol 1993;71:371–2.
50. Mazeika PK, Nadazdin A, Oakley CM. Clinical significance of abrupt vasodépression during dobutamine stress echocardiography. Am J Cardiol 1992;69:1484–6.
51. Heinle KH, Tice FD, Kisslo J. Effect of dobutamine stress echocardiography on mitral regurgitation. J Am Coll Cardiol 1995;25:122–7.
52. Keren G, Katz S, Strom J, Sonnenblick EH, Lejemtel TH. Dynamic mitral regurgitation: an important determinant of the hemodynamic response to load alterations and inotropic therapy in severe heart failure. Circulation 1989;80:306–13.
53. Tanimoto M, Pai RG, Jintapakorn W. Normal changes in left ventricular filling and hemodynamics during dobutamine stress echocardiography. J Am Soc Echocardiogr 1995;8:488–93.
54. Tanimoto M, Pai RG, Jintapakorn W, Shah PM. Mechanism of hypotension during dobutamine stress echocardiography in patients with coronary artery disease. Am J Cardiol 1995;76:26–30.
55. Pellikka PA, Oh JK, Bailey KR, Nichols BA, Monahan KH, Tajik JA. Dynamic intraventricular obstruction during dobutamine stress echocardiography: a new observation. Circulation 1992;86:1429–32.
56. Heinle SK, Tice FD, Kisslo J. Hypotension during stress echocardiography: is it related to dynamic intraventricular obstruction? Am Heart J 1995;130: 314–7.
57. Rosamond TL, Vacek JL, Hurwitz A, Rowland AJ, Beauchamp GD, Crouse LJ. Hypotension during dobutamine stress echocardiography: initial description and clinical relevance. Am Heart J 1992;123:403–7.
58. Weissman NJ, Nidorf SM, Weyman AE, Picard MH. Effect of hydration on cavity obliteration during dobutamine stress echocardiography. Clin Cardiol 1995;18:17–20.
59. Mark AL. The Bezold-Jarisch reflex revisited: clinical implications of inhibitory reflexes originating in the heart. J Am Coll Cardiol 1983;11:90–102.
60. Dubach P, Froelicher VF, Klein J, Oakes D, Grover-Mckay M, Friis R. Exercise-induced hypotension in a male population: criteria, causes and prognosis. Circulation 1988;78:1380–7.
61. Marcovitz PA, Bach DS, Mathias W, Shayana V, Armstrong WF. Paradoxic hypotension during dobutamine stress echocardiography: clinical and diagnostic implications. J Am Coll Cardiol 1993;21:1080–6.
62. Lieberman EB, Heinle SK, Wildermann N, Waugh RA, Kisslo JA, Bashore TM. Does hypotension during dobutamine stress echocardiography correlate with anatomic or functional cardiac impairment? Am Heart J 1995; 129:1121–6.
63. Coma-Canella I. Dobutamine stress test to diagnose the presence and severity of coronary artery lesions in angina. Eur Heart J 1991;12:1198–204.
64. Mairesse GH, Marwick TH, Vanoverschelde JLJ, et al. How accurate is dobutamine stress electrocardiography for detection of coronary artery disease? J Am Coll Cardiol 1994;24:920–7.
65. Gallik DM, Mahmarian JJ, Verani MS. Therapeutic significance of exercise-induced ST-segment elevation in patients without previous myocardial infarction. Am J Cardiol 1993;72:1–7.
66. Previtali M, Lanzarini L, Mussini A, Ferrario M, Angoli L, Specchia G. Dobutamine-induced ST segment elevation in a patient with angina at rest and critical coronary lesions. Eur Heart J 1992;13:997–9.
67. Elhendy A, Geleijnse ML, Roelandt JRTC, et al. Evaluation by quantitative 99m-technetium MIBI SPECT and echocardiography of myocardial perfusion and wall motion abnormalities in patients with dobutamine-induced ST-segment elevation. Am J Cardiol 1995;76:441–8.
68. Poldermans D, Fioretti PM, Boersma E, et al. Safety of dobutamine-atropine stress echocardiography in patients with suspected or proven coronary artery disease: experience in 650 consecutive examinations. Am J Cardiol 1994;73:456–9.
69. Picano E, Mathias W Jr, Pingitore R, Bigi R, Previtali M. Safety and tolerability of dobutamine-atropine stress echocardiography: a prospective, multicentre study. Lancet 1994;344:1190–2.
70. Mertes H, Sawada SG, Ryan T, et al. Symptoms, adverse effects, and complications associated with dobutamine stress echocardiography: experience in 1118 patients. Circulation 1993;88:15–9.
71. Geleijnse ML, Elhendy A, Van Domburg RT, et al. Prognostic significance of systolic blood pressure changes during dobutamine-atropine stress technetium-99m sestamibi perfusion scintigraphy in patients with chest pain and known or suspected coronary artery disease. Am J Cardiol 1997;79: 1031–5.
72. Brown JH, Taylor P. Muscarinic receptor agonists and antagonists. In: Hardman JG, Limbird LE, editors. The Pharmacological Basis of Therapeutics. New York: McGraw-Hill, 1996:141–60.

73. Hoffmann R, Lethen H, Marwick TH, et al. Analysis of interinstitutional observer agreement in interpretation of dobutamine stress echocardiograms. J Am Coll Cardiol 1996;27:330–6.
74. Bach DS, Hepner A, Marcovitz PA, Armstrong WF. Dobutamine stress echocardiography: prevalence of a nonischemic response in a low-risk population. Am Heart J 1993;125:1257–61.
75. Lieng LH, Pellikka PA, Mahoney DW, et al. Atropine augmentation in dobutamine stress echocardiography: role and incremental value in a clinical practice setting. J Am Coll Cardiol 1996;28:551–7.
76. Weissman NJ, Levangie MW, Newell JB, Guerrero LJ, Weyman AE, Picard MH. Effect of beta-adrenergic receptor blockade on the physiologic response to dobutamine stress echocardiography. Am Heart J 1995;130: 248–53.
77. Fioretti PM, Poldermans D, Salustri A, et al. Atropine increases the accuracy of dobutamine stress echocardiography in patients taking beta-blockers. Eur Heart J 1994;15:355–60.
78. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. N Engl J Med 1979;300:1350–8.
79. 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.
80. 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;67:302–9.
81. Panza JA, Curiel RV, Laurienzo JM, Quyyumi AA, Dilsizian V. Relation between ischemic threshold measured during dobutamine stress echocardiography and known indices of poor prognosis in patients with CAD. Circulation 1995;92:2095–101.
82. Olson CE, Porter TR, Deligonul U, Xie F, Anderson JR. Left ventricular volume changes during dobutamine stress echocardiography identify patients with more extensive coronary artery disease. J Am Coll Cardiol 1994;24:1268–73.
83. Orzan F, Garcia E, Mathur VS, Hall RJ. Is the treadmill exercise test useful for evaluating coronary artery disease in patients with complete left bundle branch block? Am J Cardiol 1978;42:36–40.
84. 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;17:289–95.
85. Hirzel HO, Senn M, Nuesch K, et al. Thallium-201 scintigraphy in complete left bundle branch block. Am J Cardiol 1984;53:764–9.
86. Schulman DS, Francis DK, Black HR, Wackers FJ. Thallium-201 stress imaging in hypertensive patients. Hypertension 1987;10:16–21.
87. 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;76:321–5.
88. Fitzgerald GA. Dipyridamole. N Engl J Med 1987;316:1247–57.
89. Wilson RF, Wyche K, Christensen BV, Zimmer S, Laxson DD. Effects of adenosine on human coronary arterial circulation. Circulation 1990;82: 1595–606.
90. Flameng W, Wunsten B, Schaper W. On the distribution of myocardial blood flow: II. Effects of arterial stenosis and vasodilation. Basic Res Cardiol 1974;69:435–46.
91. Demer L, Gould KL, Kirkeeide R. Assessing stenosis severity: coronary flow reserve, collateral function, quantitative coronary arteriography, positron imaging, and digital subtraction angiography: a review and analysis. Prog Cardiovasc Dis 1988;30:307–22.
92. 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;14:1216–22.
93. Nesto RW, Kowalchuck GJ. The ischemic cascade: temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. Am J Cardiol 1987;57:23C–7C.
94. Takeuchi M, Araki M, Nakashima Y, Kuroiwa A. The detection of residual ischemia and stenosis in patients with acute myocardial infarction with dobutamine stress echocardiography. J Am Soc Echocardiogr 1994;7:242–52.
95. Bigi R, Occhi G, Fiorentini C, et al. Dobutamine stress echocardiography for the identification of multivessel coronary artery disease after uncomplicated myocardial infarction: the importance of test end-point. Int J Cardiology 1995;50:51–60.
96. Elhendy A, Van Domburg RT, Roelandt JRTC, et al. Accuracy of dobutamine stress echocardiography for the diagnosis of coronary artery stenosis in patients with myocardial infarction: the impact of extent and severity of left ventricular dysfunction. Heart 1996;76:123–8.
97. Elhendy A, Geleijnse ML, Roelandt JRTC, et al. Comparison of dobutamine stress echocardiography and 99m-technetium sestamibi SPECT myocardial perfusion scintigraphy for predicting extent of coronary artery disease in patients with healed myocardial infarction. Am J Cardiol 1997;79:7–12.
98. Elhendy A, Cornel JH, Roelandt JRTC, et al. Relation between contractile response of akinetic segments during dobutamine stress echocardiography and myocardial ischemia assessed by simultaneous thallium-201 single-photon emission computed tomography. Am J Cardiol 1996;77:955–9.
99. Smart SC, Knickelbine T, Stoiber TR, Carlos M, Wynsen JC, Sagar KB. Safety and accuracy of dobutamine-atropine stress echocardiography for the detection of residual stenosis of the infarct-related artery and multivessel disease during the first week after acute myocardial infarction. Circulation 1997;95:1394–401.
100. Marcovitz PA, Bach DS, Segar DS, Armstrong W. Impact of B-mode color encoding on rapid detection of ultrasound targets: an in vitro study. J Am Soc Echocardiogr 1993;6:382–6.
101. Crouse LJ, Cheirif J, Hanly DE, et al. Opacification and border delineation improvement in patients with suboptimal endocardial border definition in routine echocardiography: results of the Phase III Albunex multicenter trial. J Am Coll Cardiol 1993;22:1491–500.
102. Palka P, Lange A, Fleming AD, Sutherland GR, Fenn LN, McDicken NW. Doppler tissue imaging: myocardial wall motion velocities in normal subjects. J Am Soc Echocardiogr 1995;8:659–68.
103. Mifunski MR, Mohr GA, Perez JE, et al. Ultrasonic tissue characterization with integrated backscatter: acute myocardial ischemia, reperfusion, and stunned myocardium in patients. Circulation 1989;80:491–503.

Chapter 2

Should the diagnosis of coronary artery disease be based on the evaluation of myocardial function or perfusion?

Geleijnse ML, Salustri A, Marwick TH, Fioretti PM

Eur Heart J 1997; 18 (Suppl D): D68-D77

Should the diagnosis of coronary artery disease be based on the evaluation of myocardial function or perfusion?

M. L. Geleijnse, A. Salustri*, T. H. Marwick† and P. M. Fioretti

*Thoraxcenter, University Hospital Dijkzigt and Erasmus University, Rotterdam, The Netherlands; *Division of Cardiology, Sandro Pertini Hospital, Roma, Italy; †Cleveland Clinic Foundation, Cleveland, Ohio, U.S.A.*

The aim of this review was to define the place of stress (exercise, dobutamine, and vasodilator) echocardiography in the context of perfusion scintigraphic techniques for the detection of coronary artery disease. Echocardiography and nuclear imaging have their strong and weak points. Echocardiography has the benefit of widespread availability, relatively low cost, portability, absence of radiation, safety, and determination of ischaemic threshold. However, echocardiographic imaging cannot be performed during treadmill exercise, the echocardiographic windows are variable with sometimes poor echogenicity, and interpretation is subjective and requires an important learning curve.

Diagnostic comparisons were focused on studies involving echocardiographic and nuclear imaging in the same patients. These direct comparisons show that exercise or dobutamine echocardiography and perfusion imaging have similar accuracies for the detection and localization of coronary artery disease. Perfusion imaging may be more sensitive in the detection of mild coronary artery disease; echocardiography, however, has a better specificity. Vasodilator perfusion imaging is superior to vasodilator echocardiography, although the new dipyridamole–atropine echocardiography test will make future reassessment neccesary. Once the condition of adequate echocardiographic training is fulfilled, we believe that the selection of one or other test should be tailored to clinical circumstances rather than be a uniform decision.
(Eur Heart J 1997; 18 (Suppl D): D68–D77)

Key words: Coronary artery disease, stress echocardiography, myocardial perfusion scintigraphy.

Introduction

Stress echocardiography and stress myocardial perfusion scintigraphy have gained wide acceptance as accurate techniques for the detection and localization of coronary artery disease. In addition to their use in combination with exercise, their clinical availability has been broadened by the use of pharmacological stress agents. This review attempts to define the place of stress echocardiography in the context of perfusion scintigraphic techniques for the detection of coronary artery disease.

A number of variables (referral bias, extent and severity of coronary disease, definition of significant coronary disease, stress protocols, medications) may potentially influence the results of either test, so that comparisons will focus on studies involving the performance of both echocardiographic and nuclear imaging in the same patients for each of the most widely used stress techniques: exercise, dobutamine and vasodilators (adenosine and dipyridamole). For these comparisons to be valid, we are assuming that the investigators in these studies are equally expert in either technique. Likewise, we assume that practitioners making choices between echocardiography and scintigraphy have equivalent expertise available in each.

M. L. Geleijnse is supported by the Dutch Heart Foundation (grant NHS 94.135)

Correspondence: Marcel L. Geleijnse, MD, Thoraxcenter BA 302, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

Basic principles of function versus perfusion for diagnosis of coronary artery disease

In the presence of a flow-limiting coronary artery stenosis, exercise or pharmacological stress results in a sequence of functional events. According to the 'ischaemic cascade' theory[1], perfusion abnormalities due to limited coronary flow reserve are followed by diminished left ventricular compliance (diastolic dysfunction), decreased myocardial contractility (systolic dysfunction), and increased left ventricular end-diastolic pressure.

Table 1 Stress echocardiography and myocardial perfusion scintigraphy for the diagnosis of coronary artery disease

	Stress echocardiography	Stress perfusion scintigraphy
Equipment	Low cost	Relatively expensive
	Portable	Laboratory-based
Personnel	Learning curve for acquisition and reading	Relatively automated
Imaging	No radiation	Radiation exposure
	Rapid, instant results	Time consuming
	On-line, real-time imaging	Off-line, 'Snapshot' at peak stress
	Function	Perfusion
	Tomographic	Planar vs SPECT
Reporting	Regional function/thickening	Regional flow heterogeneity
	Usually qualitative	Quantitation well accepted
	Global function (EF, ESV)	Global function (lung-heart ratio, gated SPECT)
Benefits	Identifies other sources of chest pain	Widespread experience
	Ischaemic threshold: safety therapy assessment	Less vulnerable to submaximal stress
Problems	Variable echo window	Artifacts due to breast tissue, left bundle branch block, or left ventricular hypertrophy
	Endocardial border definition	
	Treadmill exercise	

SPECT=single-photon emission computer tomography; EF=ejection fraction; ESV=end-systolic volume. (Reproduced from[44].)

These changes can be seen at perfusion scintigraphy by relatively reduced tracer uptake and at echocardiography by alterations in transmitral flow patterns, abnormal regional systolic function, and eventually reduction of overall left ventricular systolic function with left ventricular cavity enlargement.

The development of myocardial perfusion defects with either exercise or pharmacological stressors 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 minimally. Because the initial uptake of radiopharmaceuticals is flow-dependent within physiological ranges[2], 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. Classically, a twofold difference in relative count activity is required to detect a perfusion abnormality scintigraphically[3].

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 pharmacological stress is to increase endocardial excursion, the speed of contraction, and the degree of myocardial thickening. Indices pointing to the presence of myocardial ischaemia include stress-induced deterioration of regional endocardial excursion, delayed excursion ('tardokinesis'), and a reduction of myocardial thickening. Classically flow must be reduced to 50% in at least 5% of the myocardium to detect new wall motion abnormalities[4].

Strengths and limitations of the imaging modalities

Benefits of stress echocardiography compared with perfusion imaging

Clinical considerations

Several aspects of stress echocardiography are attractive from the standpoint of clinical feasibility (Table 1). In comparison with single-photon emission computed tomography (SPECT) cameras, echocardiography machines are smaller in size and more portable, allowing studies in the coronary care unit and emergency room, for example. The shorter time for performance and interpretation of a stress echocardiogram is attractive in the outpatient setting, although the superceding of the conventional 4-h thallium-201 protocol by more patient-friendly dual isotope techniques may reduce the importance of this benefit of echocardiography. The absence of ionizing radiation may be attractive to the public, for whom nuclear tests have a bad image, at least in The Netherlands. In addition, demonstration of echocardiographic images may assist with patient education.

Two-dimensional echocardiography has 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 if imaging is performed during the test. This cinematographic aspect of echocardiographic monitoring is very attractive, especially in patients in whom safety is a major concern (patients with suspected unstable angina or severe coronary disease). Documentation of the ischaemic threshold (during

pharmacological or bicycle stress) can give important information about the severity and extent of underlying coronary artery disease, and can assess the adequacy of therapy, by measuring the ischaemia-free stress time. In contrast, SPECT offers a snapshot of perfusion at the time of peak stress, without the ability to examine perfusion on-line.

Echocardiography has excellent spatial resolution and, combined with Doppler techniques, is capable of accurately defining systolic and diastolic function, chamber dimensions, volumes and wall thickness. Non-ischaemic explanations for patient symptoms (such as mitral valve prolapse or pericardial disease) may be apparent from visualization of valve anatomy and gradients or pericardial effusion. These aspects are unique among the non-invasive techniques in common usage for the detection of coronary artery disease.

Interpretation of stress echocardiography is performed by cardiologists, who often feel they have a better grasp of the clinical questions that need to be answered in cardiac patients than radiologists or nuclear medicine physicians. While any stress imaging study should be interpreted apart from the clinical and exercise data to obtain independent information, these data should then be applied to the patient's clinical situation. In being unaware of the patient's clinical data, the nuclear physician may be at a disadvantage, and the final synthesis of the results may be less clinically orientated.

Finally, specificity lowering artifacts which are problematic with SPECT (breast and diaphragmatic attenuation) can be more easily dealt with echocardiography.

Availability and cost

The additional strengths of echocardiography are its widespread availability and relatively low cost. In contrast to SPECT gamma cameras, most cardiologists have access to an echocardiography machine, and their clinical use is not regulated or constrained by any regulatory agencies. The average price of the machines is lower than the average SPECT gamma camera systems and the quality control is minimal. As a consequence of lower purchasing and maintenance costs, the total cost of an echocardiographic study is lower than a scintigraphic study; in The Netherlands, dipyridamole thallium scintigraphy costs about US $531 (US dollars) compared to about $185 for dobutamine stress echocardiography[5].

Benefits of stress perfusion imaging compared with echocardiography

Imaging considerations

In a large number of laboratories, especially in the United States, cardiac stress is routinely performed using the treadmill. In contrast to bicycle stress, echocardiographic imaging cannot be performed during treadmill exercise because of excessive patient motion. Consequently, the first images are taken immediately after cessation of exercise, with the patient on a bed in the left lateral decubitus position. Unfortunately, wall motion abnormalities present at peak stress may revert rapidly to normal after the discontinuation of exercise, and may be missed using post-exercise imaging. While thallium-201 may undergo redistribution between exercise and imaging, this is minimal if the delay between stress and imaging is brief, and if technetium-99m is used the image corresponds to the perfusion status at the time of injection.

Despite the well-established standardization of the routine echocardiographic examinations, the availability of standard echocardiographic windows is variable from patient to patient and, in some cases, especially in patients with chronic obstructive pulmonary disease, poor echogenicity results in suboptimal images that may make a correct interpretation difficult or impossible. In our experience, non-interpretable studies constitute a small minority of the patients (about 5%), although referral bias obviously influences these results. Importantly, it is sometimes difficult to predict which patients have poor echocardiographic images during the test, since paradoxically, the images may improve during stress. In contrast, although soft tissue attenuation may pose problems for SPECT (more with thallium-201 than technetium-99m), chronic lung disease does not pose a problem for image quality.

Even if the echocardiogram is of interpretable quality, technical problems may remain. In contrast to the relatively automated acquisition of nuclear images, with their relatively easy interpretation and computer quantitation, echocardiography is characterized by manual, technician-dependent image acquisition, problems with endocardial border definition, and visual, subjective interpretation. Inexpert use of the electrocardiographic gating, comparison of non-identical cross sections, and failure or delayed visualization of abnormal segments are all avoidable, operator-dependent problems. However, images may suffer from poor endocardial border definition even in the hands of the best sonographer.

Interpretation

The interpretation of stress echocardiograms requires an important learning curve even for experienced echocardiographers, and there is an important difference in the accuracy of echocardiographers who are and are not trained in stress echocardiography.

Subjective analysis is further hampered by the absence of a clear consensus about the definition of the ischaemic response. Whereas segments deteriorating from normal contraction to akinesis or dyskinesis are universally called ischaemic segments, controversy exists about the interpretation of basal segments, segments showing minimal hypokinesis at peak stress (in particular basal inferoposterior segments), and segments without physiological hyperkinesis during stress. Even for experts, the interpretation of studies in patients with

Table 2 Direct diagnostic comparisons between exercise echocardiography and perfusion scintigraphy

Author	No. pts	Stress	Imaging modality	CAD %DS	Sensitivity		Specificity		Sensitivity SVD		Sensitivity MVD		Exclusions
Maurer[8]	36	Treadmill	Echo	≥50	19/23	(83%)	12/13	(92%)	3/6	(50%)	16/17	(94%)	MI
			Tl-201^{Planar}		17/23	(74%)	12/13	(92%)	—		—		
Quiñones[9]	112	Treadmill	Echo	≥50	64/86	(74%)	23/26	(88%)	24/41	(58%)	40/45	(89%)	—
			Tl-201^{SPECT}		65/86	(76%)	21/26	(81%)	25/41	(61%)	40/45	(89%)	
Wann[10]	6	Supine-bike	Echo	≥50	1/3	(33%)	3/3	(100%)	0/1	(0%)	1/2	(50%)	MI, rest
			Tl-201^{Planar}		2/3	(67%)	3/3	(100%)	0/1	(0%)	2/2	(100%)	WMA
Hecht[11]	71	Supine-bike	Echo	≥50	46/51	(90%)	16/20	(80%)	17/22	(77%)	29/29	(100%)	—
			Tl-201^{SPECT}		47/51	(92%)	13/20	(65%)	21/22	(95%)	26/29	(90%)	
Pozzoli[12]	75	Upright-bike	Echo	≥50	35/49	(71%)	25/26	(96%)	20/33	(61%)	15/16	(94%)	—
			MIBI^{SPECT}		41/49	(84%)	23/26	(88%)	27/33	(82%)	14/16	(88%)	
Galanti[13]	53	Upright-bike	Echo	≥70	25/27	(93%)	25/26	(96%)	13/14	(93%)	12/13	(92%)	MI, rest
			Tl-201^{Planar}		27/27	(100%)	24/26	(92%)	14/14	(100%)	13/13	(88%)	WMA
Salustri[14]	37	Upright-bike	Echo	≥50	19/23	(83%)	12/14	(86%)	19/23	(83%)	—		MI, rest
			MIBI^{SPECT}		20/23	(87%)	10/14	(71%)	20/23	(87%)	—		WMA
Total	390		Function		209/262	(80%)	116/128	(91%)	93/134	(69%)*	97/105	(92%)	
			Perfusion		219/262	(84%)	106/128	(83%)	107/134	(80%)	95/105	(90%)	

CAD %DS=percentage diameter stenosis value for significant coronary artery disease; Echo=echocardiography; MI=myocardial infarction; MIBI=technetium-99m sestamibi; MVD=multivessel disease; Pts=patients; SVD=single vessel disease; SPECT=single-photon emission computed tomography; Tl-201=thallium-201; WMA=wall motion abnormalities; *=$P<0{\cdot}05$. (Reproduced from[44].)

abnormal resting contraction or left bundle branch block can be very difficult. Moreover, at present, few data are available on intra- and inter-observer variability, especially between observers working in different centres. In contrast, quantification of scintigraphic images is well accepted and widely used.

Influence of drug therapy

As a positive stress echocardiogram requires the induction of wall motion abnormalities (and hence, 'true' ischaemia), the use of anti-ischaemic drugs may decrease the sensitivity of the test. Although the same is true for exercise or dobutamine perfusion imaging (a submaximal heart-rate response may compromise the development of maximal vasodilation), pharmacological vasodilation may avoid this problem. Performance of stress echocardiography in patients with ongoing anti-ischaemic therapy is appropriate if the clinical question is about the efficacy of treatment for the control of angina or myocardial ischaemia, but is inappropriate if the test is performed for diagnostic purposes.

Diagnostic accuracy of the imaging modalities

Exercise or dobutamine stress echocardiography versus perfusion scintigraphy

Exercise stress testing results in a marked increase in heart rate and blood pressure. In patients unable to exercise, dobutamine can simulate exercise by activating β1-, β2- and α1-receptors[6]. Its main initial action is a positive inotropic effect and, at higher doses ($\geq 20\ \mu g \cdot kg^{-1} \cdot min^{-1}$), it increases heart rate and to a lesser extent systolic blood pressure. This augmentation of myocardial contractility, heart rate, left ventricular pressure, and wall stress increases oxygen requirements. However, in the presence of a critical coronary stenosis, the enhanced myocardial oxygen demand is not matched by a concomitant increase in blood flow. This creates a condition of regional supply–demand imbalance that results in regional myocardial dysfunction. When dobutamine is used, its strong inotropic effect facilitates the echocardiographic detection of ischaemic segments with abnormal function, as normal segments become hyperkinetic in response to the drug.

Either exercise or dobutamine can also be used in conjunction with myocardial perfusion scintigraphy, since both alter regional myocardial blood flow. Normally a dose-related increase in subepicardial and subendocardial blood flow occurs within myocardium supplied by normal coronary arteries. However, blood flow increases minimally within vascular beds supplied by significantly stenosed ateries, with most of the increase occurring within the subepicardium rather than the subendocardium[7]. This heterogeneity in myocardial blood flow can be visualized by perfusion scintigraphy.

Table 2 shows the sensitivity and specificity for the detection of coronary artery disease in seven studies, directly comparing *exercise* echocardiography and perfusion scintigraphy in the same 390 patients[8–14]. The sensitivities of both tests for the identification of coronary artery disease are comparable (80% vs 84%, respectively), although there is a higher sensitivity for perfusion imaging in the setting of single vessel disease (80% vs 69%, respectively, $P<0{\cdot}05$). There was a trend towards a better specificity for echocardiography (91% vs 83%, $P<0{\cdot}10$).

The sensitivity and specificity values reported in four studies, comprising 318 patients who underwent

Table 3 Direct diagnostic comparisons between dobutamine echocardiography and perfusion scintigraphy

Author	No. pts	Dobu-dose	Imaging modality	CAD %DS	Sensitivity		Specificity		Sensitivity SVD		Sensitivity MVD		Exclusions
Günalp[15]	19	Dobu 30	Echo	≥50	7/10	(70%)	8/9	(89%)	5/7	(71%)	2/3	(67%)	MI, rest
			$MIBI^{SPECT}$		9/10	(90%)	8/9	(89%)	6/7	(86%)	3/3	(100%)	WMA
Marwick[16]	217	Dobu 40	Echo	≥50	102/142	(72%)	62/75	(83%)	45/68	(66%)	57/74	(77%)	MI
			$MIBI^{SPECT}$		108/142	(76%)	50/75	(67%)	50/68	(74%)	58/74	(78%)	
Forster[17]	21	Dobu 40[A]	Echo	≥50	9/12	(75%)	8/9	(89%)	1/4	(25%)	8/8	(100%)	MI, rest
			$MIBI^{SPECT}$		10/12	(83%)	8/9	(89%)	3/4	(75%)	7/8	(88%)	WMA
Senior[18]	61	Dobu 40	Echo	≥50	41/44	(93%)	16/17	(94%)	12/14	(86%)	29/30	(97%)	—
			$MIBI^{SPECT}$		42/44	(95%)	12/17	(71%)	12/14	(86%)	30/30	(100%)	
Total	318		Function		159/208	(76%)	94/110	(85%)*	63/93	(68%)	96/115	(83%)	
			Perfusion		169/208	(81%)	78/110	(71%)	71/93	(76%)	98/115	(85%)	

[A]=atropine; CAD %DS=percentage diameter stenosis value for significant coronary artery disease; Dobu-dose=dobutamine dose in $\mu g \cdot kg^{-1} \cdot min^{-1}$; Echo=echocardiography; MI=myocardial infarction; MIBI=technetium-99m sestamibi; MVD=multivessel disease; Pts=patients; SVD=single vessel disease; SPECT=single-photon emission computed tomography; Tl-201=thallium-201; WMA=wall motion abnormalities; *=$P<0.01$. (Reproduced from[44].)

simultaneous *dobutamine* stress echocardiography and perfusion scintigraphy, are summarized in Table 3[15–18]. The sensitivities of both tests for the identification of coronary artery disease are comparable (76% vs 81%, respectively), although again there was a trend toward a higher sensitivity for perfusion imaging in the setting of single vessel disease (68% vs 76%, respectively). The overall results for specificity show that dobutamine echocardiography is a more specific test (85% vs 71%, $P<0.01$). These data are consistent with previous data that indicate that the high sensitivity of myocardial perfusion imaging with SPECT is at the cost of a sacrifice in specificity[19].

The results of direct comparisons of exercise and exercise-simulating (dobutamine) stress echocardiography and perfusion scintigraphy suggest that the two imaging techniques offer comparable levels of accuracy in the diagnosis of coronary artery disease (82% vs 81%, respectively, Fig. 1). The finding that echocardiography is more specific, but may be less sensitive (particularly in the detection of single vessel disease), is in line with the ischaemic cascade model. As the development of a perfusion disturbance is expected to precede the development of true ischaemia, perfusion imaging might be expected to be more sensitive than wall motion imaging for the detection of mild stenosis. However, the difference in sensitivity is less than might be expected. This might be explained by two major factors: suboptimal inducement of flow heterogeneity by exercise or dobutamine[7] 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 flow comparisons used in myocardial perfusion imaging). Some ischaemic regions may even be identified by echocardiography rather than scintigraphy, for example, abnormal wall motion due to subendocardial ischaemia may be evident before malperfusion is extensive enough to be apparent at perfusion scintigraphy.

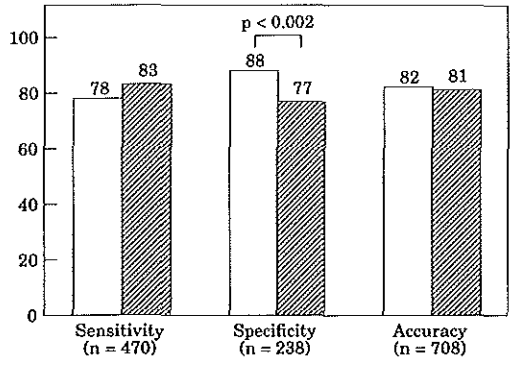


Figure 1 **Sensitivity, specificity, and accuracy of exercise or exercise-simulating (dobutamine) stress echocardiography and perfusion imaging for the detection of coronary artery disease. Open bars, function; hatched bars, perfusion. (Reproduced with permission[44].)**

Vasodilator stress echocardiography versus perfusion scintigraphy

The two most used vasodilators are adenosine and dipyridamole. Adenosine is a naturally occurring molecule that regulates blood flow in various vascular beds including the myocardium, by activation of specific cell surface receptors[20]. In particular, α_2-receptor activation in vascular smooth muscle cells ultimately leads to smooth muscle relaxation and dilatation. Dipyridamole is an indirect coronary vasodilator that increases the extracellular concentration of adenosine by blocking its intracellular transport, metabolism and inactivation[21].

In normal arteries, these vasodilators cause an increase in coronary flow, both subendocardial and subepicardial, of three to five fold[22]. However, in stenosed arteries this augmentation is limited (dependent on stenosis severity), creating flow heterogeneity, which

Table 4 Direct diagnostic comparisons between vasodilator echocardiography and perfusion scintigraphy

Author	No. pts	Stress-dose	Imaging modality	CAD %DS	Sensitivity		Specificity		Sensitivity SVD		Sensitivity MVD		Exclusions
Marwick[25]	97	Adeno 0·18	Echo	≥50	34/59	(58%)	33/38	(87%)	16/31	(52%)	18/28	(64%)	MI
			$MIBI^{SPECT}$		51/59	(86%)	27/38	(71%)	25/31	(81%)	26/28	(93%)	
Nguyen[26]	25	Adeno 0·14	Echo	≥50	12/20	(60%)	5/5	(100%)	—		—		—
			$Tl\text{-}201^{SPECT}$		18/20	(90%)	5/5	(100%)	—		—		
Amanullah[27]	40	Adeno 0·14	Echo	≥50	25/34	(74%)	6/6	(100%)	—		—		—
			$MIBI^{SPECT}$		32/34	(94%)	6/6	(100%)	—		—		
Perin[28]	25	Dipy 0·56	Echo	≥50	11/19	(58%)	6/6	(100%)	—		—		—
			$Tl\text{-}201^{Planar}$		18/19	(95%)	3/6	(50%)	—		—		
Simonetti[29]	35	Dipy 0·84	Echo	≥75	19/22	(86%)	12/13	(92%)	—		—		MI
			$Tl\text{-}201^{Planar}$		20/22	(91%)	13/13	(100%)	—		—		
Total	222		Function		101/154	(66%)*	62/68	(91%)§	16/31	(52%)†	18/28	(64%)‡	
			Perfusion		139/154	(90%)	54/68	(79%)	25/31	(81%)	26/28	(93%)	

Adeno=adenosine (dose in $mg \cdot kg^{-1} \cdot min^{-1}$); CAD %DS=percentage diameter stenosis value for significant coronary artery disease; Dipy=dipyridamole (dose in $mg \cdot kg^{-1}$); Echo=echocardiography; MI=myocardial infarction; MIBI=technetium-99m sestamibi; MVD=multivessel disease; Pts=patients; SVD=single vessel disease; SPECT=single-photon emission computed tomography; Tl-201=thallium-201; *=$P<0{\cdot}0001$; †=$P<0{\cdot}02$; ‡=$P<0{\cdot}01$; §=$P<0{\cdot}05$. (Reproduced from[44].)

can be detected by perfusion scintigraphy. Echocardiographically detected functional evidence of ischaemia is not caused by marked changes in blood pressure or heart rate (which change only minimally) but by coronary steal, either 'vertical' (subepicardium from subendocardium)[7,23] or 'horizontal' (non-stenotic from stenotic vessel territory)[24].

As seen in Table 4, pooled data from five studies[25–29] directly comparing vasodilator (dipyridamole or adenosine) echocardiography and perfusion scintigraphy in the same 222 patients show that the sensitivity of vasodilator perfusion scintigraphy is superior to that of vasodilator echocardiography (90% vs 66%, $P<0{\cdot}0001$). Only Marwick *et al.*[25] reported sensitivities according to the extent of disease. In this study, the sensitivity of vasodilator perfusion scintigraphy was superior to echocardiography, both for single (81% vs 52%, $P<0{\cdot}02$) and multivessel disease (93% vs 64%, $P<0{\cdot}01$). These results are not surprising, since vasodilators create primarily blood flow heterogeneity (detected by perfusion scintigraphy and not echocardiography) and true ischaemia in only a limited number of patients.

Dobutamine stress echocardiography versus vasodilator perfusion imaging

In the many patients who are unable to exercise adequately, the optimal pharmacological stressors for echocardiography and scintigraphy are fundamentally different. On the basis of the underlying principles of the tests, the necessity of ischaemia for the development of abnormal wall motion would suggest that dobutamine would be more effective than a vasodilator for stress echocardiography. A comparison performed in an animal model[7] indicated that dobutamine was the most appropriate stress to demonstrate abnormal wall motion due to ischaemia. Pooled data from seven published studies[30] directly comparing dobutamine vs a vasodilator for stress echocardiography in the same 517 patients showed that dobutamine was more sensitive than both dipyridamole (78% vs 67%, $P<0{\cdot}002$) and adenosine (82% vs 52%, $P<0{\cdot}001$), and equally specific. Off note, up to this moment there are no direct comparisons available using the new promising dipyridamole–atropine stress echocardiography protocol[31].

In the same animal model[7], dipyridamole caused the greatest blood flow heterogeneity, making it particularly suited for myocardial perfusion studies. Published clinical data, however, are not uniform about the superiority of vasodilators to dobutamine for perfusion scintigraphy. Kumar *et al.*[32] found that dipyridamole thallium scintigraphy correlated better with coronary score. However, these results were based on a very small group of patients, the authors did not report test accuracy, used an insufficient dobutamine dose ($20\ \mu g \cdot kg^{-1} \cdot min^{-1}$) and included patients with previous myocardial infarction. In a larger series of 97 patients, without previous myocardial infarction and using high-dose dobutamine, Marwick *et al.*[25] found that the accuracy of dobutamine technetium-99m perfusion scintigraphy was comparable with adenosine technetium-99m perfusion scintigraphy (77% vs 80%, respectively).

The most appropriate means of comparing pharmacological stress echocardiography and scintigraphy seems, therefore, to be to use dobutamine with the former and a vasodilator stress with the latter. Unfortunately, reports directly comparing dobutamine stress echocardiography with vasodilator perfusion scintigraphy are also scarce. The only two published reports with available angiographic data in 97 and 120 patients[25,33] showed that the tests were equally sensitive (85% vs 86% and 85% vs 89%, respectively). However, there was a trend toward a higher specificity of dobutamine stress echocardiography (82% vs 71% and 93% vs 85%, respectively). Based on these results, and considering the

advantages of echocardiography over perfusion scintigraphy (Table I) it can be anticipated that the use of dobutamine stress echocardiography will grow in the future.

Assessment of the localization of coronary artery disease

The detection of disease in the circumflex coronary artery is a major problem for both perfusion scintigraphy and echocardiography. In addition to the 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. Echocardiography suffers from problems with resolution of the lateral wall endocardium because of the parallel orientation of the wall and the ultrasound beam. These circumflex disease detection problems are reflected in Fig. 2, which shows the sensitivities (Fig 2(a)) and specificities (Fig 2(b)) of exercise or exercise-simulating (dobutamine) stress echocardiography and perfusion scintigraphy for individual vessels as reported in three studies[11,12,18]. Comparison of regional function vs perfusion studies showed the respective sensitivities to be 83% vs 73% (P=ns) for the left anterior descending artery, 60% vs 60% (P=ns) for the left circumflex artery, and 80% vs 84% (P=ns) for right coronary disease. Specificities were 90% vs 89% (P=ns), 94% vs 95% (P=ns), and 89% vs 80% (P<0·05), respectively. The sensitivity for detection of circumflex disease vs left anterior or right coronary disease was lower for both imaging techniques (60% vs 82% for function, P<0·002 and 60% vs 78% for perfusion, P<0·01, respectively). To compensate for the variation in blood supply of the posterior wall (by either the right or circumflex artery, depending on their relative size) Marwick *et al.*[16] divided the blood supply of the heart into two systems: an anterior (left anterior descending artery) and a posterior (right and/or circumflex artery) system. Neither imaging modality was found to be superior on a regional basis; in 34 patients with only anterior system disease, the sensitivity of echocardiography was 62%, compared with 76% by scintigraphy (P=ns) and in 34 with only posterior system disease both imaging modalities had a sensitivity of 71%.

Assessment of the extent of coronary artery disease

The relative ability of echocardiography and perfusion scintigraphy to predict the extent of coronary artery disease has been investigated at two centres. In a study by Senior *et al.*[18] dobutamine stress echocardiography identified 70% of the 30 patients with multivessel coronary artery disease as having functional abnormalities in more than one coronary territory, compared with

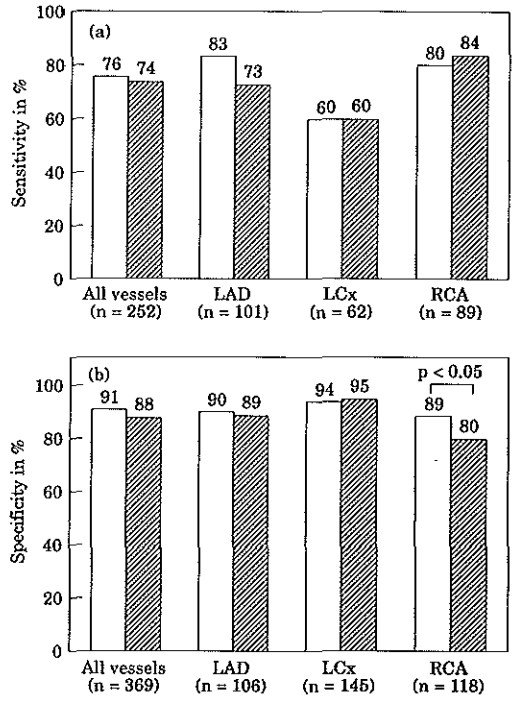


Figure 2 **(a) Sensitivity and (b) specificity of exercise or exercise-simulating (dobutamine) stress echocardiography and perfusion imaging for identification of disease in individual coronary arteries. LAD=left anterior descending coronary artery; LCx=left circumflex coronary artery; RCA=right coronary artery. Open bars, function; hatched bars, perfusion. (Reproduced with permission[44].)**

scintigrams showing a multivessel pattern in 77% (P=ns). Specificities were 90% and 94%, respectively. In 74 patients with multivessel coronary artery disease *but without prior infarction*, Marwick *et al.*[16] reported the recognition of multivessel coronary artery disease by echocardiography to be only 18%, compared with scintigrams showing a multivessel pattern in 34% (P=ns). On the other hand, echocardiography was more specific for multivessel coronary artery disease, which it predicted incorrectly in 9% of patients having single vessel coronary artery disease, compared with 19% falsely predicted as being multivessel coronary artery disease by perfusion imaging. The ability of each test to recognize multivessel coronary artery disease was also analysed by correlating the echocardiographic or perfusion extent score (calculated from the number of segments demonstrating abnormal regional function or perfusion, expressed as a percentage of the visible segments), with an angiographic score of disease extent (modified from the Gensini score). The echocardiographic and scintigraphic correlation with the angiographic score corresponded to a similar degree, with respective R values of 0·45 and 0·35. These data indicate that the imaging modalities

have similar overall accuracy for the identification of multivessel coronary artery disease, although both probably underestimate it. The underestimation of multivessel coronary artery disease by stress tests can be explained by the premature cessation of stress because of the development of limiting ischaemia in one region, imperfect assignment of myocardial regions to coronary arteries, collateral circulations, anatomically significant but functionally non-significant lesions, and (for perfusion imaging) diffuse hypoperfusion.

Combination of stress echocardiography and perfusion scintigraphy

The roles of functional and perfusion imaging might potentially be complementary in the diagnosis of coronary artery disease. In particular, a strategy starting with echocardiography (because of the lower cost) followed by the addition of perfusion scintigraphy in subgroups of patients seems attractive. Two studies have analysed the usefulness of the addition of perfusion scintigraphy to echocardiography. Both Marwick *et al.*[16] and Senior *et al.*[18] found that the addition of perfusion scintigraphy to all echocardiographic studies negative for ischaemia maximized sensitivity (from 72% to 89% and from 93% to 98%, respectively), but compromised the specificity markedly (from 83% to 52% and from 94% to 71%) by combining the false positives of each methodology. In these two studies, additional perfusion studies were required in 47% and 31% of the patients, respectively. Clearly, this option is therefore not feasible on grounds of cost or results.

A more attractive alternative is to add perfusion studies to those echocardiographic tests in which the yield is most likely to be the highest, for example, in patients with submaximal dobutamine stress, since perfusion scintigraphy is known to be less compromised by submaximal stress[34,35]. Only Marwick *et al.*[16] looked at this option and found that with the addition of perfusion scintigraphy only to negative, submaximal echocardiography studies (14% of the patients) sensitivity increased from 72% to 80% and specificity decreased from 83% to 77%. Their definition of submaximal stress was the presence of β-blocking drugs or failure to attain the maximal dobutamine dose. The option of addition of perfusion scintigraphy to echocardiography in studies simply not reaching target heart rate (or a target rate-pressure product) was not examined. Such a strategy may, perhaps, improve the results of combining the two techniques.

Stress echocardiography versus perfusion scintigraphy — a probabilistic approach

While values for sensitivity and specificity have a useful role in comparing tests, the use of these investigations in diagnostic practice is to assist in the clinical recognition of coronary artery disease. In this sense, tests are used to reclassify the initial clinical impression of the probability of coronary artery disease into high-, low-, and intermediate-risk subgroups. According to Bayes' theorem, the likelihood of a positive test result is determined by the probability of coronary artery disease in the patient studied, as well as the accuracy of the test. A comparison of tests using probability analysis permits examination of their performance in groups with various pretest likelihoods of coronary artery disease.

We performed such an analysis in 223 patients without a previous myocardial infarction, studied with dobutamine echocardiography and technetium-99m perfusion imaging[30]. The pre-test and post-test probability of coronary artery disease (derived from the pre-test probability and the likelihood ratios calculated from values for sensitivity and specificity) were estimated in all patients. The population was grouped into those at high- (>80%), intermediate- (10-80%) and low-probability (<10%) of coronary artery disease, before and after the performance of each test, and the ability of each test to restratify patients was analysed. According to the pre-test likelihood of coronary artery disease, 68 patients (30%) were regarded as having a low- or high-probability of coronary artery disease. By application of Bayes' theorem, echocardiography defined 121 patients (54%) as being in the high or low post-test probability groups, compared with 97 (43%) using perfusion scintigraphy ($P<0{\cdot}05$), thus leaving more patients in the intermediate-probability group after scintigraphy. Importantly, the accuracy of predicting coronary artery disease in the high-probability group, and the absence of coronary artery disease in the low-probability group was similar for echocardiography (105/121, 87%) and scintigraphy (88/97, 91%).

Conclusions

This review has concentrated on the direct comparisons of stress myocardial perfusion imaging and echocardiography for diagnostic purposes. Some features of stress testing with echocardiography and perfusion scintigraphy are comparable, for example, their accuracy for the diagnosis of coronary artery disease, and their ability to identify the site (and to a lesser degree, the extent) of coronary artery disease. Both techniques also have their strong and weak points. Echocardiography requires less equipment (and costs less) than perfusion scintigraphy. However, at the present state of development, stress echocardiography is highly operator dependent. Irrespective of other considerations, if there is limited local expertise in stress echocardiography, its use in preference to the nuclear techniques is highly inappropriate. However, once the condition of adequate training is fulfilled, we believe that the selection of one or other test should be tailored to clinical circumstances rather than be a uniform decision. To this end, we propose the following guidelines.

Perfusion imaging is more useful in:
(1) Patients with poor echocardiographic windows.
(2) Patients requiring vasodilator stress (those unable to exercise and with contraindications to dobutamine testing).

Echocardiography is more useful in:
(1) Patients requiring dobutamine stress (those unable to exercise and with contraindications to vasodilator testing).
(2) Patients in whom safety is a major concern (potentially unstable or severely ischaemic). Using echocardiography, ischaemia may be observed on-line and the appropriate action taken.
(3) Studies being performed to assess the adequacy of therapy — as echocardiography visualizes ischaemia rather than perfusion heterogeneity, and provides an additional index of disease severity by measuring the ischaemia-free stress time.
(4) Patients with a suspicion of significant valvular, myocardial or pericardial components to their presentation.
(5) Patients with coronary stenosis of questionable functional significance.
(6) Patients with left ventricular hypertrophy or left bundle branch block. Stress echocardiography seems to be more specific than perfusion scintigraphy in these situations (although these data await confirmation).

The combination of echocardiography and perfusion scintigraphy cannot be recommended because of cost constraints. However, as particular features of stress testing have been identified in which echocardiography is inaccurate (submaximal stress), it may be useful to perform stress echocardiography as the procedure of choice, with the ability to inject technetium-99m in such circumstances. This option has become feasible only with the availability of technetium-99m, which does not undergo redistribution, and is a potentially cost-efficient strategy.

Future developments

Important technical improvements are expected in the near future (some of which are already available) in both echocardiography and perfusion imaging, that will probably require the reassessment of the relative role of the two imaging modalities.

The assessment of stress echocardiography has been mainly visual (semiquantitative), potentially leading to low reproducibility, especially if the studies are read by investigators of different institutions[36]. Edge detection based on backscatter analysis and acoustic quantification[37] with colour coding for the assessment of the time course of endocardial motion, tissue Doppler imaging[38,39], and the use of contrast agents[40], will hopefully enhance the ability to characterize and quantify wall motion in the near future, and may provide a new and more reproducible approach to stress echocardiography. Contrast echocardiography may eventually offer a means of evaluating both myocardial perfusion and function using the same technique, at both rest and stress. Finally, the role of three dimensional echocardiography has to be explored.

Perfusion scintigraphy also has a great potential for improvement due to some new technical developments. The use of multiple headed gamma cameras will reduce the acquisition time and improve spatial resolution. Likewise, the examination of left ventricular function (with first-pass studies) and perfusion after the same injection of technetium-99m-labelled radiotracers, and the use of new algorithms for the attenuation correction using transmission scans[41] are factors that will strengthen the information obtainable from scintigraphic studies.

It is very difficult to forsee the 'winner' among the different available imaging methods, in this era of very rapid developments. New techniques (e.g. coronary magnetic resonance angiography[42] and electron beam tomography[43]) that are not yet in routine practice permit non-invasive imaging of the coronary artery and although it is unlikely they will replace stress imaging, they will hopefully assist in evaluating patients in whom interpretation of stress imaging is difficult.

References

[1] Nesto RW, Kowalchuck GJ. The ischemic cascade: Temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. Am J Cardiol 1987; 57: 23C–7C.
[2] Leppo JA, Meerdink DA. Comparison of the myocardial uptake of a technetium-labeled isonitrile analogue and thallium. Circ Res 1989; 64: 632–9.
[3] Gould KL. Noninvasive assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilation. I. Physiologic basis and experimental validation. Am J Cardiol 1978; 41: 267–78.
[4] Armstrong WF. Echocardiography in coronary artery disease. Progr Cardiovasc Dis 1988; 30: 267–88.
[5] Poldermans D, Fioretti PM, Forster T *et al.* Dobutamine stress echocardiography for assessment of perioperative cardiac risk in patients undergoing major vascular surgery. Circulation 1993; 87: 1506–12.
[6] Ruffolo RR Jr. The pharmacology of dobutamine. Am J Med Sci. 1987; 294: 244–8.
[7] 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– 51.
[8] 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: 720–7.
[9] 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: 1026–31.
[10] Wann LS, Faris JV, Childress RH, Dillon JC, Weyman AE, Feigenbaum H. Exercise cross-sectional echocardiography in ischemic heart disease. Circulation 1979; 60: 1300–8.

[11] Hecht HS, Debord L, Shaw R *et al.* Supine bicycle stress echocardiography versus tomographic thallium-201 exercise imaging for the detection of coronary artery disease. J Am Soc Echocardiogr 1993; 6: 177–85.
[12] 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: 350–5.
[13] 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: 1609–16.
[14] 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.
[15] 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: 889–94.
[16] Marwick T, D'Hondt A, Baudhuin T *et al.* 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: 159–67.
[17] Forster T, McNeill AJ, Salustri A *et al.* 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: 1591–6.
[18] 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: 713–18.
[19] Van Train KF, Maddahi J, Berman DS *et al.* and Participants of the Multicenter Trial. Quantitative analysis of tomographic stress thallium-201 myocardial scintigrams: A multicenter trial. J Nucl Med 1990; 31: 1168–79.
[20] Berne RM. The role of adenosine in the regulation of coronary blood flow. Circ Res 1980; 47: 807–13.
[21] Fitzgerald GA. Dipyridamole. N Engl J Med 1987; 316: 1247–56.
[22] Wilson RF, Wyche K, Christensen BV, Zimmer S, Laxson DD. Effects of adenosine on human coronary arterial circulation. Circulation 1990; 82: 1595–606.
[23] Flameng W, Wunsten B, Schaper W. On the distribution of myocardial blood flow: II. Effects of arterial stenosis and vasodilation. Basic Res Cardiol 1974; 69: 435–6.
[24] Demer L, Gould KL, Kirkeeide R. Assessing stenosis severity: Coronary flow reserve, collateral function, quantitative coronary arteriography, positron imaging, and digital subtraction angiography: A review and analysis. Prog Cardiovasc Dis 1988; 30: 307–22.
[25] 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: 345–54.
[26] Nguyen T, Heo J, Ogilby JD, Iskandrian AS. Single photon emission computed tomography with thallium-201 during adenosine-induced coronary hyperemia: correlation with coronary arteriography, exercise thallium imaging and two-dimensional echocardiography. J Am Coll Cardiol 1990; 16: 1375–83.
[27] Amanullah AM, Bevegard S, Lindvall K, Aasa 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: 983–9.
[28] 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: 417–20.
[29] Simonetti I, Rezai K, Rossen JD *et al.* Physiological assessment os sensitivity of noninvasive testing for coronary artery disease. Circulation 1991; 83 (Suppl III): III-43–III-49.
[30] 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.
[31] 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: 1216–22.
[32] Kumar EB, Steel SA, Howey S, Caplin JL, Aber CP. Dipyridamole is superior to dobutamine for thallium stress imaging: a randomised crossover study. Br Heart J 1994; 71: 129–34.
[33] Takeuchi M, Araki M, Nakashima Y, Kuroiwa A. Comparison of dobutamine stress echocardiography and stress thallium-201 single-photon emission computed tomography for detecting coronary artery disease. J Am Soc Echocardiogr 1993; 6: 593–602.
[34] Marwick TH, D'Hondt AM, Mairesse GH *et al.* Comparative ability of dobutamine and exercise stress in inducing myocardial ischemia in active patients. Br Heart J 1994; 72: 31–8.
[35] Elhendy A, Geleijnse ML, Roelandt JRTC *et al.* Dobutamine-induced hypoperfusion without transient wall motion abnormalities: Less severe ischemia or less severe stress? J Am Coll Cardiol 1996; 27: 323–9.
[36] 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: 330–6.
[37] Yvorchuk KJ, Davies RA, Chang KL. Measurement of left ventricular ejection fraction by acoustic quantification and comparison with radionuclide angiography. Am J Cardiol 1994; 74: 1052–6.
[38] 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: 441–58.
[39] Uematsu M, Miyatake K, Tanake N *et al.* Myocardial velocity gradient as a new indicator of regional left ventricular contraction: detection by a two-dimensional tissue Doppler imaging technique. J Am Coll Cardiol 1995; 26: 217–23.
[40] 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: 1440–3.
[41] Jaszczak RJ, Gilland DR, Hanson MW, Jang S, Greer KL, Coleman RE. Fast transmission CT for determining attenuation maps using a collimated line source, rotable air-copper-lead attenuators and fan-beam collimation. J Nucl Med 1993; 34: 1577–86.
[42] Manning WJ, Li W, Edelman RR. A preliminary report comparing magnetic resonance coronary angiography with conventional angiography. N Engl J Med 1993; 328: 828–32.
[43] Simons BD, Schwartz RS, Edwards WD, Sheedy PF, Breen JF, Rumberger JA. Noninvasive definition of anatomic coronary artery disease by ultrafast computed tomographic scanning: A quantitative pathologic comparison study. J Am Coll Cardiol 1992; 20: 1118–26.
[44] Marwick TH. Cardiac stress testing and imaging. A clinician's guide. New York: Churchill Livingstone, 1996.

Chapter 3

Dobutamine-induced hypoperfusion without transient wall motion abnormalities: less severe ischemia or less severe stress?

Elhendy A, Geleijnse ML, Roelandt JRTC,
Van Domburg RT, TenCate FJ, Cornel JH,
Reijs AEM, El-Said GM, Fioretti PM

J Am Coll Cardiol 1996; 27: 323-329

Dobutamine-Induced Hypoperfusion Without Transient Wall Motion Abnormalities: Less Severe Ischemia or Less Severe Stress?

ABDOU ELHENDY, MD, PhD, MARCEL L. GELEIJNSE, MD, JOS R. T. C. ROELANDT, MD, FACC, RON T. VAN DOMBURG, MSc, FOLKERT J. TENCATE, MD, FACC, JAN H. CORNEL, MD, AMBROOS E. M. REIJS, MSc, GALAL M. EL-SAID, MD, FACC, PAOLO M. FIORETTI, MD, PhD

Rotterdam, The Netherlands

Objectives. This study sought to compare the clinical characteristics, hemodynamic response and severity of ischemia in patients with coronary artery disease and reversible perfusion defects on dobutamine 2-methoxy isobutyl isonitrile (MIBI) single-photon emission computed tomography (SPECT) with or without transient wall motion abnormalities.

Background. The occurrence of reversible perfusion defects without concomitant wall motion abnormalities in patients with coronary artery disease was attributed to less severe ischemia. However, little data are available to support this observation.

Methods. Fifty-four consecutive patients with significant coronary artery disease and reversible perfusion defects on dobutamine (up to 40 μg/kg body weight per min) MIBI SPECT were studied (mean [±SD] age 59 ± 11 years; 38 men, 16 women). All patients underwent simultaneous echocardiography. The myocardium was divided into six matched segments, and ischemic perfusion score was quantitatively derived in myocardial segments with reversible defects.

Results. New or worsening wall motion abnormalities occurred in 40 patients (74%) (group A) and were absent in 14 (26%) (group B). There was no significant difference between the two groups with respect to age, previous myocardial infarction, number of abnormal coronary arteries (1.8 ± 0.8 vs. 1.6 ± 0.9), number of reversible perfusion defects (1.6 ± 0.9 vs. 1.8 ± 0.7) or ischemic perfusion score (412 ± 750 vs. 526 ± 553). Patients in group A had a higher prevalence of male gender (80% vs. 43%, $p < 0.01$), higher peak systolic blood pressure (147 ± 30 vs. 127 ± 31 mm Hg, $p < 0.05$), higher peak rate-pressure product (19,632 ± 4,081 vs. 16,939 ± 4,344, $p < 0.01$) and a higher prevalence of angina (53% vs. 14%) and ST segment depression (55% vs. 14%) than group B ($p < 0.05$ for both).

Conclusions. In patients with coronary artery disease and ischemia on dobutamine MIBI SPECT, the absence of transient wall motion abnormalities is associated with a similar extent and severity of reversible perfusion defects, a lower stress rate-pressure product and a higher prevalence of female gender than patients with transient wall motion abnormalities. Mechanically silent ischemia should not be regarded as a marker of less severe ischemia on myocardial perfusion scintigraphy.

(J Am Coll Cardiol 1996;27:323–9)

The diagnosis of myocardial ischemia relies on the detection of different pathophysiologic sequelae of coronary artery disease. These include reversible hypoperfusion and wall motion abnormalities, ST segment depression and typical anginal pain (1–3). Reversible perfusion and wall motion abnormalities during exercise or pharmacologic stress testing are the most accurate markers of myocardial ischemia in patients referred for evaluation of coronary artery disease (1–14). It has been demonstrated that hypoperfusion precedes the occurrence of wall motion abnormalities in the ischemic cascade (15,16). The severity of myocardial ischemia assessed by thallium scintigraphy has been reported to determine the occurrence or absence of concomitant transient wall motion abnormalities during a dobutamine stress test (17). If this is confirmed by other studies, a combination of reversible perfusion defects and transient wall motion abnormalities would identify patients with severe ischemia and provide additional data for the management and prognostic stratification of patients with coronary artery disease. The present study sought to compare the clinical, hemodynamic and scintigraphic variables in patients with coronary artery disease and reversible perfusion defects on dobutamine 2-methoxy isobutyl isonitrile (MIBI) single-photon emission computed tomography (SPECT), with and without transient wall motion abnormalities, on simultaneous echocardiography.

Methods

Patient selection. The study included 54 consecutive patients with chest pain and inability to perform an adequate exercise test who were referred to our cardiac stress imaging laboratory for dobutamine stress echocardiography in conjunction with MIBI SPECT myocardial perfusion imaging. All

From the Thoraxcenter and Department of Nuclear Medicine, University Hospital Rotterdam-Dijkzigt and Erasmus University, Rotterdam, The Netherlands. This study was supported in part by the Department of Cardiology, Cairo University Hospital, Cairo, Egypt, and the Dutch Heart Foundation, Den Haag, The Netherlands, by Grant NHS 94.135.

Manuscript received June 13, 1995; revised manuscript received September 7, 1995, accepted September 15, 1995.

Address for correspondence: Dr. Paolo M. Fioretti, Thoraxcenter, Ba 300, 3015 GD Rotterdam, The Netherlands.

patients fulfilled the following criteria: the presence of reversible perfusion defects on MIBI SPECT in the vascular territory of one or more stenotic coronary arteries and adequate imaging quality (mean [±SD] age 59 ± 11 years, range 32–80; 38 men, 16 women). Thirty-one patients (57%) were receiving antianginal medications, including beta-adrenergic blocking agents in 28 (52%). Thirty-seven patients (69%) had a previous myocardial infarction.

Dobutamine stress test. Dobutamine was infused through an antecubital vein starting at a dose of 10 μg/kg body weight per min and increasing by 10 μg/kg per min every 3 min to a maximum of 40 μg/kg per min. Atropine (up to 1 mg) was given in patients not achieving 85% of their age- and gender-predicted maximal heart rate (18). The electrocardiogram was monitored continuously and recorded each minute. Blood pressure was measured every 3 min. The test was interrupted if severe chest pain, ST segment depression >2 mm, significant tachyarrhythmias or a systolic blood pressure decrease >40 mm Hg occurred during the test.

Stress echocardiography. Echocardiographic images were acquired at rest and during the test and recovery. The left ventricular wall was divided into 16 segments (19) and scored using a four-point scale: 1 = normal; 2 = hypokinesia; 3 = akinesia; 4 = dyskinesia (4,5). Both wall motion and thickening were considered for analysis. Wall motion score was obtained by summation of the individual scores of the 16 segments. The diagnosis of ischemia relied on the occurrence of wall motion abnormalities in one or more normal segments or the occurrence of akinesia or dyskinesia in one or more hypokinetic segments at rest. As we previously concluded (20), ischemia was not considered if akinetic segments became dyskinetic without improvement at low dose dobutamine. The echocardiograms were recorded on videotape and digitized on optical disk (Vingmed CFM 800). Images were compared side by side in quad-screen format. Image interpretation was performed by two experienced observers without knowledge of clinical, demographic or scintigraphic data. In case of disagreement, a majority decision was achieved by adding a third investigator. We previously reported an interobserver and intraobserver agreement for dobutamine stress echocardiographic assessment in our laboratory of 91% and 92%, respectively (21).

SPECT imaging. Approximately 1 min before the termination of the stress test, an intravenous dose of 370 MBq of MIBI was administered. Stress images were acquired 1 h after termination of dobutamine infusion. For rest studies, 370 MBq of MIBI was injected at least 24 h after the stress study (8). For each study, six oblique (short-axis) slices from the apex to the base and three sagittal (vertical long-axis) slices from the septum to the lateral wall were defined. Each of the six short-axis slices was divided into eight equal segments. The interpretation of the scan was semiquantitatively performed by visual analysis assisted by the circumferential profiles analysis. Stress and rest tomographic views were reviewed in side by side pairs by an experienced observer who was unaware of the patient's clinical or echocardiographic data. A *reversible perfusion defect* was defined as a perfusion defect on stress images that partially or completely resolved at rest in two or more contiguous segments or slices. This was considered diagnostic of ischemia. A *fixed perfusion defect* was defined as a perfusion defect on stress images in two or more contiguous segments or slices that persisted on rest images. Echocardiographic and scintigraphic images were classified into six major segments: anterior, inferior, septal (subdivided into anterior and posterior), posterolateral and apical. To assess the severity of *hypoperfusion*, each of the six major left ventricular segments was scored on a four-grade scale: 0 = normal, and 3 = severely reduced or absent uptake. The *perfusion score* was derived by adding the scores of the six myocardial segments. The *visual ischemic score* was obtained by subtracting the rest score from the stress score. The *perfusion defect score* was quantitatively calculated by measuring the area between the lower limit of normal values (±2 SD) and the actual circumferential profile in six short-axis slices. The *ischemic score* was derived by subtracting the rest score from the stress score in segments with reversible defects.

Coronary angiography. Coronary angiography was performed, using the Judkins technique, within 3 months in all patients. Significant coronary artery disease was defined as a diameter stenosis ≥50% in one or more major epicardial arteries. Coronary arteries were assigned to particular myocardial segments as previously described (4).

Statistical analysis. Unless specified, data are presented as mean value ± SD. The chi-square test and Fisher exact test were used to compare differences between proportions. The Student *t* test was used for analysis of continuous data; $p < 0.05$ was considered statistically significant.

Results

Dobutamine stress test. Heart rate increased from 69 ± 12 beats/min at rest to 131 ± 18 beats/min at peak stress ($p < 0.0001$) and systolic blood pressure from 129 ± 20 mm Hg at rest to 141 ± 30 mm Hg at peak stress ($p < 0.01$).

MIBI SPECT results. Reversible perfusion defects were detected in all patients (by inclusion criteria). A total of 97 reversible defects were identified. Those were completely reversible in 53 segments (55%, 34 patients) and partially reversible in 44 (45%, 32 patients). In 30 segments, a fixed perfusion defect was detected (21 patients). Among 97 segments with a reversible defect, 8 (8%) were not associated with a significant stenosis of the related artery (7 in inferior wall, 1 in anterior septum). These defects were not included in the calculation of ischemic perfusion defect score.

Stress echocardiography. Wall motion abnormalities were detected in 35 patients (65%) at rest. New or worsening wall motion abnormalities were detected in 40 (74%). These patients comprised group A. Group B comprised 14 patients (26%) without stress-induced wall motion abnormalities. Nine patients in group B had baseline wall motion abnormalities that were confined to the infarct region in all of them. Four of these patients showed improvement of contraction in the infarct region, whereas five patients had unchanged wall

Table 1. Clinical Features and Hemodynamic Data in 54 Patients With Reversible Perfusion Defects on Dobutamine MIBI SPECT With and Without Transient Wall Motion Abnormalities

	Transient WMA Present (n = 40)	Transient WMA Absent (n = 14)
Age (yr)	61 ± 10	57 ± 12
Female gender	8 (20%)	8 (57%)*
Previous infarction	26 (65%)	11 (79%)
Beta-blocker medication	23 (58%)	5 (36%)
Rest HR (beats/min)	70 ± 13	68 ± 11
Peak HR (beats/min)	134 ± 16	125 ± 18
Rest SBP (mm Hg)	130 ± 18	128 ± 23
Peak SBP (mm Hg)	147 ± 30	127 ± 31†
Rest rate–pressure product	9,160 ± 2,553	8,765 ± 2,535
Peak rate–pressure product	19,632 ± 4,081	16,939 ± 4,344*
85% of target HR achieved	22 (55%)	4 (29%)
Angina during test	21 (53%)	2 (14%)‡
ST segment depression	17 (55%)‡	2 (14%)†

*$p < 0.01$. †$p < 0.05$. ‡In patients with interpretable electrocardiographic results. Data presented are mean value ± SD or number (%) of patients. HR = heart rate; SBP = systolic blood pressure; WMA = wall motion abnormalities.

Table 2. Echocardiographic and Angiographic Data for 54 Patients With Reversible Perfusion Defects on Dobutamine MIBI SPECT With and Without Transient Wall Motion Abnormalities

	Transient WMA Present (n = 40)	Transient WMA Absent (n = 14)
Rest WMA	26 (65%)	9 (64%)
Rest wall motion score	22 ± 6	20 ± 4
Stress wall motion score	26 ± 7	20 ± 4*
Multivessel disease	22 (55%)	5 (37%)
No. of stenotic arteries	1.8 ± 0.8	1.6 ± 0.9
LAD disease	27 (68%)	10 (71%)
LCx disease	18 (45%)	5 (36%)
RCA disease	25 (63%)	7 (50%)

*$p < 0.01$. Data presented are mean value ± SD or number (%) of patients. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery; WMA = wall motion abnormalities.

motion during dobutamine infusion. In group A, all patients had transient wall motion abnormalities in the vascular territories of one or more abnormal coronary arteries. A total of 83 ischemic segments were detected, 6 of them (7%) not in the vascular territory of an abnormal artery (3 inferior, 1 lateral, 2 anterior segments). In group B, a negative echocardiographic response was associated with a reversible perfusion defect confined to a dyssynergic segment in four patients (29%). The involved segments were hypokinetic in three patients and akinetic in one. Two of these patients had a lessening of thickening during dobutamine infusion.

Clinical characteristics and hemodynamic response. There was no significant difference between groups A and B with respect to age, previous myocardial infarction, risk factors or beta-blocker therapy. In patients with previous myocardial infarction, the infarct location was anterior in 13 (50%) in group A and 3 (27%) in group B. Patients in group B had a higher prevalence of female gender, a lower peak rate–pressure product, a lower peak systolic blood pressure, a lower incidence of angina and ST segment depression during the test (Table 1) and a trend to a lower peak dobutamine dose (37.9 ± 5.8 vs. 39.8 ± 1.6 μg/kg per min, $p = 0.06$) than group A. Systolic blood pressure increased significantly from rest to peak stress in group A ($p < 0.01$) but not in group B. Atropine was given to 20 patients in group A (50%) and 6 in group B (43%). A decrease or failure of increase of systolic blood pressure from rest to peak stress occurred in 12 patients (30%) in group A and 9 (64%) in group B ($p < 0.05$). The test was interrupted in nine patients (23%) in group A (angina in six, ST segment depression in three) and in three (21%) (all with angina) in group B (p = NS). Twenty-two patients in group A (55%) and four in group B (29%) achieved 85% of the maximal exercise heart rate predicted for age and gender ($p = 0.09$).

Echocardiographic, angiographic and scintigraphic data. There was no significant difference between groups with respect to prevalence of multivessel disease, number and distribution of abnormal coronary arteries or rest wall motion score. Peak wall motion score was higher in group A. The number of reversible perfusion defects as well as stress, rest and ischemic perfusion scores was not different between groups (Table 2). The distribution of reversible defects in the six segments was similar (Table 3), except for a higher prevalence of anterior defects in group B ($p < 0.01$). Inclusion in group A of the five patients of group B who had unchanged wall motion during dobutamine infusion did not change the comparable variables of reversible hypoperfusion in the two groups.

All patients with left bundle branch block (n = 6) and left ventricular hypertrophy (n = 3) had transient wall motion abnormalities. Scintigraphic and echocardiographic images of a patient in group A are shown in Figure 1.

Table 3. Distribution of Reversible Perfusion Defects and Perfusion Defect Score in 54 Patients With and Without Transient Wall Motion Abnormalities

	Transient WMA Present (n = 40)	Transient WMA Absent (n = 14)
Anterior	10 (25%)	9 (64%)
Inferior	18 (45%)	6 (36%)
Posterolateral	8 (20%)	1 (7%)
Anterior septum	8 (20%)	4 (29%)
Posterior septum	9 (23%)	3 (21%)
Apex	11 (28%)	3 (21%)
No. of reversible defects	1.6 ± 0.9	1.8 ± 0.7
Rest perfusion defect score	1,032 ± 1,286	600 ± 559
Stress perfusion defect score	1,362 ± 1,642	1,135 ± 988
Quantitative ischemic score	412 ± 750	526 ± 553
Visual ischemic score	3.5 ± 2	3.8 ± 1.2

*$p < 0.01$. Data presented are mean value ± SD or number (%) of patients. WMA = wall motion abnormalities.

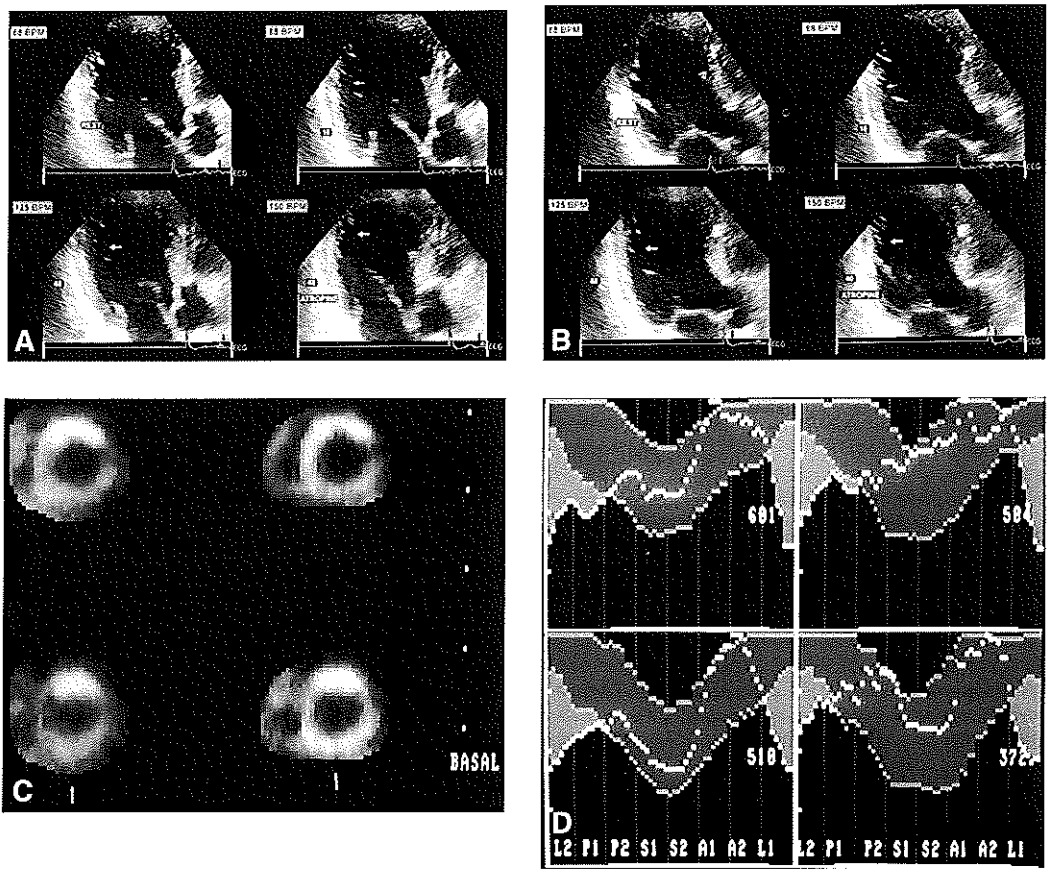


Figure 1. Diastolic (A) and systolic (B) echocardiographic frames from the apical long-axis view in a 56-year old man with left circumflex coronary artery disease, an old inferior myocardial infarction and exertional chest pain. At baseline, low dose dobutamine (10 μg/kg per min), high dose dobutamine (40 μg/kg per min) and atropine show hypokinesia of the posterior wall at rest deteriorating to akinesia at high dose and atropine images (arrows). Simultaneous perfusion scintigraphic image in the basal short-axis slice (C) and the corresponding circumferential profile (D) in the same patient show a defect in the posterolateral wall (arrows) at stress image (right) that was reversible at rest image (left). A = anterior; BPM = beats per minute; ECG = electrocardiogram; L = lateral; P = posterior; S = septal; 1 to 2 = clockwise division of segments in short-axis slices.

Variables associated with female gender. A negative response on the stress echocardiogram was obtained in 8 (50%) of 16 women and 6 (16%) of 38 men ($p < 0.01$). The following variables were not different between women and men: age (62 ± 13 vs. 58 ± 9 years), rest wall motion score (19.7 ± 4.5 vs. 22.7 ± 5.9), peak systolic blood pressure (140 ± 28 vs. 142 ± 32 mm Hg), rate–pressure product (17,403 ± 4,385 vs. 19,210 ± 4,384, $p = 0.2$), number of abnormal coronary arteries (1.5 ± 0.9 vs. 1.8 ± 0.8, $p = 0.2$) and number of reversible defects (1.8 ± 0.8 vs. 1.6 ± 0.9). Male gender was associated with a higher peak heart rate (135 ± 15 vs. 124 ± 16 beats/min, $p < 0.05$), peak wall motion score (25.6 ± 7 vs. 21.2 ± 0.5, $p < 0.05$), and prevalence of multivessel disease (61% vs. 25%, $p < 0.05$); a trend to a higher prevalence of previous infarction (76% vs. 50%, $p = 0.06$); and a higher stress perfusion score (1,609 ± 1,590 vs. 598 ± 937, $p < 0.05$), rest score (1,132 ± 1,212 vs. 416 ± 832, $p < 0.05$) and ischemic score (554 ± 795 vs. 181 ± 172, $p < 0.05$) than was female gender.

Beta-blocker therapy. There was no significant difference between patients with and those without beta-blocker therapy with regard to age, gender, extent of coronary artery disease, prevalence of ischemia on echocardiography or quantitative perfusion defect score. Patients taking beta-blockers had a lower peak heart rate (126 ± 17 vs. 139 ± 15 beats/min, $p < 0.01$), a lower peak rate–pressure product (17,869 ± 4,250 vs. 20,116 ± 3,706, $p < 0.05$) and a higher maximal dobutamine

dose (40 ± 0 vs. 37 ± 6 μg/kg per min, $p < 0.05$) than those not taking beta-blockers. Among patients receiving beta-blockers, peak heart rate was higher in group A than in group B (130 ± 18 vs. 108 ± 16 beats/min, $p < 0.05$).

Discussion

Identification of stress test variables associated with more severe ischemia is important in the management and prognostic stratification of patients with coronary artery disease, especially in the presence of equivocal indications for revascularization (22). The echocardiographic method of evaluation of wall motion during a stress test used in clinical practice depends on a semiquantitative visual evaluation with a limited scoring scale of different grades of dyssynergy (4–12). Conversely, the detection of a reversible perfusion defect with the relatively automated myocardial SPECT imaging is assisted by quantitative analysis of perfusion defect size. Theoretically, this can explain the lack of stress-induced wall motion abnormalities in patients with reversible hypoperfusion on the basis of less severe flow malperfusion and presumably less severe ischemia (14). Therefore, it is important to determine whether the absence of inducible wall motion abnormalities identifies a population with different clinical characteristics and extent and severity of ischemia, different hemodynamic response to dobutamine or extent of coronary artery disease.

The results of our study are derived from a symptomatic patient cohort with coronary artery disease and reversible defects on dobutamine perfusion scintigraphy. The data show that the presence or absence of transient wall motion abnormalities in conjunction with a reversible perfusion defect is not related to the severity of ischemia assessed by quantitative MIBI SPECT imaging. The absence of transient wall motion abnormalities correlated with a lower peak rate–pressure product, impaired systolic blood pressure response at peak stress and higher prevalence of female gender. The lower rate–pressure product in the group with a negative response on echocardiography can be explained by the occurrence of hypoperfusion earlier than wall motion abnormalities in the ischemic cascade (15,16). Consequently, diagnostic techniques dependent on the detection of wall motion abnormalities may be more vulnerable to a submaximal stress than with perfusion imaging techniques (12). The association between transient wall motion abnormalities and a higher prevalence of ST segment depression or angina, or both, during stress may be explained by the late occurrence of angina and ST segment depression after impairment of perfusion and function in the ischemic cascade (15,16,23). Because the latter stops before the occurrence of mechanical dysfunction in patients without transient wall motion abnormalities, these patients were more likely to have less angina and ST segment depression. There was a higher prevalence of reversible perfusion defects in the anterior wall in patients with than without transient wall motion abnormalities, which may result from the difficulties in delineation of the entire endocardium of the anterior wall in the apical two-chamber view. The apparent trend to a higher rest wall motion and perfusion defect score in patients with transient wall motion abnormalities may be related to the relatively higher prevalence of anterior myocardial infarction in the former group. All patients with left bundle branch block or left ventricular hypertrophy had a positive echocardiographic study response. This is not surprising, because diagnostic problems in this cohort were described with scintigraphy (24,25) and not with echocardiography, which was reported to be more accurate in patients with than without left ventricular hypertrophy (11).

Comparison with previous studies. To our knowledge, this is the first study to evaluate severity of myocardial ischemia in patients with reversible perfusion defects in the presence or absence of simultaneous transient wall motion abnormalities during stress testing. Coma-Canella et al. (17) studied patients after recent myocardial infarction by dobutamine stress with radionuclide angiography and thallium-201 SPECT on two separate days. They concluded that mild to moderate ischemia on the basis of visual analysis of reversible thallium defects is compatible with improvement or no change of regional function, whereas severe ischemia results in worsening of function. Unlike radionuclide angiography, echocardiography allows tomographic evaluation of both endocardial excursion and wall thickening, improving the detection of mechanical dysfunction. The difference between the two studies may be explained by the tomographic assessment of wall motion and quantitative assessment of perfusion in our study.

Accuracy of dobutamine stress testing in women. Despite the finding that exercise perfusion scintigraphy is more accurate than electrocardiography in women (26), there are some inherent diagnostic problems of perfusion scintigraphy in women, including false positive test results caused by a shifting breast artifact. In our study, women had a higher incidence of negative responses on echocardiography, a lower peak heart rate, a lower peak wall motion score and a lower ischemic perfusion defect score. It cannot be precisely concluded whether these findings are related to the lower prevalence of multivessel disease, a lower peak heart rate or a difference in inducibility or detection of wall motion abnormalities in women. It has been reported (27) that exercise echocardiography is an accurate method for the diagnosis of coronary artery disease in women. Because the predicted maximal exercise heart rate is higher in men than women at a given age (28), a similar calculation of maximal heart rate during dobutamine stress testing may not be appropriate for women undergoing dobutamine stress echocardiography, where the detection of ischemia may be critically dependent on heart rate increment.

Accuracy of dobutamine stress testing at various levels of stress. Previous studies have shown that a submaximal dobutamine stress test response, defined as a test in patients receiving beta-blockers or unable to complete the standard protocol, is associated with reduced sensitivity of echocardiography, whereas the effect on sensitivity of perfusion scintigraphy is less prominent (11,12). Because the dobutamine stress test is an exercise-simulating stress modality, a significant

increase in rate–pressure product is required to yield a high accuracy, especially for the detection of abnormal wall motion. We previously showed (29) that in an unselected patient cohort with suspected myocardial ischemia who underwent dobutamine stress echocardiography with simultaneous MIBI SPECT, the addition of MIBI study results to echocardiographic study results that are negative for ischemia at submaximal testing was particularly useful for the prediction of cardiac events.

Effect of beta-blockers. In our study, the prevalence of ischemia detected at echocardiography was not different with or without beta-blocker therapy. This may be a result of the adminstration of atropine, which was reported to increase sensitivity, particularly in patients receiving beta-blockers (30), and of the higher dobutamine dose in patients receiving beta-blockers, which may compensate for the lower rate–pressure product by exerting a greater positive inotropic effect. Additionally, in patients receiving beta-blockers, peak heart rate was higher in patients with than without ischemia on echocardiography.

Role of systolic blood pressure response. High dose dobutamine infusion induces myocardial ischemia by increasing metabolic demand through an increase in heart rate and myocardial contractility (31–33). Coronary vasodilation and flow heterogeneity result from the increased myocardial demand and a weak vasodilator effect (33). The effect of dobutamine on systolic blood pressure is influenced by mechanisms related to contractility and systemic vascular resistance (34). Therefore, the importance of a systolic blood pressure response in the attainment of an adequate stress test level has not been proved. An interesting finding of our study is that patients with negative echocardiographic responses had an impaired systolic blood pressure response in contrast to those with positive responses. This difference is unlikely to be related to myocardial ischemia because in this situation, an impaired systolic blood pressure response is expected to occur in the group with rather than without mechanical dysfunction. Conversely, an impaired systolic blood pressure response is most likely the reason for a negative echocardiographic response and can be explained by a possible predominant peripheral vasodilator response in these particular patients. The role of a systolic blood pressure response is supported by the reported findings of a significant increase in systolic blood pressure with dobutamine, even comparable to that obtained with exercise in some studies (7,35). Echocardiography was reported to have good sensitivity, comparable to that of perfusion scintigraphy, when used with stress modalities associated with heart rate and systolic blood pressure increases, such as exercise (1,2) and dobutamine (8,9), whereas sensitivity is low compared with that for perfusion scintigraphy when applied with vasodilator stress testing with dipyridamole (36), in which there is a mild increase in heart rate during which systolic blood pressure either decreases or does not change. For echocardiographic imaging, the sensitivity of dobutamine and exercise was found to be higher than that of dipyridamole (37). It can be postulated that in particular patients, a modest but critical increment in systolic blood pressure during dobutamine infusion is required to increase the left ventricular wall stress and result in subendocardial ischemia and deterioration of function that can be detected by visual assessment. This may not be as critical for reversible hypoperfusion that occurs at a lower stress level.

Limitations of the study. The number of patients with negative echocardiographic responses was small. The patient cohort was heterogeneous and included some patients with a previous myocardial infarction. However, only one patient had a negative echocardiographic study response and a reversible perfusion defect confined to an akinetic segment. Assessment of the severity of ischemia by perfusion scintigraphy may have some pitfalls because the latter detects flow malperfusion as well as true ischemia. Difference in perfusion may be attenuated in patients with multivessel disease (17). Finally, some patients were receiving medications, including beta-blockers. Nevertheless, we previously showed (30) that the addition of atropine increases the sensitivity of dobutamine echocardiography, especially in patients receiving beta-blockers.

Clinical implications. Because a lower peak rate–pressure product correlated with a negative dobutamine echocardiographic test response in patients with reversible perfusion defects, great attention should be given to achieving a higher product in patients undergoing dobutamine stress echocardiography alone. This may include stopping beta-blockers and implementing a stress protocol aimed at the attainment of a higher heart rate, including atropine administration (18,30) or the use of a longer dobutamine infusion time (38). The occurrence of mechanically silent ischemia manifested as reversible perfusion defects without transient wall motion abnormalities should be disregarded in the management of patients with coronary artery disease as a marker of less severe ischemia as assessed by myocardial perfusion scintigraphy.

We are grateful to René Frowyn, MSc and Joyce Postma-Tjoa, MSc for their invaluable technical assistance.

References

1. Salustri A, Pozzoli MM, Hermans W, et al. Relationship 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.
2. Quinones MA, Verani MS, Haichin RM, Mahmarian JJ, Suarez J, Zoghbi WA. Exercise echocardiography versus Tl-201 single photon emission computed tomography in evaluation of coronary artery disease. Analysis of 292 patients. Circulation 1992;85:1026–31.
3. Mahmarian JJ, Pratt CM, Cocaonugher MK, Verani MS. Altered myocardial perfusion in patients with angina pectoris or silent ischemia during exercise as assessed by quantitative thallium-201 single photon emission computed tomography. Circulation 1990;82:1305–15.
4. Sawada SG, Segar DS, Ryan T, et al. Echocardiographic detection of coronary artery disease during dobutamine infusion. Circulation 1991;83: 1605–14.
5. Salustri A, Fioretti PM, Pozzoli MMA, McNeill AJ, Roelandt JRTC. Dobutamine stress echocardiography: its role in the diagnosis of coronary artery disease. Eur Heart J 1992;13:70–7.
6. Segar DS, Brown SE, Sawada SG, Rayan T, Feigenbaum H. Dobutamine stress echocardiography: correlation with coronary lesion severity as determined by quantitative angiography. J Am Coll Cardiol 1992;19:1197–202.

7. Berthe C, Pierard LA, Hiernaux M, et al. Predicting the extent and location of coronary artery disease in acute myocardial infarction by echocardiography during dobutamine infusion. Am J Cardiol 1986;58:1167–72.
8. Forster T, McNeill AJ, Salustri A, et al. Simultaneous dobutamine stress echocardiography and technetium-99m isonitrile single-photon emission computed tomography in patients with suspected coronary artery disease. J Am Coll Cardiol 1993;21:1591–6.
9. Marwick T, Willemart B, D'Hondt AM. Selection of the optimal nonexercise stress for the evaluation of ischemic regional myocardial dysfunction and malperfusion: comparison of dobutamine and adenosine using echocardiography and Tc-99m MIBI single photon emission computed tomography. Circulation 1993;87:345–54.
10. Mairesse GH, Marwick TH, Vanoverschelde J-LJ, et al. How accurate is dobutamine stress electrocardiography for detection of coronary artery disease? Comparison with two-dimensional echocardiography and technetium-99m methoxyl isobutyl isonitrile (MIBI) perfusion scintigraphy. J Am Coll Cardiol 1994;24:920–7.
11. Marwick TH, D'Hondt AM, Baudhuin T, et al. Optimal use of dobutamine stress for the detection and evaluation of coronary artery disease: combination with echocardiography, scintigraphy or both? J Am Coll Cardiol 1993;22:159–67.
12. Marwick TH, D'Hondt AM, Mairesse GH, et al. Comparative ability of dobutamine and exercise stress in inducing myocardial ischemia in active patients. Br Heart J 1994;72:31–8.
13. Hays JT, Mahmarian JJ, Cochran AJ, Verani MS. Dobutamine thallium-201 tomography for evaluating patients with suspected coronary artery disease unable to undergo exercise or vasodilator pharmacologic stress testing. J Am Coll Cardiol 1993;21:1583–90.
14. Marwick TH. Stress Echocardiography: Its Role in the Diagnosis and Evaluation of Coronary Artery Disease. Dordrecht, The Netherlands: Kluwer, 1994:167–9.
15. Nesto RW, Kowalchunck GJ. The ischemic cascade: temporal response of hemodynamic, electrocardiographic and symptomatic expression of ischemia. Am J Cardiol 1987;57:23C–7C.
16. Hauser AM, Vellappillil G, Ramos RG, et al. Sequence of mechanical, electrocardiographic and clinical effects of repeated coronary artery occlusion in human beings: echocardiographic observations during coronary angioplasty. J Am Coll Cardiol 1985;5:193–7.
17. Coma-Canella I, Gomes Martinez MV, Rodrigo F, Castro Beiras JM. The dobutamine stress test with thallium-201 single-photon emission computed tomography and radionuclide angiography: postinfarction study. J Am Coll Cardiol 1993;22:399–406.
18. McNeill AJ, Fioretti PM, El-Said EM, Salustri A, Forster T, Roelandt JRTC. Enhanced sensitivity for detection of coronary artery disease by addition of atropine to dobutamine stress echocardiography. Am J Cardiol 1992;70: 41–6.
19. Schiller NB, Shah PM, Crawford M. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. J Am Soc Echocardiogr 1989;2:358–67.
20. Arnese M, Fioretti PM, Cornel JH, Postma-Tjoa J, Reijs AEM, Roelandt JRTC. Akinesis becoming dyskinesis during high-dose dobutamine stress echocardiography: a marker of myocardial ischemia or a mechanical phenomenon? Am J Cardiol 1994;73:896–8.
21. Bellotti P, Fioretti PM, Forster T, et al. Reproducibility of the dobutamine–atropine echocardiography stress test. Echocardiography 1993;10:93–7.
22. Machecourt J, Longere P, Fagret D, Vanzetto G, Wolf JE, Polidori C. Prognostic value of thallium-201 single-photon emission computed tomographic myocardial perfusion imaging according to extent of myocardial defect. Study in 1,926 patients with follow-up at 33 months. J Am Coll Cardiol 1994;23:1096–106.
23. Elhendy A, Geleijnse ML, Roelandt JRTC, Cornel JH, Domburg RT, Fioretti PM. Stress-induced left ventricular dysfunction in silent and symptomatic myocardial ischemia during dobutamine stress test. Am J Cardiol 1995;75:1112–5.
24. DePuey EG, Guertler-Krauczynska E, Robbins WL. Thallium 201 SPECT in coronary disease patients with left bundle branch block. J Nucl Med 1988;29:1479–85.
25. DePuey EG, Guertler-Krauczynska E, Perkins JV, Robbins WL, Whelchel JD, Clements SD. Alteration in myocardial thallium 201 distribution in patients with chronic systemic hypertension undergoing single photon emission computed tomography. Am J Cardiol 1988;62:234–8.
26. Melin JA, Wijns W, Vanbutsele RJ, et al. Alternative diagnostic strategies for coronary artery disease in woman: demonstration of the usefulness and efficiency of probability analysis. Circulation 1985;71:535–42.
27. Marwick TH, Anderson T, Williams J, et al. Exercise echocardiography is an accurate and cost-efficient technique for detection of coronary artery disease in women. J Am Coll Cardiol 1995;26:335–41.
28. Sheffield LT, Maloof JA, Sawayer JA, Roitman D. Maximal heart rate and treadmill performance of healthy woman in relation to age. Circulation 1978;57:79–84.
29. Geleijnse ML, Elhendy A, Domburg RT, et al. Optimal use of dobutamine stress test for risk stratification in patients with suspected myocardial ischemia: echocardiography, scintigraphy or both? [abstract] Circulation 1994;90 Suppl(Pt 2):I-454.
30. Fioretti PM, Poldermans D, Salustri A, et al. Atropine increases the accuracy of dobutamine stress echocardiography in patients taking beta-blockers. Eur Heart J 1994;15:355–60.
31. Ruffolo RR. The pharmacology of dobutamine. Am J Med Sci 1987;294: 244–8.
32. Warltier DC, Zyvoloski M, Gross GJ, Hardman HF, Brooks HL. Redistribution of myocardial blood flow distal to a dynamic coronary arterial stenosis by sympathomimetic amines: comparison of dopamine, dobutamine and isoproterenol. Am J Cardiol 1981;48:269–79.
33. McGillem MJ, DeBoe SF, Friedman HZ, Mancini GBJ. The effects of dopamine and dobutamine on regional function in the presence of rigid coronary stenosis and subcritical impairments of reactive hyperemia. Am Heart J 1988;115:970–7.
34. Mazeika PK, Nadazin A, Oakley CM. Clinical significance of abrupt vasodepression during dobutamine stress echocardiography. Am J Cardiol 1992;69:1484–7.
35. Mazeika PK, Nadazdin A, Oakley CM. Dobutamine stress echocardiography for detection and assessment of coronary artery disease. J Am Coll Cardiol 1992;19:1203–11.
36. Perin EC, Moore W, Blume M, Hernandz G, Dhekne R, DeCastro M. Comparison of dipyridamole echocardiography with dipyridamole thallium scintigraphy for the diagnosis of myocardial ischemia. Clin Nucl Med 1991;16:417–20.
37. Dagianti A, Penco M, Agati L, et al. Stress echocardiography: comparison of exercise, dipyridamole and dobutamine in detecting and predicting the extent of coronary artery disease. J Am Coll Cardiol 1995;62:18–25.
38. Weissman NJ, Nidorf SM, Guerrero JL, Weyman AE, Picard M. Optimal stage duration in dobutamine stress echocardiography. J Am Coll Cardiol 1995;25:605–9.

Part B – Diagnostic merits

Chapter 4

Optimal pharmacological stress testing for the diagnosis of coronary artery disease: a probabilistic approach

Geleijnse ML, Marwick TH, Boersma E,

Deckers JW, Melin JA, Fioretti PM

Eur Heart J 1995; 16 (Suppl M): 3-10

Optimal pharmacological stress testing for the diagnosis of coronary artery disease: a probabilistic approach

M. L. GELEIJNSE*, T. H. MARWICK†‡, E. BOERSMA*, J. W. DECKERS*, J. A. MELIN† AND P. M. FIORETTI*

*Thoraxcenter and The Department of Nuclear Medicine, University Hospital Dijkzigt and Erasmus University Rotterdam, The Netherlands; †Divisions of Cardiology and Nuclear Medicine, Cliniques Universitaires St. Luc, University of Louvain, Brussels, Belgium

KEY WORDS: Coronary artery disease, pharmacological stress, diagnostic value, probabilistic approach.

Previous reports have suggested that dobutamine stress echocardiography compares favourably with other stress agent–imaging modality combinations for the detection of coronary artery disease. However, in daily clinical practice the value of a test is defined on a probability basis. To study the relative diagnostic contribution of clinical and dobutamine stress test variables, Bayesian analysis was performed in 223 patients with suspected coronary artery disease, who underwent coronary angiography and a high-dose dobutamine stress test in conjunction with electrocardiography, echocardiography and Technetium-99m sestamibi SPECT myocardial perfusion scintigraphy. According to the pre-test (clinical) probabilities, patients were divided into low-, intermediate- and high-risk groups; 155 patients were in the intermediate-risk group. After dobutamine stress echocardiography the number of patients in this intermediate-risk group was reduced to 102 (P<0·0001). This reduction of patients in the intermediate-risk group by echocardiography was better than perfusion scintigraphy (102 vs 126 patients, P<0·05) or classic markers of ischaemia such as angina and/or ST-segment changes (102 vs 150, P<0·0001). Moreover, there was a good correlation between the echocardiographic post-test probabilities and the true distribution of coronary artery disease.

Introduction

The diagnostic value of the different pharmacological stress agents and imaging modalities for the detection of coronary artery disease is usually presented in relation to the coronary anatomy (sensitivity, specificity and accuracy). These values reported from different institutions, differed widely within the same stress agent or imaging modality, and also when the different stress agents and imaging modalities were compared[1]. This may be explained by the influence of many factors including patient selection, stress protocol and expertise in performing and interpreting the examinations[2]. Therefore, comparisons between different stress agents or imaging modalities are most appropriate if applied in a direct, head-to-head study design. Moreover, the clinical benefit of performing an investigation needs to be placed in the clinical context of the patient. Incorporation of both clinical data and stress test results would permit the results to be expressed in a continuous quantitative manner (probability of disease) rather than in a binary fashion (having disease or not).

This paper reviews the data on the existing direct comparisons between the different stress agents and imaging modalities. In addition, it provides an example of a probabilistic (Bayesian) approach to compare different stress test variables used in conjunction with dobutamine stress, obtained from electrocardiographic, perfusion scintigraphic and echocardiographic studies.

‡Present address: Cardiology Department, Cleveland Clinical Foundation, Cleveland, Ohio, U.S.A.

Correspondence: Paolo M. Fioretti, MD, PhD, University Hospital Rotterdam-Dijkzigt, Thoraxcenter, Ba 300, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

Pharmacological stress agents and imaging modalities

Pharmacological stress testing plays an important role in the diagnosis of coronary artery disease in patients who are unable to perform an adequate exercise test. At the Thoraxcenter, Erasmus University Rotterdam, up to 23% of all stress tests are performed with pharmacological stress agents (Fig. 1). In general, the most popular pharmacological stress agents are dobutamine (an exercise simulator[3]) and dipyridamole or adenosine (vasodilators[4]). These agents act through completely different biochemical and haemodynamic mechanisms, with the same ultimate goals: the induction of blood flow heterogeneity and myocardial ischaemia in the territory dependent on a 'critical' stenosis. This blood flow heterogeneity and ischaemia may be visualized by perfusion scintigraphy and two-dimensional echocardiography, respectively.

Which is the optimal stress agent–imaging modality combination?

Reports on the sensitivity and specificity of echocardiography and scintigraphy using the different stress agents for the detection of coronary artery disease vary widely[1]. Therefore, direct comparisons are the most appropriate but these data are scarce. Reviewing the six reports on dobutamine vs dipyridamole echocardiography[5–10] (Table 1) and the two reports on

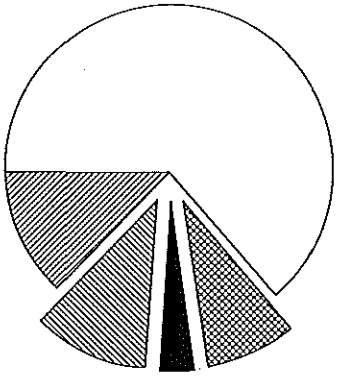


Figure 1 Distribution of the different stress test modalities performed at the Thoraxcenter Rotterdam in 1993 (n=2131). (□=Exercise ECG (n=1372); ▨=Exercise+SPECT (n=265); ▧=Pharmacological ECHO (n=236); ■=Pharmacological SPECT (n=72); ▩=Pharmacological ECHO+SPECT (n=186)).

dobutamine vs adenosine echocardiography[5–11] (Table 2), dobutamine was more sensitive (78% vs 67%, $P<0.002$ and 82% vs 52%, $P<0.0001$ respectively) and equally specific. Accepting dobutamine to be the best stress agent for echocardiography, the next step is to compare the use of this stress agent with the different imaging modalities: echocardiography and perfusion scintigraphy. In Table 3, three direct comparisons between dobutamine stress echocardiography and perfusion scintigraphy[12–14] are presented. On the basis of these reports echocardiography is more specific (85% vs 69%, $P<0.05$). Another remaining question to be answered is the value of vasodilator perfusion scintigraphy, claimed by some authors to be superior to dobutamine perfusion scintigraphy[15]. However, the existing direct comparisons between dobutamine stress echocardiography and vasodilator perfusion scintigraphy[11,16] all favour the former. In view of these comparable levels of accuracy, as well as the availability and lower cost of dobutamine stress echocardiography, we believe the latter is the optimal first line non-exercise stress–imaging

Table 1 Direct comparisons between dobutamine (40 μg kg^{-1} min^{-1}) and dipyridamole (0·84 mg kg^{-1}) echocardiography

Author	Stress	No pts	No MI pts	CAD %DS	No pts N/1V/MVD	Sens (%, 95% CI)	Spec (%, 95% CI)	Acc (%, 95% CI)	Sens (%) SVD	Sens (%) MVD
Martin[5]	dobu	40	14	≥50	15/7/18	76 (63–89)	60 (45–75)	70 (56–84)	?	?
	dipy					56 (41–71)	67 (52–81)	60 (45–75)	?	?
Salustri[6]	dobu	46	15	≥50	18/10/18	57 (43–71)	78 (66–90)	65 (51–79)	40	67
	dipy					64 (50–78)	89 (80–98)	74 (61–87)	50	72
Lanzarini[7]	dobu	80	15	≥?	23/24/33	79 (70–88)*	83 (74–91)	80 (71–89)	62	91
	dipy					60 (49–70)	96 (91–100)	70 (60–80)	33	79
Previtali[8]	dobu	35	1	≥70	7/16/12	68 (52–83)	100	74 (60–89)	50	92
	dipy					57 (41–74)	100	66 (50–81)	31	92
Boccanelli[9]	dobu	83	77	≥70	14/40/29	83 (74–91)	100	86 (78–93)	75	93
	dipy					70 (60–79)	100	75 (65–84)	60	82
Beleslin[10]	dobu	136	77	≥50	17/108/11	82 (76–89)	76 (69–84)	82 (75–88)	82	82
	dipy					74 (66–81)	94 (90–98)	76 (69–84)	72	91
All combined	dobu	420	199		94/205/121	78 (74–82)‡	81 (77–85)	79 (75–83)*	74†	86
	dipy					67 (62–71)	90 (87–93)	72 (68–76)	61	82

pts=patients; MI=myocardial infarction; CAD %DS=% diameter stenosis value for significant coronary artery disease; N=no significant CAD; 1V=one vessel disease; MVD=multivessel disease; Sens=sensitivity; 95% CI=95% confidence interval; Spec=specificity; Acc=accuracy; SVD=single vessel disease; dobu=dobutamine; dipy=dipyridamole; *=$P<0.05$; †=$P<0.01$; ‡=$P<0.002$.

Table 2 Direct comparisons between adenosine (≥0·84 mg kg^{-1}) and dobutamine (40 μg kg^{-1} min^{-1}) echocardiography

Author	Stress	No pts	No MI pts	CAD %DS	No pts N/1V/MVD	Sens (%, 95% CI)	Spec (%, 95% CI)	Acc (%, 95% CI)	Sens (%) SVD	Sens (%) MVD
Martin[5]	adeno	40	14	≥50	15/7/18	40 (25–55)†	93 (86–100)‡	60 (45–75)	?	?
	dobu					76 (63–89)	60 (45–75)	70 (56–84)	?	?
Marwick[11]	adeno	97	0	≥50	38/31/28	58 (48–67)§	87 (80–94)	69 (60–78)‡	52†	64*
	dobu					85 (77–92)	82 (74–89)	84 (76–91)	84	86
All combined	adeno	137	14	≥50	53/38/46	52 (44–61)‖	89 (83–94)	66 (58–74)‡	52†	64*
	dobu					82 (76–89)	75 (68–83)	80 (73–86)	84	86

pts=patients; MI=myocardial infarction; CAD %DS=% diameter stenosis value for significant coronary artery disease; N=no significant CAD; 1V=one vessel disease; MVD=multivessel disease; Sens=sensitivity; 95% CI=95% confidence interval; Spec=specificity; Acc=accuracy; SVD=single vessel disease; dobu=dobutamine; adeno=adenosine; *=$P<0.05$; †=$P<0.01$; ‡=$P<0.02$; §=$P<0.001$; ‖=$P<0.0001$.

Table 3 Direct comparisons between dobutamine (40 μg kg^{-1} min^{-1}) echocardiography and perfusion scintigraphy

Author	Stress	No pts	No MI pts	CAD %DS	No pts N/1V/MVD	Sens (%, 95% CI)	Spec (%, 95% CI)	Acc (%, 95% CI)	Sens (%) SVD	Sens (%) MVD
Gunalp[12]	echo	27	0	≥50	9/9/9	83 (69–76)	89 (77–100)	85 (72–99)	77	100
	mibi					94 (86–100)	89 (77–100)	93 (83–100)	88	88
Marwick[13]	echo	217	0	≥50	75/68/74	72 (66–78)	83 (78–88)‡	76 (70–82)	66	77
	mibi					76 (70–82)	67 (60–73)	73 (67–79)	74	78
Stoiber[14]	echo	53	0	≥50	26/18/9	89 (80–97)	88 (80–97)	89 (80–97)†	89	89
	mibi					70 (58–83)	69 (57–82)	70 (57–82)	83	44
All combined	echo	297	0	≥50	110/95/92	75 (70–80)	85 (80–89)*	79 (74–83)	72	80
	mibi					77 (72–82)	69 (63–75)	74 (69–79)	77	76

pts=patients; MI=myocardial infarction; CAD %DS=% diameter stenosis value for significant coronary artery disease; N=no significant CAD; 1V=one vessel disease; MVD=multivessel disease; Sens=sensitivity; 95% CI=95% confidence interval; Spec=specificity; Acc=accuracy; SVD=single vessel disease; echo=echocardiography; mibi=Technetium-99m sestamibi SPECT; *=$P<0.01$; †=$P<0.02$; ‡=$P<0.05$.

combination for the detection of coronary artery disease.

Probabilistic approach to the diagnosis of coronary artery disease

The diagnosis of coronary artery disease on the basis of history and physical examination alone is often difficult, and a stress test is frequently used as the initial non-invasive investigation in the evaluation of patients suspected of having coronary artery disease. Despite the fact that sensitivity (proportion of correctly identified patients with disease) and specificity (proportion of correctly identified patients without disease) define the strength of a stress test, the final result cannot be satisfactorily interpreted unless the pre-test probability of disease is considered. These pre-test probabilities are related to multiple clinical variables such as sex, age, and chest pain characteristics and were described by Diamond and Forrester[17] in a series of over 60 000 patients (Table 4).

The use of Bayes' theorem of conditional probability can assist in the interpretation of a test result and can also provide a meaningful estimate of the post-test probability in the individual patient. According to this theorem post-test probability is a function of pre-test probability, and the sensitivity and specificity of the test. Under the assumption of the independence of the stress test result from the clinical (pre-test) data, post-test probability can be calculated according to the following formula[18].

post odds = prior odds × likelihood ratio (LR)

where, odds = probability/(1 − probability)
LR = sensitivity/(1 − specificity) in case of a positive test
= (1 − sensitivity)/specificity in case of a negative test

So, the better (very high or very low) the likelihood ratio of the test (determined by sensitivity and specificity), the more discriminant a test is.

Table 4 Pre-test probability of CAD in patients according to age, sex and chest pain characteristics

Age (years)	Sex	Non-anginal chest pain	Atypical angina	Typical angina
30–39	M	5·2 ± 0·8	21·8 ± 2·4	69·7 ± 3·2
	F	0·8 ± 0·3	4·2 ± 1·3	25·8 ± 6·6
40–49	M	14·1 ± 1·3	46·1 ± 1·8	87·3 ± 1·0
	F	2·8 ± 0·7	13·3 ± 2·9	55·2 ± 6·5
50–59	M	21·5 ± 1·7	58·9 ± 1·5	92·0 ± 0·6
	F	8·4 ± 1·2	32·4 ± 3·0	79·4 ± 2·4
60–69	M	28·1 ± 1·9	67·1 ± 1·3	94·3 ± 0·4
	F	18·6 ± 1·9	54·4 ± 2·4	90·6 ± 1·0

For example, given a patient with a pre-test probability of disease of 40% and test sensitivity and specificity of both 90% and a positive test result, the prior odds will be 0·4/(1 − 0·4)=0·67, LR will be 0·9/(1 − 0·9)=9, and post odds will be 0·67 × 9=6. Calculating the odds back to probabilities (probability=odds/(1+odds)), the post-test probability will be 86%.

Figure 2 represents the effect of two tests with different diagnostic accuracies (test A with a low sensitivity and specificity of both 60% and test B with a high sensitivity and specificity of both 80%) on the post-test probability of disease in two patients with different pre-test probabilities. The first patient is a 55-year-old male with typical angina, while the second is a 45-year-old female with typical angina. In the first case the pre-test probability of coronary artery disease is so high (92%) that a positive response after both tests does not appreciably increase the final post-test probability (95% for test A and 98% for test B respectively). However, in the second patient, the pre-test probability of coronary artery disease is intermediate (55%). In this patient, a positive response to test A would not be of diagnostic benefit (post-test probability would increase to only 65%). On the other hand, a positive response to test B would be highly diagnostic (post-test probability would increase to 83%). Therefore, the diagnostic potential of a stress test is, as a general rule, of most help in patients

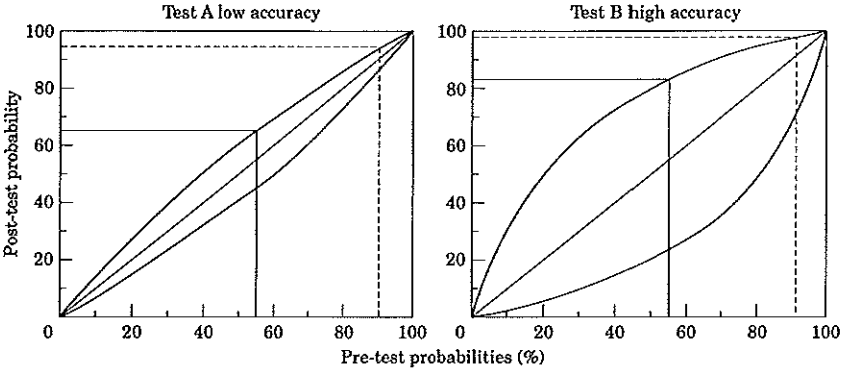


Figure 2 Schematic representation of the effect on post-test probability of two different diagnostic procedures (test A and B) with different diagnostic accuracies. Two patients (patient 1 (– – –) and 2 (——)) were studied with different pre-test probabilities (92% and 55%) of CAD. See text for explanation.

with intermediate pre-test probabilities, and so patients with very low or high pre-test probabilities should not be referred for diagnostic stress testing. This does not, of course, exclude the usefulness of performing a stress test in high-risk patients for other purposes, such as risk stratification[19].

Methods

PATIENT SELECTION

The study group included 223 patients with suspected coronary artery disease, 197 from St. Luc University Brussels and 26 from the Thoraxcenter, Erasmus University Rotterdam. None of the patients had historical or electrocardiographic evidence of previous myocardial infarction, unstable angina, cardiomyopathy, severe valvular disease, severe hypertension, ventricular hypertrophy, bundle branch block or was using digitalis. All patients underwent a high-dose dobutamine stress test in conjunction with electrocardiography, echocardiography and Technetium-99m sestamibi SPECT myocardial perfusion scintigraphy and in all patients coronary arteriography was performed within 3 months of the dobutamine stress test.

DOBUTAMINE STRESS

The dobutamine stress test was performed as previously described[13,20] in conjunction with simultaneous electrocardiography, Technetium-99m sestamibi SPECT myocardial perfusion scintigraphy and echocardiography, using a similar protocol in both centres with a maximal dobutamine dose of 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$. A test was considered abnormal in cases of chest discomfort not decreasing in intensity with increasing heart rate, 0·1 mV or more horizontal or downsloping ST-segment depression or ST-segment elevation at 60 ms after the J point, a perfusion defect or a wall motion abnormality, respectively. All test results were interpreted by experienced observers who had no knowledge of the clinical, angiographic or other test results.

CORONARY ARTERIOGRAPHY

Coronary arteriography was performed using the Judkins technique in all patients and was quantitively assessed as previously described[21,22]. A coronary artery narrowing of at least 50% diameter stenosis was considered significant.

STATISTICAL ANALYSIS

Data are expressed as mean ± SD, unless specified. Where appropriate, 95% confidence intervals are given. The calculation of sensitivity, specificity and accuracy relied on the standard definition. Paired and unpaired t-tests were performed when appropriate to compare data. A *P*-value of less than 0·05 was considered significant.

The pre-test probability of coronary artery disease was calculated according to a table using age, gender and symptoms[17]. The patient group was divided according to probability estimates, into a high-risk group defined as having a pre-test probability of >80%, an intermediate-risk group with a probability of 10% to 80%, and a low-risk group with a probability of <10%. The likelihood ratio associated with a positive test was calculated as sensitivity/(1 − specificity), and for a negative test as (1 − sensitivity)/specificity. Post-odds were calculated as the product of pre-test probability, with the likelihood ratio of a positive or negative test. Conversion to post-test probability was derived as: (post-test odds)/(1 + post-test odds).

To compare and visualize the diagnostic value of the different clinical and stress variables, we used a Receiver-Operating Characteristics curve (ROC curve). In this curve, sensitivity vs specificity of a test

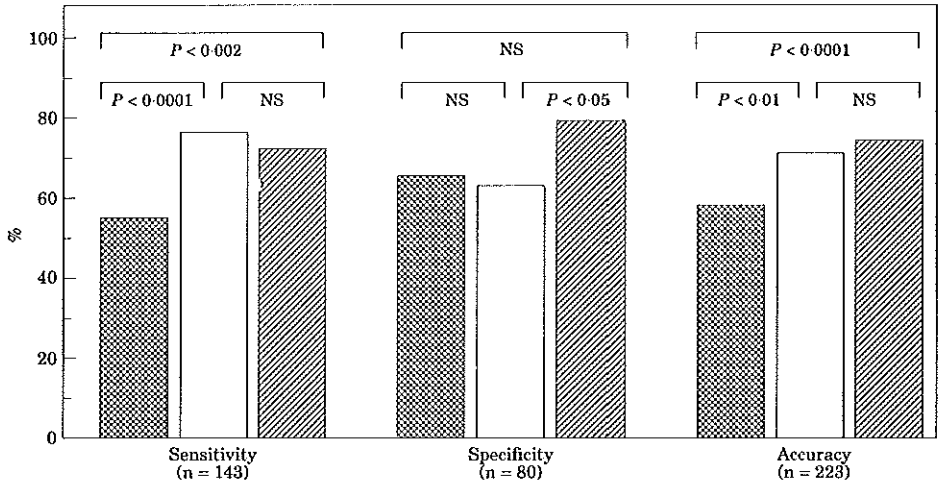


Figure 3 Results of dobutamine stress electrocardiography and/or chest pain (ECG/AP; ▨), perfusion scintigraphy (MIBI SPECT; □) and echocardiography (ECHO; ▨) for the diagnosis of CAD.

is plotted (where sensitivity is the fraction of positive classifications for all patients who satisfy the endpoint criteria and specificity is the fraction of negative classifications for all patients who satisfy the non-endpoint criteria). This curve, when generated for different tests, provides a direct comparison of results over the entire range of measurements.

Results

PATIENT CHARACTERISTICS

The study group included 153 men and 70 women, aged 58 ± 10 years. Fifty-one (23%) patients took beta-adrenoreceptor antagonists on the day of the test. The mean pre-test probability of disease, calculated for each patient on the basis of age, gender and chest pain characteristics[17] was 55 ± 28%.

DOBUTAMINE STRESS

In the overall group, dobutamine increased the heart rate from 68 ± 12 beats . min^{-1} to 112 ± 26 beats . min^{-1}. Systolic blood pressure increased from 147 ± 18 mmHg to 174 ± 25 mmHg. Peak heart rate blood pressure product was 19 522 ± 5161. Electrocardiographic evidence of ischaemia was induced in 47 (21%) patients. Angina during stress was induced in 85 (38%) patients, either ECG changes or angina were induced in 106 (48%) patients. Scintigraphic and echocardiographic markers of coronary artery disease were found in 138 (62%) and 120 (54%) patients, respectively. In five patients this diagnosis was made on the basis of a resting wall abnormality or fixed perfusion defect only (reversible perfusion defects and new or worsening wall motion abnormalities were found in 133 and 115 patients, respectively.

DETECTION OF 'SIGNIFICANT' CORONARY ARTERY DISEASE

The overall results of the stress test variables for the detection of coronary artery disease are summarized in Fig. 3. Dobutamine electrocardiography included both ECG changes and/or angina. Of the patients 143 had significant coronary artery stenosis, 81 had single vessel disease and 62 had multivessel disease. Seventy-eight patients were identified by electrocardiography (sensitivity 55%), compared with 108 by perfusion scintigraphy (sensitivity 76%) and 103 by echocardiography (sensitivity 72%). Both perfusion scintigraphy and echocardiography were more sensitive than electrocardiography (76% vs 55%, $P<0{\cdot}0001$ and 72% vs 55%, $P<0{\cdot}002$, respectively). In 80 patients with mild or no coronary artery disease, the specificity of electrocardiography, perfusion scintigraphy and echocardiography was, respectively, 65%, 63% and 79%. Echocardiography was more specific than perfusion scintigraphy (79% vs 63%, $P<0{\cdot}05$). The overall accuracy of electrocardiography perfusion scintigraphy and echocardiography was, respectively, 58%, 71% and 74%. Both perfusion scintigraphy and echocardiography were more accurate than electrocardiography (71% vs 58%, $P<0{\cdot}01$ and 74% vs 58%, $P<0{\cdot}0001$, respectively).

BAYESIAN ANALYSIS

According to the pre-test probabilities 15 patients were in the low-risk group, 53 patients were in the high-risk group and the remaining 155 patients were in the intermediate-risk group. After the dobutamine stress

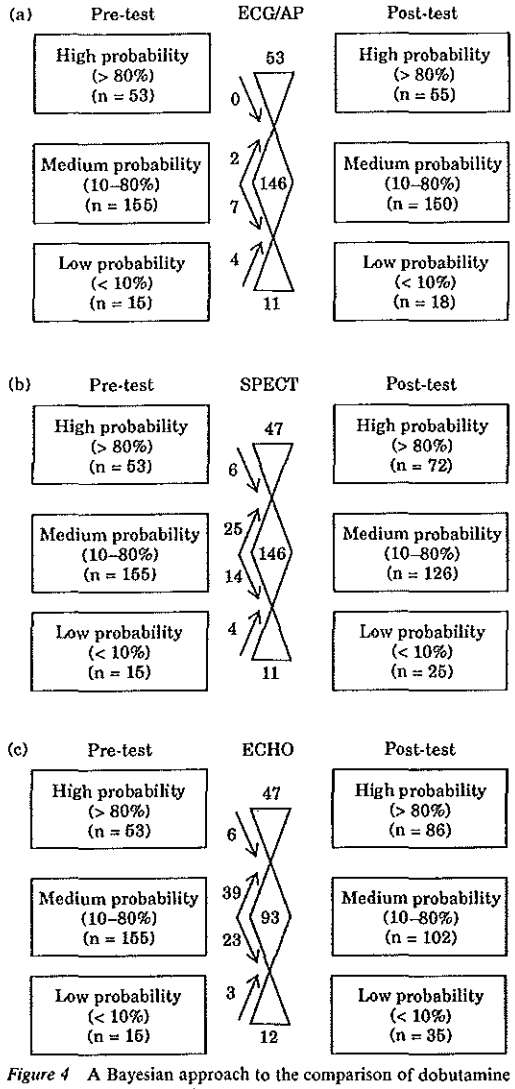


Figure 4 A Bayesian approach to the comparison of dobutamine electrocardiography and/or pain (ECG/AP, top; Fig. 4(a), perfusion scintigraphy (SPECT, middle; Fig. 4(b) and echocardiography (ECHO, bottom; Fig. 4(c)) for the diagnosis of CAD. Patients are classified before and after the test into low-, intermediate- and high-probability of CAD, and the ability of each test to reclassify them accurately is compared. See text for explanation.

test some patients stayed in the same risk group (but with a different, new post-test probability of disease) and others moved to a higher (after a positive test) or a lower (after a negative test) risk group. Figure 4 (a, b and c) clearly illustrates the reclassification in the three risk groups of all individual patients for ECG and/or angina, perfusion scintigraphy and echocardiography, respectively. As reported in Fig. 5, only perfusion scintigraphy and echocardiography reduced the number of patients in the intermediate-risk group (155 vs 126, $P<0{\cdot}005$ and 155 vs 102, $P<0{\cdot}0001$). The reduction of patients in this intermediate-risk group was better for echocardiography than for perfusion scintigraphy (102 vs 126, $P<0{\cdot}05$). Importantly, the accuracy of predicting coronary disease in the high-probability group, and the absence of disease in the low-probability group tended to be better for echocardiography (105/121, 87%) and scintigraphy (88/97, 91%) compared to clinical (pre-test) probabilities (56/68, 82%).

To see to what extent the post-test probabilities after the different stress test variables improved the detection of coronary artery disease, a ROC curve (Fig. 6) was calculated, representing the clinical history only and the additional effects of the different stress results. Again, it can be appreciated that dobutamine stress echocardiography provides more additive information than the ECG and/or angina and perfusion abnormalities. Figure 7 represents the true prevalence of coronary artery disease in the different post-probabilities groups after the dobutamine stress echocardiography test, and showed particularly in the high-risk group, the excellent correlation between the post-test probabilities and the actual distribution of significant coronary artery disease.

Conclusions

Reviewing the data from the literature on pharmacological stress testing for the diagnosis of coronary artery disease, a limited number of studies has addressed direct comparisons of different stress or imaging modalities. Out of the several stress agents in which adequate comparative studies were performed, dobutamine stress test in conjunction with echocardiography appeared to be more accurate for the diagnosis of coronary artery disease than dipyridamole or adenosine echocardiography, particularly in patients with single vessel disease. When dobutamine stress echocardiography was compared to dobutamine or vasodilator perfusion scintigraphy, dobutamine echocardiography was equally sensitive, but slightly more specific than perfusion scintigraphy. This is not surprising, since stress-induced wall motion abnormalities represent a true ischaemic marker, while transient perfusion abnormalities represent true ischaemia and/or malperfusion. Because of its diagnostic accuracy, availability and low cost, dobutamine stress echocardiography may have a role as the first line pharmacological stress test in patients with suspected coronary artery disease who are unable to perform an adequate exercise test.

In most published studies, the outcome of the test is reported in the 'classical' way in terms of sensitivity, specificity and predictive accuracy. Although this approach provides important information on the diagnostic quality of the test, we should remember that the sensitivity and specificity of any diagnostic test rely, among other factors, on the characteristics of the study population. In addition, it seems more informative and

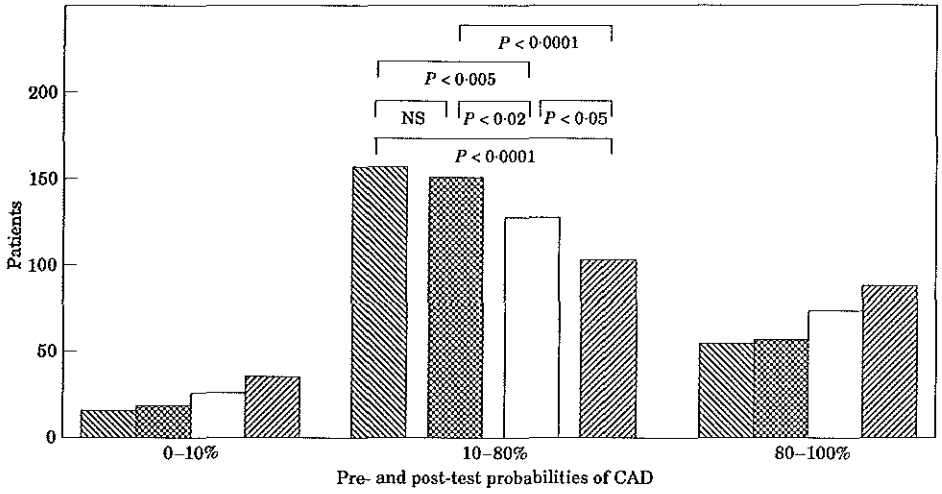


Figure 5 Histogram showing the distribution of Bayesian probabilities of CAD after four diagnostic strategies. The bars represent the number of patients classified in a given probability group at the end of each strategy. (▨=Clinical; ▩=+ECG/AP; □=+SPECT; ▨=+ECHO).

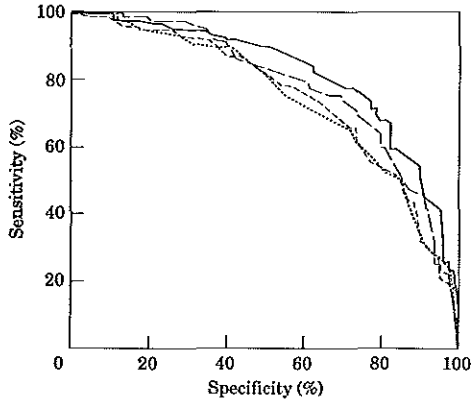


Figure 6 Specificity vs sensitivity of clinical data alone (clinical (- - -)) and additional dobutamine electrocardiography and/or pain (+ECG/AP (– – –)), perfusion scintigraphy (+SPECT (——)) and echocardiography (+ECHO (——)) for the diagnosis of CAD.

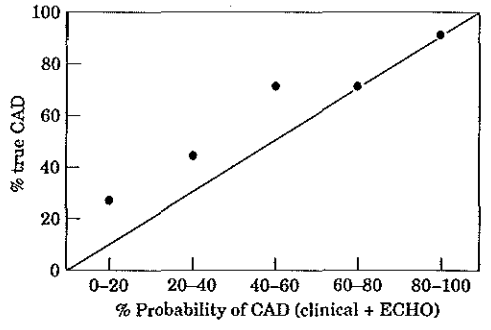


Figure 7 Plot of actual prevalence of CAD in each double decile vs the predicted probability of CAD after clinical+echocardiographic data (●). The continuous line represents the identity line.

didactic to express the results of the test in probabilistic (Bayesian) terms, rather than in binary terms (having disease or not). With this approach, both clinical and stress test variables are incorporated, and the outcome of the test is reported as a post-test probability of having coronary artery disease. However, it should be emphasized that, to apply Bayesian analysis, dependency of clinical variables and stress test results may affect the application of Bayes' theorem.

In the present paper, an example of a probabilistic (Bayesian) approach is given, based on dobutamine stress testing in 223 patients with suspected coronary artery disease. In this study the value of age, gender, chest pain characteristics and different diagnostic markers from dobutamine stress testing (angina, ST-segment changes, wall motion abnormalities and perfusion defects) were compared. The main findings of the study were: (1) dobutamine stress echocardiography, when added to clinical information, re-classified a larger number of patients with an intermediate-risk into low- or high-risk groups compared to ST-segment changes and/or angina and Technetium-99m sestamibi SPECT myocardial perfusion defects, and (2) post-test probabilities derived from clinical plus dobutamine stress echocardiographic data are well correlated to the actual prevalence of coronary artery disease.

The rapid evolution of new stress agent combinations (atropine added to dobutamine[23], atropine added to dipyridamole[24] and dobutamine added to dipyridamole[25]) and imaging modalities (gated SPECT perfusion[26]) requires a careful assessment of their

additional value compared to the clinical data alone or the 'old' methods, in order to provide a guideline for the practicing clinician. For this purpose, new (large scale multicentre) prospective studies should be initiated. It will be challenging to perform these studies in the framework of Bayesian or multivariate analysis[27]. These studies should not only include the limited clinical variables used in this study, but also the risk factors for coronary artery disease. Moreover, the stress test results should be analysed in more detail[28] and the interpretation of these results and the gold standard used as a reference should be standardized.

The authors gratefully acknowledge P. P. Kint for his friendly and excellent assistance in preparing the figures.

References

[1] Iliceto S, Galiuto L, Marangelli V, Rizzon P. Clinical use of stress echocardiography: factors affecting diagnostic accuracy. Eur Heart J 1994; 15: 672–80.

[2] 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 1990; 17: 666–9.

[3] Ruffolo RR, The pharmacology of dobutamine. Am J Med Sci 1987; 294: 244–8.

[4] Picano E. Stress echocardiography, from pathophysiological toy to diagnostic tool. Circulation 1992; 85: 1604–12.

[5] Martin TW, Seaworth JF, Johns JP, Pupa LE, Condos WR. Comparison of adenosine, dipyridamole and dobutamine in stress echocardiography. Ann Int Med 1992; 116: 190–6.

[6] Salustri A, Fioretti PM, McNeill AJ, Pozzoli MMA, Roelandt JRTC. Pharmacological stress echocardiography in the diagnosis of coronary artery disease and myocardial ischaemia: a comparison between dobutamine and dipyridamole. Eur Heart J 1992; 13: 1356–62.

[7] Lanzarini L, Fetiveau R, Poli A, Mussini A, Previtali M. Comparison of dobutamine and dipyridamole stress echo with exercise test for coronary artery disease diagnosis. J Am Coll Cardiol 1993; 21: 89A (Abstr).

[8] Previtali M. Lanzarini L, Ferrario M, Tortorici M, Mussini A, Montemartini C. Dobutamine versus dipyridamole echocardiography in coronary artery disease. Circulation 1993; 83 (III): 27–31.

[9] Boccanelli A, Piazza V, Greco C, Zanchi E, Cecchetti C. Comparison of diagnostic value of dipyridamole and dobutamine stress echocardiography in the diagnosis of coronary artery disease. J Am Coll Cardiol 1993; 21: 393A (Abstr).

[10] Beleslin BD, Ostojic M, Stepanovic J *et al.* Stress echocardiography in the detection of myocardial ischemia. Head-to-head comparison of exercise, dobutamine, and dipyridamole tests. Circulation 1994; 90: 1168–76.

[11] 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: 345–54.

[12] Günalp B, Dokumaci B, Uyan C, Vardareli E *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: 889–94.

[13] Marwick T, D'Hondt A, Baudhuin T *et al.* 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: 159–67.

[14] Stoiber TR, Smart SC, Hellman RS *et al.* Comparison of dobutamine stress echocardiography to dobutamine SPECT isonitrile perfusion for the detection of coronary artery disease. J Am Coll Cardiol 1994; 23: 55A (Abstr).

[15] Kumar EB, Steel SA, Howey S, Caplin JL, Aber CP. Dipyridamole is superior to dobutamine for thallium stress imaging: a randomized crossover study. Br Heart J 1994; 71: 129–34.

[16] Wynsen JC, Duchak JM, Smart SC *et al.* Dobutamine stress echocardiography versus dipyridamole SPECT isonitrile perfusion imaging for detection of coronary artery disease. Circulation 1992; 86(I): I-128 (Abstr).

[17] Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. N Engl J Med 1979; 300: 1350–8.

[18] Altman X. Practical Statistics for Medical Research. London: Chapman and Hall, 1991: 414–7.

[19] Poldermans D, Fioretti PM, Forster T *et al.* Dobutamine stress echocardiography for assessment of perioperative cardiac risk in patients undergoing major vascular major vascular surgery. Circulation 1993; 87: 1506–12.

[20] Forster T, McNeill AJ, Salustri A *et al.* 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: 1591–6.

[21] Renkin J, Melin J, Robert A *et al.* Detection of restenosis after successful coronary angioplasty: improved clinical decision making with use of a logistic model combining procedural and follow-up variables. J Am Coll Cardiol 1990; 16: 1333–40.

[22] Reiber JHC, Serruys PW, Kooijman CJ *et al.* Assessment of short-, medium-, and long-term variations in arterial dimensions from computer-assisted quantitation of coronary cineangiograms. Circulation 1985; 71: 280–8.

[23] McNeill AJ, Fioretti PM, El-Said M, Salustri A, Forster T, Roelandt JRTC. Enhanced sensitivity for detection of coronary artery disease by addition of atropine to dobutamine stress echocardiography. Am J Cardiol 1992; 70: 41–6.

[24] 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; 16: 1216–21.

[25] Ostojic MC, Picano E, Belislin BD *et al.* Dipyridamole-dobutamine echocardiography: a novel test for the detection of coronary artery disease. J Am Coll Cardiol 1994; 23: 1115–22.

[26] Mochizuki T, Murase K, Fujiwara T *et al.* Assessment of systolic thickening with Thallium-201 ECG-gated single photon emission computed tomography: a parameter for local left ventricular function. J Nucl Med 1991; 32: 1496–500.

[27] Robert AR, Melin JA, Detry JR. Logistic discriminant analysis improves diagnostic accuracy of exercise testing for coronary artery disease in women. Circulation, 1991; 83: 1202–9.

[28] Detrano R, Salcedo E, Passalacqua M, Friis R. Exercise electrocardiographic variables: a critical appraisal. J Am Coll Cardiol 1986; 4: 836–47.

Chapter 5

Comparison of dobutamine stress echocardiography and 99m-technetium sestamibi SPECT myocardial perfusion scintigraphy for predicting extent of coronary artery disease in patients with healed myocardial infarction

Elhendy A, Geleijnse ML, Roelandt JRTC, Van Domburg RT,
TenCate FJ, Nierop PR, Bax JJ, El-Refaee M,
Ibrahim MM, El-Said GM, Fioretti PM

Am J Cardiol 1997; 79: 7-12

Comparison of *Dobutamine* Stress Echocardiography and 99m-Technetium Sestamibi SPECT Myocardial Perfusion Scintigraphy for Predicting Extent of Coronary Artery Disease in Patients With Healed Myocardial Infarction

Abdou Elhendy, MD, PhD, Marcel L. Geleijnse, MD, Jos R.T.C. Roelandt, MD, PhD, Ron T. van Domburg, MSc, Folkert J. Ten Cate, MD, PhD, Peter R. Nierop, MD, Jeroen J. Bax, MD, PhD, Medhat El-Refaee, MD, M. Mohsen Ibrahim, MD, Galal M. El-Said, MD, and Paolo M. Fioretti, MD, PhD

This study compares the value of dobutamine stress echocardiography and 99m-technetium methoxyisobutyl-isonitrile (MIBI) single-photon emission computed tomography (SPECT) in the assessment of extent and location of coronary narrowing in patients with healed myocardial infarction. Dobutamine (up to 40 μg/kg/min)–atropine (up to 1 mg) stress echocardiography (DSE) in conjunction with MIBI SPECT was performed in 72 patients (52 men, mean age 57 ± 11 years) with healed myocardial infarction referred for evaluation of myocardial ischemia. Ischemia was defined as new or worsened wall motion abnormalities at DSE and reversible perfusion defects at MIBI SPECT. Significant stenosis (≥50% luminal diameter stenosis) of the infarct-related artery was detected in 45 patients and of other coronary arteries in 22 patients. Sensitivity and specificity of remote ischemia for diagnosis of remote coronary stenosis were 68% (95% confidence interval [CI] 57 to 80) and 93% (CI 86 to 99) for DSE, and 64% (CI 52 to 76), and 90% (CI 83 to 98) for MIBI SPECT, respectively. The positive predictive value and specificity of peri-infarction ischemia for the diagnosis of infarct-related artery stenosis were 89% (CI 81 to 97) and 82% (CI 73 to 92) for DSE, and 87% (CI 79 to 95) and 82% (CI 73 to 92) for SPECT, respectively. The agreement between both techniques was higher for the diagnosis of remote than peri-infarction ischemia (84% vs 66%, p = 0.02). It is concluded that in patients with myocardial infarction undergoing dobutamine stress testing, both echocardiography and MIBI SPECT are clinically useful methods for the diagnosis of remote and infarct-related coronary artery stenosis. *© 1997 by Excerpta Medica, Inc.*

(Am J Cardiol 1997;79:7–12)

Dobutamine stress testing is increasingly used for the diagnosis and functional evaluation of coronary artery disease (CAD), particularly in patients with limited exercise capacity.[1–12] Results of recent studies demonstrate the value of echocardiographic and myocardial perfusion scintigraphic imaging in conjunction with dobutamine stress testing in the diagnosis and localization of CAD in patients without previous myocardial infarction with a fairly similar accuracy.[13,14] However, the relative value of both techniques in conjunction with dobutamine stress testing for assessing the extent of CAD in patients with myocardial infarction has not been evaluated. Detection of myocardial ischemia in this population is important for identifying patients at high risk of future cardiac events and for selecting patients in whom coronary angiography and revascularization may be indicated.[15,16] This study compares the accuracy of dobutamine stress echocardiography (DSE) and 99m-technetium methoxyisobutyl-isonitrile (MIBI) single-photon emission computed tomography (SPECT) for the diagnosis and localization of coronary artery stenosis in patients with healed myocardial infarction.

METHODS

Patient selection: The study group comprised 72 patients (52 men, mean age 57 ± 11 years) who were unable to perform an adequate exercise test, referred for evaluation of myocardial ischemia, and fulfilled the following criteria: (1) healed myocardial infarction diagnosed on the basis of the standard criteria of prolonged chest pain, cardiac enzymes and serial electrocardiographic changes; and (2) absence of severe heart failure, unstable angina, severe valvular heart disease, left bundle branch block, or left ventricular hypertrophy. Fifty-five patients were referred for evaluation of chest pain classified as typical angina in 16; 17 patients were referred for routine functional assessment. Forty-two patients (58%) were receiving nitrates and/or calcium antagonists and 40

From the Thoraxcenter and the Department of Nuclear Medicine, University Hospital Rotterdam-Dijkzigt and Erasmus University, Rotterdam, The Netherlands. This study was supported in part by the Department of Cardiology, Cairo University Hospital, Cairo, Egypt and the Dutch Heart Foundation, Den Haag, The Netherlands (Grant NHS 94.135). Manuscript received April 9, 1996; revised manuscript received and accepted July 22, 1996.

Address for reprints: Abdou Elhendy, MD, PhD, Thoraxcenter, Ba 300, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

TABLE 1 Accuracy of Ischemic-Pattern at Dobutamine Stress Echocardiography and 99m-Technetium Methoxyisobutyl-Isonitrile (MIBI) Single-Photon Emission Computed Tomography (SPECT) for the Diagnosis of Significant Coronary Artery Stenosis in Patients With Previous Myocardial Infarction

	Echocardiography (95% CI)	MIBI SPECT (95% CI)
Overall diagnosis		
Sensitivity	65 (54–76)	61 (50–73)
Specificity	87 (79–95)	73 (63–84)
Positive predictive value	95 (90–100)	90 (83–97)
Negative predictive value	39 (28–51)	33 (22–44)
Accuracy	69 (59–80)	64 (53–75)
Remote coronary stenosis		
Sensitivity	68 (57–80)	64 (52–76)
Specificity	93 (86–99)	90 (83–98)
Positive predictive value	83 (74–93)	78 (67–88)
Negative predictive value	84 (75–93)	82 (73–92)
Accuracy	84 (75–93)	81 (71–91)
Multivessel ischemic pattern		
Sensitivity	40 (29–51)	36 (25–47)
Specificity	96 (91–100)	96 (91–100)
Positive predictive value	83 (75–92)	82 (73–91)
Negative predictive value	75 (65–85)	74 (64–84)
Accuracy	76 (67–86)	75 (65–85)
Infarct-related artery stenosis		
Sensitivity	56 (43–68)	44 (32–57)
Specificity	82 (73–92)	82 (73–92)
Positive predictive value	89 (81–97)	87 (79–95)
Negative predictive value	41 (29–53)	36 (24–48)
Accuracy	63 (51–75)	55 (42–67)

Values are presented as percentage and 95% confidence interval (CI).

(56%) were receiving β blockers. Myocardial infarction was recent ($\leq$1 month) in 23 patients (32%). In the remaining patients, the mean time from infarction was 3.7 $\pm$ 5.3 years. Q waves on the electrocardiogram were present in 55 patients (76%). The infarction was anterior (or anterolateral) in 28 patients (39%), inferior (or inferolateral) in 30 patients (42%), and in both locations in 4 patients (6%). In patients without Q waves, the infarct localization was based on the clinical diagnosis obtained from the patients' records in the acute phase together with the localization of resting wall motion and perfusion abnormalities. The location of infarction was not defined in 10 patients without Q waves who had normal resting perfusion and wall motion (n = 5) or discordant location of resting wall motion and perfusion abnormalities (n = 5). These 10 patients were not included in the diagnosis of infarct-related artery stenosis. Those with discordant location of abnormalities were not included in the diagnosis of remote coronary stenosis.

Dobutamine stress test: Dobutamine was infused through the antecubital vein starting at a dose of 10 μg/kg/min, increasing by 10 μg/kg/min (3-minute stages) to a maximum of 40 μg/kg/min. Atropine (up to 1 mg) was given to patients not achieving 85% of the predicted maximal heart rate.[17] The electrocardiogram was monitored continuously and recorded each minute. Blood pressure was measured every 3 minutes. The test was interrupted if severe chest pain, ST-segment depression >2 mm, significant tachyarrhythmias, or symptomatic systolic blood pressure decrease of >40 mm Hg occurred during the test.

Stress echocardiography: Echocardiographic images were acquired at rest and during the test and recovery. The left ventricular wall was divided into 16 segments and scored using a 4-point scale, where 1 = normal, 2 = hypokinesia, 3 = akinesia, and 4 = dyskinesia. Wall motion score index was defined as the summation of the individual score of the 16 segments divided by 16. Ischemia was defined as new or worsened wall motion abnormalities. As we have previously concluded, ischemia was not considered if akinetic segments at rest became dyskinetic during stress without improvement with low-dose dobutamine.[18,19] Ischemic score was derived by subtracting rest from peak wall motion score in segments with new or worsening wall motion abnormalities. The echocardiograms were recorded on videotapes and digitized on optical disk (Vingmed Sound Als, Horten, Norway). Images were compared side by side in quad-screen format by 2 independent observers without the knowledge of patients' clinical, scintigraphic, or angiographic data. In case of disagreement, a majority decision was achieved by a third investigator. We have previously reported an inter- and intraobserver agreement for DSE assessment of 91% and 92%, respectively.[20]

SPECT imaging: Approximately 1 minute before termination of the stress test, an intravenous dose of 370 MBq of MIBI was administered.[2,21] Stress images were acquired 1 hour after termination of the test. For resting studies, 370 Mbq of MIBI were injected at least 24 hours after the stress study. For each study 6 oblique (short-axis) slices from the apex to the base and 3 sagittal (vertical long-axis) slices from the septum to the lateral wall were defined. Each of the 6 short-axis slices was divided into 8 equal segments. In all, 47 segments per patient were analyzed (after exclusion of the septal part of the 2 basal slices). Interpretation of the scan was semiquantitatively performed by visual analysis assisted by the circumferential profiles analysis. Stress and rest tomographic views were reviewed side by side by an experienced observer who was unaware of the patients' clinical, echocardiographic, or angiographic data. A reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved at rest in $\geq$2 contiguous segments or slices. This was considered diagnostic of ischemia. A fixed perfusion defect was defined as a perfusion defect on stress images in $\geq$2 contiguous segments or slices, which persists on rest images. Echocardiographic and scintigraphic images were matched into 6 segments: anterior, inferior, septal (subdivided into anterior or posterior), posterolateral, and apical. Perfusion defect score was quantitatively calculated by measuring the area between the lower limit of normal values ($\pm$ 2 SD) and the actual circumferential profile in 6 short-axis slices. Ischemic score was derived by subtracting rest from stress score in segments with reversible perfusion defects.

Coronary angiography: Coronary angiography was performed within 3 months. Lesions were quantified as previously described.[22] In short, the 35-mm films were analyzed using the Cardiovascular Angiography Analysis System II (CAAS II, Pie Medical, Maastricht, The Netherlands). For edge detection, a region of interest of 512 × 512 pixels was selected and digitized using a high-fidelity charge-coupled device video camera. The vessel diameter was determined by computing the shortest distance between the right and left contours. A computer-derived estimation of the original arterial dimension was used to calculate the interpolated reference diameter. Significant CAD was defined as a diameter stenosis ≥50% in ≥1 major epicardial artery. Coronary arteries were assigned to myocardial segments as previously described.[13] Peri-infarction zone was defined as myocardial segments in the distribution of infarct-related artery.

Statistical analysis: Unless specified, data are presented as mean ± SD. The chi-square test was used to compare differences between proportions. The Student's *t* test was used for analysis of continuous data. A p value <0.05 was considered statistically significant. Agreement between DSE and MIBI SPECT on the diagnosis of myocardial ischemia was expressed by the kappa value. Values between 0.75 and 1 were considered indicative of strong, between 0.40 and 0.75 of fair to good, and between 0 and 0.40 of poor agreement.[23]

RESULTS

Dobutamine stress test: Heart rate increased from 67 ± 13 beats/min at rest to 131 ± 19 beats/min at peak stress (p <0.0001), and rate-pressure product increased from 8,755 ± 2,749 to 18,408 ± 4,349 mm Hg·beats/min (p <0.00001). Angina occurred in 28 patients (39%), ST-segment depression in 20 (28%), and ST-segment elevation in 22 (31%). Forty-seven patients (65%) reached the target heart rate (≥85% of the maximal exercise heart rate predicted for age and sex). The test was interrupted before reaching the target heart rate because of angina (n = 9), ST-segment depression (n = 5), and arrhythmias (n = 3); 8 patients failed to reach the target heart rate despite receiving the maximal dobutamine and atropine dose.

Coronary angiography: Significant CAD was detected in 57 patients (79%). Thirty-two patients (44%) had 1-vessel CAD, 16 (22%) had 2-vessel CAD, and 9 (13%) had 3-vessel CAD. Normal coronary arteries or <50% lesions were present in 15 patients. Significant infarct-related CAD was detected in 45 of the 62 patients (73%) with defined infarct location. Remote CAD was assessed in 63 patients defined after exclusion of patients with combined anterior and inferior infarcts (n = 4), and patients without Q waves in whom the locations of fixed abnormalities were discordant (n = 5). Remote CAD was detected in 22 of these 63 patients (35%).

Stress echocardiography: Wall motion abnormalities were detected in 58 patients (81%) at the baseline echocardiogram. Ischemia was detected in 37 of 57 patients (65%) with and in 2 of the 15 patients (13%) without significant CAD (Table I). One of the 2 false-positive results occurred in the peri-infarction region. Sensitivity was 53% in patients with 1-vessel CAD (17 of 32), 75% in 2-vessel CAD (12 of 16), and 89% in 3-vessel CAD (8 of 9). Sensitivity was significantly higher in patients with multivessel than with 1-vessel CAD (80% [20 of 25] vs 53% [17 of 32], p <0.05). An ischemic pattern in 2 different vascular territories, suggestive of multivessel involvement, occurred in 10 of 25 patients with multivessel CAD and in 2 of 47 patients with 1-vessel CAD or without significant CAD (Table I). In the 62 patients with well-defined infarct location, ischemia was detected in 25 of 45 patients with and in 3 of 17 patients without significant stenosis of the infarct-related artery. In the 63 patients considered for remote CAD, ischemia was detected in 15 of 22 patients with and in 3 of 41 patients without remote CAD. Of these 22 patients with remote CAD, ST-segment depression occurred in 9 (sensitivity = 41%, p = 0.07 vs DSE).

MIBI SPECT: Perfusion defects on resting images were detected in 61 patients (85%). Ischemia (partially or completely reversible perfusion defects) was detected in 35 of the 57 patients with (61%) and in 4 of 15 patients (27%) without significant CAD (Table I). Three of the 4 false-positive results occurred in peri-infarction regions without significant infarct-related CAD. Sensitivity was 53% in patients with 1-vessel CAD (17 of 32), 69% in 2-vessel CAD (11 of 16), and 78% in 3-vessel CAD (7 of 9). There was a trend to a higher sensitivity in patients with multivessel than with 1-vessel CAD (72% [18 of 25] vs 53% [17 of 32], p = 0.1). An ischemic pattern in 2 different vascular territories, suggestive of multivessel CAD, occurred in 9 of 25 patients with multivessel CAD and in 2 of 47 patients with 1-vessel or no CAD. In the 62 patients with defined infarct location, ischemia was detected in 20 of 45 patients with and in 3 of 17 patients without CAD of the infarct-related artery. Ischemia was detected in 14 of 22 patients with and in 4 of 41 patients without remote CAD.

Comparison of dobutamine stress echocardiography and MIBI SPECT: There was no significant difference between DSE and SPECT with regard to sensitivity, specificity, and accuracy for the overall and regional diagnosis of significant CAD (Table I). Ischemic score was higher in patients with multivessel than 1-vessel CAD (p <0.01 for DSE, Figure 1A; p <0.01 for SPECT, Figure 1B). The agreement between both methods was higher for remote than peri-infarction ischemia (p = 0.02) (Figure 2). In the peri-infarction area, reversible perfusion defects were confined to segments with akinesia at rest in 4 of the 8 patients with peri-infarction ischemia only at SPECT, whereas 6 of the 13 patients with peri-infarction ischemia by only DSE had ischemia confined to hypokinetic segments becoming akinetic during stress and

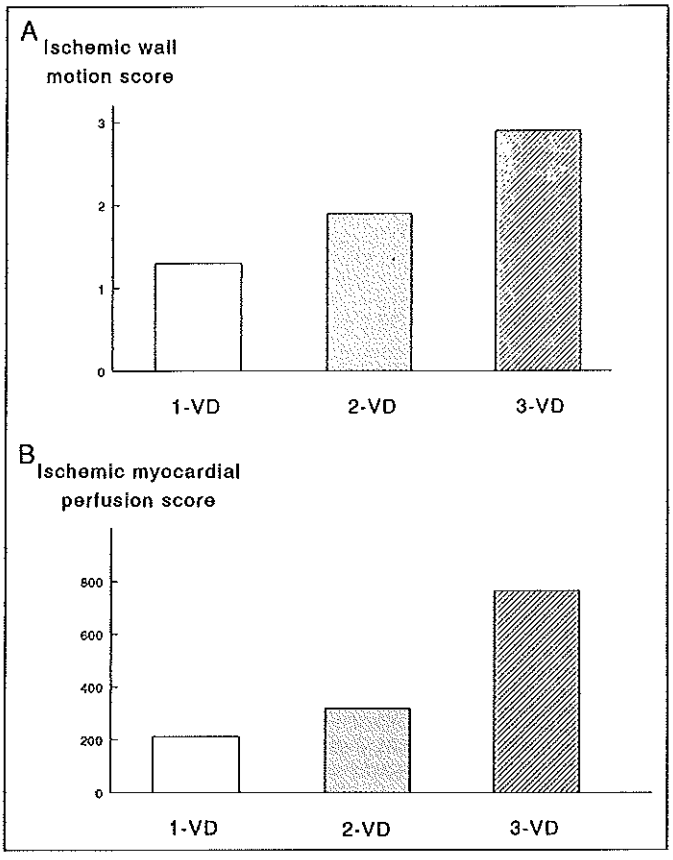


FIGURE 1. *A,* ischemic wall motion score as assessed by dobutamine stress echocardiography. *B,* ischemic myocardial perfusion score as assessed by dobutamine stress 99m-technetium methoxyisobutyl-isonitrile single-photon emission computed tomography in patients with healed myocardial infarction according to the number of diseased vessels. VD = vessel disease.

demonstrating a fixed defect at SPECT. When MIBI was added to DSE for the diagnosis of remote CAD, there were 3 additional true-positive and 2 false-negative tests giving a sensitivity of 82%, specificity of 88%, and accuracy of 86%.

Specificity of fixed abnormalities for infarct-related artery stenosis: Among the 17 patients without significant infarct-related CAD, 7 had wall motion abnormalities at rest and 9 had fixed perfusion defects in the infarct region at resting MIBI studies. Thus, specificity of resting wall motion and perfusion abnormalities for infarct-related CAD was 59% and 47%, respectively.

DISCUSSION

Our study shows that in patients with healed myocardial infarction, DSE and MIBI SPECT have a comparable moderate sensitivity and high specificity for the diagnosis of remote coronary artery stenosis. Myocardial ischemia was more severe in patients with multivessel than 1-vessel disease, inferring the utility of both methods in assessing the extent of CAD. Peri-infarction ischemia assessed by either technique had a high positive predictive value and specificity for significant stenosis of the infarct-related artery. The sensitivity of ischemia for the presence of significant coronary artery stenosis was relatively higher in patients with multivessel than 1-vessel disease, which ensures the detection of a high proportion of patients with multivessel disease in whom prognosis is less favorable.[24] Several factors may contribute to the absence of myocardial ischemia in some patients with remote CAD including the difference in ischemic threshold, vascular overlap, discrepancy between coronary anatomy and function, submaximal stress, medications, and the methodologic problems in image acquisition and interpretation.[25,26] Finally, reduction of the dimensions of a dilated ventricle at high-dose dobutamine may reduce wall stress and counteract the provoking mechanisms of myocardial ischemia. The overall agreement between both techniques was poor, mainly due to discordant diagnosis of peri-infarction ischemia. This may be related to the difference in the pathophysiologic basis of the detection of myocardial ischemia by both techniques, which represent different sequelae of CAD and have different orders in the ischemic cascade.[27,28] Particular disagreement in the peri-infarction region may be related to limitations of both techniques in detecting ischemia in dyssynergic segments. DSE detects worsening of wall motion abnormalities, whereas perfusion defects in these segments at stress MIBI images may not demonstrate reversibility on resting images because of the known limitations of MIBI in assessing myocardial viability.[29] This is shown by the presence of 6 patients with peri-infarction ischemia confined to hypokinetic segments becoming akinetic at DSE with corresponding fixed defects at MIBI SPECT. Conversely, in akinetic segments, ischemia could not be detected by DSE and was detected in the corresponding segments by MIBI SPECT in 4 patients. The specificity of resting perfusion and wall motion abnormalities for infarct-related CAD was low because residual myocardial dysfunction may occur after thrombolysis or revascularization. Previous studies showed that the use of resting wall motion abnormalities in patients with myocardial infarction as criteria of significant CAD

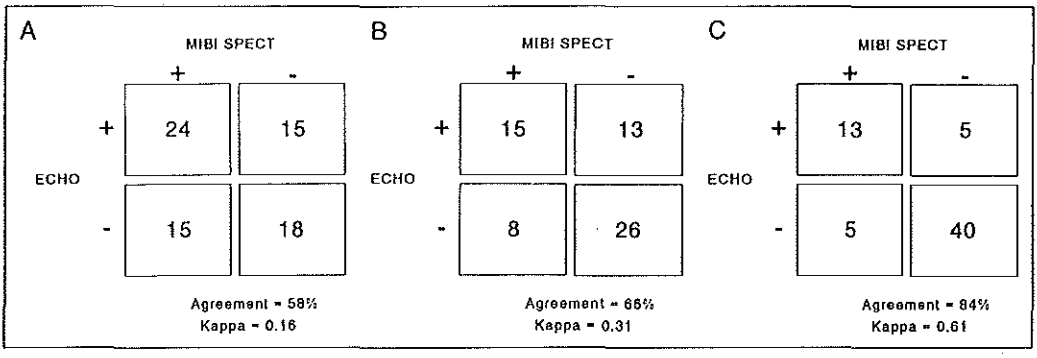


FIGURE 2. Agreement between dobutamine stress echocardiography (ECHO) and 99m-technetium methoxyisobutyl-isonitrile single-photon emission computed tomography (MIBI SPECT) on the overall diagnosis of myocardial ischemia *(A)*, peri-infarction ischemia *(B)*, and remote ischemia *(C)* in patients with healed myocardial infarction.

resulted in a high prevalence of false-positive studies.[30,31] These findings discourage the use of fixed abnormalities as criteria of significant infarct-related CAD.

Comparison with previous studies: This is the first study comparing the use of stress echocardiography and myocardial perfusion scintigraphy for assessing the extent of CAD in patients with healed myocardial infarction. The sensitivity of DSE (80%) and MIBI SPECT (72%) in patients with multivessel CAD in our study are comparable to those reported by Marwick et al[13] in patients without previous infraction (77% and 78%, respectively). Sensitivity of DSE for detecting remote CAD (68%) is comparable to our previous finding[32] in symptomatic patients with old myocardial infarction (73%). However, sensitivity was less when detecting infarct-related CAD (56% vs 76%). This may have been due to the different patient population in the previous study, consisting of symptomatic patients with a lower prevalence of β-blocker administration. Berthe et al[5] reported a sensitivity of 85% and a specificity of 88% for the diagnosis of multivessel CAD using DSE in 30 patients after a recent myocardial infarction. Takeuchi et al[6] reported a sensitivity and specificity of 93% and 91% using DSE for detecting infarct-related CAD after a recent infarction. In a previous study from our laboratory,[33] the sensitivity of dobutamine thallium SPECT for detecting remote (74%) and infarct-related CAD (71%) was relatively higher than dobutamine MIBI in this study (64% and 44%, respectively). This may be explained by the higher prevalence of multivessel CAD and symptoms in the previous study and the potential limitations of MIBI compared with thallium in detecting viable ischemic myocardium in the infarct zone.

Dobutamine versus vasodilator stress testing in conjunction with perfusion imaging: Kumar et al[34] reported that dipyridamole had a sensitivity superior to dobutamine for thallium stress imaging in the diagnosis of CAD. However, the study included only 30 patients and the maximal dobutamine dose was 20 μg/kg/min. In contrast, Marwick et al[1] reported a comparable sensitivity of adenosine and dobutamine MIBI SPECT in the diagnosis of CAD. Takeuchi et al[35] reported that DSE and thallium-201 SPECT (in conjunction with exercise or dipyridamole) had a comparable accuracy for diagnosing CAD. If myocardial perfusion scintigraphy is a useful method in conjunction with exercise, it is expected that dobutamine, which acts like exercise by increasing myocardial oxygen demand, can be useful when combined with perfusion scintigraphy.

Study limitations: A limitation of this study is the relatively small sample size. The prevalence of multivessel disease was not high (44%). Additionally, the prevalence of coronary stenosis was higher in the infarct-related artery compared with remote arteries (73% vs 35%). However, these patients represent the usual population encountered in clinical practice in which noninvasive evaluation of CAD is required. Fifty-six percent of patients were receiving β blockers, which may have contributed to a lower sensitivity of both methods.

Clinical implications and conclusions: DSE and MIBI SPECT are clinically useful methods for diagnosing remote CAD in patients with healed myocardial infarction with a moderate sensitivity and a high specificity. The agreement between both techniques is higher in remote than in peri-infarction regions. Peri-infarction ischemia with either technique has a high positive predictive value and a high specificity for infarct-related CAD. The presence of fixed wall motion and perfusion abnormalities are not reliable criteria for the diagnosis of significant infarct-related CAD.

1. Marwick T, Willemart B, Dhondt AM, Baudhuin T, Wijns W, Detry JM, Melin J. 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.
2. Forster T, McNeill AJ, Salustri A, Reijs AEM, El-Said EM, Roelandt JRTC, Fioretti PM. Simultaneous dobutamine stress echocardiography and 99-m technetium isonitrile single photon emission computed tomography in patients with suspected coronary artery disease. *J Am Coll Cardiol* 1993;21:1591–1596.

3. Sawada SG, Segar DS, Ryan T, Brown SE, Dohan AM, Williams R, Fineberg NS, Armstrong WF, Feigenbaum H. Echocardiographic detection of coronary artery disease during dobutamine infusion. *Circulation* 1991;83:1605–1614.
4. Elhendy A, Geleijnse ML, Roelandt JRTC, Cornel JH, van Domburg RT, El-Refaee M, Ibrahim MM, El-Said GM, Fioretti PM. Assessment of patients after coronary artery bypass grafting by dobutamine stress echocardiography. *Am J Cardiol* 1996;77:1234–1236.
5. Berthe C, Pierard LA, Hiernaux M, Trotteur G, Lempereur P, Carlier J, Kulbertus HE. Predicting the extent and location of coronary artery disease in acute myocardial infarction by echocardiography during dobutamine infusion. *Am J Cardiol* 1986;58:1167–1172.
6. Takeuchi M, Araki M, Nakshima Y, Kuroiwa A. The detection of residual ischemia and stenosis in patients with acute myocardial infarction with dobutamine stress echocardiography. *J Am Soc Echocardiogr* 1994;7:242–252.
7. Bigi R, Occhi G, Fiorentini C, Partesana N, Bandini P, Sponzilli C, Inglese L. Dobutamine stress echocardiography for the identification of multivessel coronary artery disease after uncomplicated myocardial infarction. *Int J Cardiol* 1995;50:51–60.
8. Hays JT, Mahmarian JJ, Cochran AJ, Verani MS. Dobutamine thallium-201 tomography for evaluating patients with suspected coronary artery disease unable to undergo exercise or vasodilator pharmacologic stress testing. *J Am Coll Cardiol* 1993;21:1583–1590.
9. Pennell DJ, Underwood SR, Swanton RH, Walker JM, Ell PJ. Dobutamine thallium myocardial perfusion tomography. *J Am Coll Cardiol* 1991;18:1471–1479.
10. Mason JR, Palac RT, Freeman ML, Virupannavar S, Loeb HS, Kaplan E, Gunnar RM. Thallium scintigraphy during dobutamine infusion: nonexercise-dependent screening test for coronary disease. *Am Heart J* 1984;107:481–485.
11. Coma-Canella I, Gomes Martinez MV, Rodrigo F, Castro Beiras JM. The dobutamine stress test with thallium-201 single-photon emission computed tomography and radionuclide angiography: postinfarction study. *J Am Coll Cardiol* 1993;22:399–406.
12. Cornel JH, Balk AHMM, Arnese M, Maat PWM, Elhendy A, Salustri A, Ten Cate FJ, Fioretti PM. Safety and feasibility of dobutamine-atropine stress echocardiography in patients with ischemic left ventricular dysfunction. *J Am Soc Echocardiogr* 1996;9:27–32.
13. Marwick TH, D'Hondt AM, Baudhuin T, Willemat A, Wijns W, Detry J, Melin J. Optimal use of dobutamine stress for the detection and evaluation of coronary artery disease: combination with echocardiography, scintigraphy or both? *J Am Coll Cardiol* 1993;22:159–167.
14. Günalp B, Dokumaci B, Uyan C, Vardareli E, Işik E, Bayhan H, Özgüven M, Ozturk E. Value of dobutamine technetium-99m-sestamibi SPECT and echocardiography in detection of coronary artery disease compared with coronary angiography. *J Nucl Med* 1993;34:889–894.
15. Brown KA, Weiss RM, Clements JP, Wackers FJTh. Usefulness of residual ischemic myocardium within prior infarct zone for identifying patients at high risk late after acute myocardial infarction. *Am J Cardiol* 1987;60:15–19.
16. Olona M, Candell-Riera J, Permanyer-Miralda G, Castel J, Barrabes JA, Domingo E, Rossello J, Vaque J. Strategies for prognostic assessment of uncomplicated first myocardial infarction: 5-year follow-up study. *J Am Coll Cardiol* 1995;25:815–822.
17. Fioretti PM, Poldermans D, Salustri A, Forster T, Belloti E, Boersma E, McNeill AJ, El-Said ESM, Roelandt JRTC. Atropine increases the accuracy of dobutamine stress echocardiography in patients taking beta-blockers. *Eur Heart J* 1994;15:355–360.
18. Elhendy A, Cornel JH, Roelandt JRTC, van Domburg RT, Fioretti PM. Akinesis becoming dyskinesis during dobutamine stress echocardiography: a predictor of poor functional recovery after surgical revascularization. *Chest*; In press.
19. Elhendy A, Cornel JH, Roelandt JRTC, van Domburg RT, Nierop PR, Geleÿnse ML, El-Said GM, Fioretti PM. Relation between contractile response of akinetic segments during dobutamine stress echocardiography and ischemia assessed by simultaneous 201 thallium SPECT. *Am J Cardiol* 1996;77:955–959.
20. Belloti P, Fioretti PM, Forster T, McNeill AJ, El-Said EM, Salustri A, Roelandt JRTC. Reproducibility of the dobutamine-atropine echocardiography stress test. *Echocardiography* 1993;10:93–97.
21. Elhendy A, Geleijnse ML, Roelandt JRTC, van Domburg RT, Cornel JH, Ten Cate FJ, Postma-Tjoa J, Reijs AEM, El-Said GM, Fioretti PM. Evaluation by quantitative 99m-technetium MIBI SPECT and echocardiography of myocardial perfusion and wall motion abnormalities in patients with dobutamine-induced ST-segment elevation. *Am J Cardiol* 1995;76:441–448.
22. Baptista J, Arnese M, Roelandt JRTC, Fioretti P, Keane D, Escaned J, Boersma E, Di Mario C, Serruys PW. Quantitative coronary angiography in the estimation of the functional significance of coronary stenosis: correlation with dobutamine-atropine stress test. *J Am Coll Cardiol* 1994;23:1434–1439.
23. Fleiss JL. Statistical Methods for Rates and Proportions. 2nd ed. New York: John Wiley, 1981.
24. Proudfit WJ, Bruschke AVG, MacMillan JP, Williams GW. Sones FM. Fifteen year survival study of patients with obstructive coronary artery disease. *Circulation* 1983;68:986–997.
25. Rigo P, Bailey IK, Griffith LSC, Pitt B, Burow RD, Wagner HN Jr, Becker LC. Value and limitations of segmental analysis of stress thallium myocardial imaging for localization of coronary artery disease. *Circulation* 1980;61:973–981.
26. Marwick TH, Nemec JJ, Pashkow FJ, Stewart WJ, Salcedo EE. Accuracy and limitations of exercise echocardiography in a routine clinical setting. *J Am Coll Cardiol* 1992;19:74–81.
27. Nesto RW, Kowalchunck GJ. The ischemic cascade: temporal response of hemodynamic, electrocardiographic and symptomatic expression of ischemia. *Am J Cardiol* 1987;57:23C–27C.
28. Elhendy A, Geleijnse ML, Roelandt JRTC, van Domburg RT, Ten Cate FJ, Cornel JH, Reijs AEM, El-Said GM, Fioretti PM. Dobutamine-induced hypoperfusion without transient wall motion abnormalities: less severe ischemia or less severe stress? *J Am Coll Cardiol* 1996;27:323–329.
29. Sawada SG, Allman KC, Muzik O, Beanlands RS, Wolfe ER Jr, Gross M, Fig L, Schwaiger M. Positron emission tomography detects evidence of viability in rest technetium-99m sestamibi defects. *J Am Coll Cardiol* 1994;23:92–98.
30. Marcovitz PA, Armstrong WF. Accuracy of dobutamine stress echocardiography in detecting coronary artery disease. *Am J Cardiol* 1992;69:1269–1273.
31. Armstrong WF, O'Donnell J, Rayan T, Feigenbaum H. Effect of prior myocardial infarction and extent and location of coronary artery disease on accuracy of exercise echocardiography. *J Am Coll Cardiol* 1987;10:531–538.
32. Elhendy A, van Domburg RT, Roelandt JRTC, Geleijnse ML, Cornel JH, El-Said GM, Fioretti PM. Accuracy of dobutamine stress echocardiography for the diagnosis of coronary artery stenosis in patients with myocardial infarction: the impact of extent and severity of left ventricular dysfunction. *Heart* 1996; 76:123–128.
33. Elhendy A, Cornel JH, Roelandt JRTC, van Domburg RT, Geleijnse ML, Hoeymans PAJ, Reijs AEM, Ten Cate FJ, Fioretti PM. Dobutamine 201-thallium SPECT imaging for the assessment of peri-infarction and remote myocardial ischemia. *J Nucl Med*; In press.
34. Kumar EB, Steel SA, Howey S, Caplin JL, Aber CP. Dipyridamole is superior to dobutamine for thallium stress imaging: a randomised crossover study. *Br Heart J* 1994;71:129–134.
35. Takeuchi M, Araki M, Nakashima Y, Kuroiwa A. Comparison of dobutamine stress echocardiography and stress thallium single photon emission computed tomography for detecting coronary artery disease. *J Am Soc Echocardiogr* 1993;6:593–602.

Chapter 6

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

Elhendy A, Geleijnse ML, Van Domburg RT, Bax JJ, Nierop PR, Beerens SAM, Valkema R, Krenning EP, Ibrahim MM, Roelandt JRTC

Eur J Nucl Med 1998; 25: 69-78

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

Abdou Elhendy[1], Marcel L. Geleijnse[1], Ron T. van Domburg[1], Jeroen J. Bax[1], Peter R. Nierop[1], Suzan A.M. Beerens[1], Roelf Valkema[2], Eric P. Krenning[2], M. Mohsen Ibrahim[1], Jos R.T.C. Roelandt[1]

[1] Thoraxcenter, University Hospital Rotterdam-Dijkzigt, Rotterdam, The Netherlands
[2] Department of Nuclear Medicine, University Hospital Rotterdam-Dijkzigt, Rotterdam, The Netherlands

Received 10 July and in revised form 19 September 1997

Abstract. Stress echocardiography has been considered an accurate method for the diagnosis of coronary artery disease in hypertensive patients and in patients with left ventricular hypertrophy. In contrast, the specificity of myocardial perfusion scintigraphy in these patients has been questioned. The aim of this study was to compare the accuracy of these two imaging modalities in conjunction with dobutamine stress test for the diagnosis of coronary artery disease in hypertensive patients with and without left ventricular hypertrophy. Dobutamine (up to 40 μg $kg^{-1}min^{-1}$) stress echocardiography in conjunction with sestamibi (MIBI) single-photon emission tomography (SPET) was performed in 84 patients with the diagnosis of systemic hypertension who had been referred for evaluation of myocardial ischaemia. Ischaemia was defined as new or worsened wall motion abnormalities at echocardiography and reversible perfusion defects at SPET. Significant coronary artery disease (≥50% luminal diameter stenosis) was detected in 66 patients (79%). The sensitivity, specificity and accuracy of the ischaemic pattern at echocardiography for the diagnosis of coronary artery disease were 73% (CI 63%–82%), 83% (CI 75%–91%) and 75% (CI 66%–84%), those for MIBI were 67% (CI 57%–77%), 83% (CI 75%–91%) and 70% (CI 60%–80%) respectively (P = NS vs echocardiography). Significant stenosis was detected in 123 (49%) of the 252 analysed coronary arteries. The sensitivity, specificity and accuracy of echocardiography for the regional diagnosis of coronary artery disease were 63% (CI 56%–69%), 90% (CI 86%–94%) and 77% (CI 72%–82%). Those for MIBI were 58% (CI 51%–64%), 91% (CI 87%–94%) and 75% (CI 69%–80) respectively (P = NS vs echocardiography). Left ventricular hypertrophy was detected in 59 patients (70%) by echocardiography and did not influence the overall or regional specificity of echocardiography or MIBI SPET. It is concluded that in hypertensive patients, dobutamine stress echocardiography and MIBI SPET have a comparable accuracy for the overall and regional diagnosis of coronary artery disease. Hypertensive patients with or without left ventricular hypertrophy should not be considered unsuitable candidates for stress myocardial perfusion scintigraphy.

Key words: Hypertension – Sestamibi single-photon emission tomography – Echocardiography – Coronary artery disease

Eur J Nucl Med (1998) 25:69–78

Introduction

Hypertension is a major risk factor for the development of coronary artery disease (CAD) and is a frequent finding in patients undergoing stress myocardial perfusion scintigraphy [1, 2]. Abnormal exercise thallium results have been previously reported in patients with systemic hypertension in the absence of CAD [3–5]. However, few data are available regarding the impact of these findings on the clinical utility of stress myocardial perfusion scintigraphy for the diagnosis of CAD in hypertensive patients. Echocardiographic evaluation of left ventricular wall motion during exercise or pharmacological stress testing is a valuable method for the diagnosis of CAD [6, 7]. Transient wall motion abnormalities provide a

This work was presented in part at the 46th Annual Scientific Sessions of The American College of Cardiology, Anaheim, California 1997

Correspondence to: A. Elhendy, Thoraxcenter, Ba 302, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

specific marker of myocardial ischaemia due to significant coronary artery stenosis. Recent studies have indicated a high accuracy of dobutamine stress echocardiography for the detection of CAD in hypertensive patients [8, 9]. It has also been recommended that echocardiography should be preferred to myocardial perfusion scintigraphy in patients with left ventricular hypertrophy, based on the low specificity of the latter for the diagnosis of CAD in that particular patient population [10]. However, no study has addressed whether the assessment of wall motion abnormalities offers a significant advantage over perfusion abnormalities for the detection of CAD in hypertensive patients. The aim of this study was to compare the accuracy of dobutamine stress echocardiography and simultaneous technetium-99m methoxyisobutylisonitrile (sestamibi; MIBI) single-photon emission tomographic (SPET) imaging for the diagnosis and localization of CAD in hypertensive patients with and without left ventricular hypertrophy who had been referred for evaluation of myocardial ischaemia.

Materials and methods

Patient selection. The study population was derived from a consecutive series of patients with limited exercise capacity who had been referred for evaluation of myocardial ischaemia and who fulfilled the following criteria:

1. Established hypertension defined as repeated blood pressure measurements >140/90 mmHg on different occasions. The diagnosis was confirmed by medical reports from the referring physicians.
2. Absence of severe heart failure, unstable angina, myocardial infarction <3 months, severe valvular heart disease or left bundle branch block.
3. Coronary angiography performed within 3 months of dobutamine stress test.
4. Adequate echocardiographic and scintigraphic imaging quality.

Eighty-four patients fulfilled these criteria (only one patient in this series was excluded because of a poor echocardiographic window). Mean age was 60±10 years. There were 53 men and 31 women. The resting electrocardiogram was diagnostic of left ventricular hypertrophy in eight patients (10%) and Q wave myocardial infarction in 32 patients (38%). Forty patients had typical anginal complaints, 26 patients had atypical chest pain, six patients had dyspnoea and/or fatigue and 12 patients were asymptomatic. Beta-blockers were taken by 38 patients (45%) alone or in combination. Other medications included nitrates in 44 patients (52%), calcium channel blockers in 52 patients (62%), diuretics in 37 patients (44%) and angiotensin-converting enzyme inhibitors in 49 patients (58%).

Dobutamine stress test. Dobutamine was infused through an antecubital vein starting at a dose of 5 μg kg^{-1} min^{-1} followed by 10 μg kg^{-1} min^{-1} (3-min stages), increasing by 10 μg kg^{-1} min^{-1} every 3 min to a maximum of 40 μg kg^{-1} min^{-1}. Atropine (up to 1 mg) was given in patients not achieving 85% of age-predicted maximal heart rate and dobutamine infusion was continued. The electrocardiogram was continuously monitored and was recorded each minute. Cuff blood pressure was measured at rest and every 3 min during stress. The test was interrupted if severe chest pain, ST-segment depression >2 mm, significant ventricular or supraventricular arrhythmia, hypertension (blood pressure ≥240/120 mmHg), systolic blood pressure fall >40 mmHg or any intolerable side-effect regarded as being due to dobutamine occurred during the test. Metoprolol (1–5 mg) was used intravenously to reverse the effects of dobutamine if they did not subside quickly. Ischaemia at ECG was defined as ≥0.1 mV horizontal or downsloping ST-segment depression 80 mS from the J point compared to baseline or ≥0.1 mV ST-segment elevation in ECG leads corresponding to segments without resting wall motion abnormalities [11].

Stress echocardiography. Echocardiographic images were acquired using the standard views at rest and during stress and recovery. The left ventricular wall was divided into 16 segments (Fig. 1) and scored using a four-point scale, where 1 = normal, 2 = hypokinesis, 3 = akinesis and 4 = dyskinesis. Ischaemia was defined as new or worsened wall motion abnormalities. In agreement with our previous conclusions, ischaemia was not considered if akinetic segments at rest became dyskinetic during stress without improvement at low-dose dobutamine [12, 13]. The echocardiograms were recorded on video tapes and digitized on optical disk (Vingmed – CFM 800, Vingmed Sound A/S, Horten, Norway). Images were compared side by side in quad-screen format by two independent observers without knowledge of the patients' clinical, scintigraphic or angiographic data. In cases of disagreement, a majority decision was achieved by a third investigator. The inter- and intra-observer agreement for dobutamine stress echocardiographic assessment in our laboratory are 91% and 92% respectively [14].

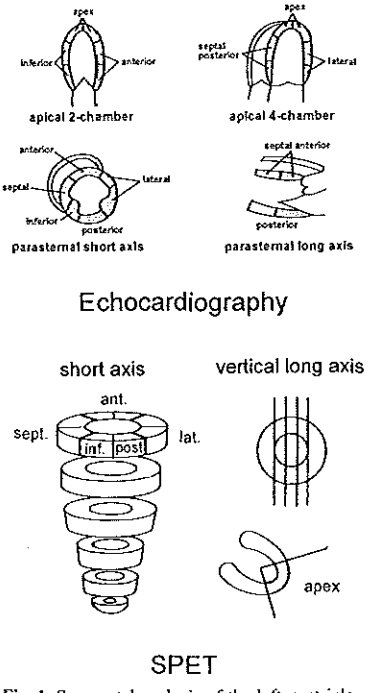


Fig. 1. Segmental analysis of the left ventricle using echocardiography and SPET

Echocardiographic assessment of left ventricular hypertrophy. Left ventricular mass was calculated using Troy's method and measurements were made in accordance with the American Society of Echocardiography criteria [15] as follows: LV mass (g) = 1.04 [(IVS + LVID + PWT)^3–(LVID)^3], where LV = left ventricle; IVS = interventricular septal thickness in cm; and PWT = left ventricular posterior wall thickness in cm. The result was then corrected by the following equation [16] to correlate with necropsy mass: LV mass (g) = 0.8 (LV mass) + 0.6. Left ventricular mass was indexed by body surface area using normal limits from the Framingham Heart Study [17]. Left ventricular hypertrophy was defined as left ventricular mass index >131 g/m^2 for men and >100 g/m^2 for women.

SPET imaging. Approximately 1 min before the termination of the stress test, an intravenous dose of 370 MBq of MIBI was administered [11]. Stress images were acquired 1 h after termination of the test. For resting studies 370 MBq of MIBI was injected at least 24 h after the stress study. For each study six oblique (short-axis) slices from the apex to the base and three sagittal (vertical long-axis) slices from the septum to the lateral wall were defined (Fig. 1). Each of the six short-axis slices was divided into eight equal segments. A total of 47 segments per patient were analysed (after exclusion of the septal part of the two basal slices). The interpretation of the scan was semiquantitatively performed by visual analysis assisted by circumferential profiles analysis. Stress and rest tomographic views were reviewed side by side by an experienced observer who was unaware of the patients' clinical, echocardiographic or angiographic data. A reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved at rest in two or more contiguous segments or slices. This was considered diagnostic of ischaemia. A fixed perfusion defect was defined as a perfusion defect on stress images in two or more contiguous segments or slices which persisted on rest images. Echocardiographic and scintigraphic images were matched into six segments: anterior, inferior, septal anterior, septal posterior, posterolateral and apical [11, 18, 19].

Coronary angiography. Coronary angiography was performed within 3 months of the dobutamine stress test. Lesions were quantified as previously described [20]. Significant CAD was defined as a diameter stenosis ≥50% in one or more major epicardial arteries. Coronary arteries were assigned to myocardial segments as previously described [10]. The anterior, apical, septal and anteroseptal wall was assigned to the left anterior descending coronary artery (LAD), the posterior and lateral wall to the left circumflex (LCx) and inferior and basal septal segments to the right coronary artery (RCA). The apical lateral segment was considered an overlap segment between the LAD and the LCx and the apical inferior segments was considered an overlap segments between the LAD and the RCA. Overlap segments were assigned to the regions with concomitant abnormalities. Because of the frequent vascular overlap in the posterior and inferior walls [21, 22], these two regions were assigned to both the LCx and the RCA.

Statistical analysis. Unless specified, data are presented as mean values ±SD. The chi-square test was used to compare differences between proportions. Student's *t* test was used for analysis of continuous data. A *P* value <0.05 was considered statistically significant. Agreement between echocardiography and MIBI SPET on the diagnosis of myocardial ischaemia was expressed by the kappa value. Values between 0.75 and 1 were considered indicative of strong agreement, those between 0.40 and 0.75 of fair to good agreement and those between 0 and 0.40 of poor agreement [23]. Sensitivity, specificity and accuracy were derived according to the standard definitions and were represented with the 95% confidence intervals (95% CI).

Results

Dobutamine stress test

Heart rate increased from 71±14 at rest to 133±17 beats/min at peak stress (P<0.0001) and rate-pressure product increased from 9918±2998 to 18398±4706 (P<0.00001). There was no significant increase in systolic blood pressure (137±21 vs 138±31 mmHg). Atropine was administered in 38 patients (45%). Angina occurred in 39 (46%) patients. Sixty-four patients (76%) reached the target heart rate (≥85% of the maximal exercise heart rate predicted for age and sex). The test was interrupted before reaching the target heart rate because of angina in ten patients, ST-segment depression in two patients, arrhythmias in two patients and hypotension in one patient; five patients failed to reach the target heart rate despite using the maximal dobutamine and atropine dose.

Coronary angiography

Significant coronary artery stenosis was detected in 66 patients (79%, 25 with and 41 without Q wave infarction). Twenty-four patients (29%) had single-vessel disease, 27 (32%) had two-vessel disease and 15 (18%) had three-vessel disease. Normal coronary arteries or <50% lesions were present in 18 patients (21%). Nine patients (11%) had an ejection fraction <40%.

Prediction of CAD by angina and electrocardiographic changes

Typical angina occurred in 39 patients during the test. CAD was present in 33 of them (sensitivity of stress-induced angina = 50%, CI 39%–61%; specificity = 67%, CI 57%–77%; accuracy = 54%, CI 43%–64%). In the 76 patients without electrocardiographic diagnosis of left ventricular hypertrophy, ischaemic electrocardiographic changes occurred in 24 of 60 patients with and in 3 of 16 patients without CAD (sensitivity = 40%, CI 29%–51%; specificity = 81%, CI 72%–90%; accuracy = 49%, CI 37%–60%).

Stress echocardiography

Echocardiographic criteria of left ventricular hypertrophy were met in 59 patients (70%). Ischaemia was detected in 48 of 66 patients with (73%) and in 3 of the 18 patients (17%) without significant CAD (Table 1). Diag-

Table 1. Accuracy of ischaemic pattern at dobutamine stress echocardiography and ^{99m}Tc-MIBI SPET for the diagnosis of significant coronary artery stenosis in hypertensive patients

	Echocardiography	pts nr	MIBI SPET	pts nr
Overall diagnosis				
Sensitivity	73 (63–82)	48/66	67 (57–77)	44/66
Specificity	83 (75–91)	15/18	83 (75–91)	15/18
Accuracy	75 (66–84)	63/84	70 (60–80)	59/84
LAD stenosis				
Sensitivity	69 (59–79)	31/45	62 (52–73)	28/45
Specificity	85 (77–92)	33/39	90 (83–96)	35/39
Accuracy	76 (67–85)	64/84	75 (66–84)	63/84
LCX stenosis				
Sensitivity	63 (52–73)	22/35	60 (50–70)	21/35
Specificity	94 (89–99)	46/49	94 (89–99)	46/49
Accuracy	81 (72–89)	68/84	79 (71–88)	67/84
RCA stenosis				
Sensitivity	56 (45–66)	24/43	51 (40–62)	22/43
Specificity	90 (84–97)	37/41	88 (81–95)	36/41
Accuracy	73 (63–82)	61/84	69 (59–79)	58/84
All arteries				
Sensitivity	63 (56–69)	77/123	58 (51–64)	71/123
Specificity	90 (86–94)	116/129	91 (87–94)	117/129
Accuracy	77 (72–82)	193/252	75 (69–80)	188/252

Values are presented as percentage and (95% confidence interval)

nostic accuracy was higher than angina and electrocardiography ($P<0.05$). The sensitivity was 58% in patients with single-vessel CAD (14/24), 81% in patients with two-vessel CAD (22/27) and 80% in patients with three-vessel CAD (12/15). The sensitivity was significantly higher in patients with multivessel than in those with single-vessel CAD [81% (34/42) vs 58% (14/24), $P<0.05$]. An ischaemic pattern in two different vascular territories, suggestive of multivessel CAD, occurred in 20 of 42 patients with and in 1 of 42 patients without multivessel CAD (sensitivity = 48%, CI 37%–58%; specificity = 98%, CI 94%–100%; accuracy = 73%, CI 63%–82%). The accuracy for the detection of significant stenosis of individual coronary arteries is shown in Table 1. In the 32 patients with previous Q wave myocardial infarction, sensitivity, specificity and accuracy were 80% (CI 66%–94%), 71% (CI 56%–87%) and 78% CI (64%–92%), respectively. Peri-infarction ischaemia was detected in 14 of 21 patients with and in 2 of 11 patients without significant infarct-related artery stenosis (sensitivity = 67%, CI 50%–83%; specificity = 82%, CI 68%–95%; accuracy = 72%, CI 57%–87%). Sensitivity for infarct-related artery stenosis was 67% (6/9) in patients with an ejection fraction <40%. Remote CAD was detected in 13 patients (41%). Sensitivity, specificity and accuracy of dobutamine stress echocardiography for remote CAD were 69% (CI 53%–85%), 89% (CI 79%–100%) and 81% (CI 68%–95%), respectively. In the 52 patients without previous Q wave myocardial infarction, sensitivity, specificity and accuracy were 68% (CI 56%–81%), 91% (CI 83%–99%) and 73% (CI 61%–85%), respectively. The addition of resting wall motion abnormalities as a marker of CAD in patients without Q wave myocardial infarction resulted in four true-positive and one false-positive diagnoses. The accuracy increased to 79% (P = NS). The addition of resting wall abnormalities for the detection of individual coronary artery stenosis increased sensitivity from 58% (32/55) to 69% (38/55) and accuracy from 82% (128/156) to 84% (131/156), whereas specificity decreased from 95% (96/101) to 92% (93/101). This comprised six true-positive and three false positive studies.

MIBI SPET

Ischaemia (partially or completely reversible perfusion defects) was detected in 44 of 66 patients with (67%) and in 3 of 18 patients (17%) without significant CAD (Table 1). Diagnostic accuracy was higher than angina and electrocardiography ($P<0.05$). The sensitivity was 58% in patients with single-vessel CAD (14/24), 70% in patients with two-vessel CAD (19/27) and 73% in patients with three-vessel CAD (11/15). An ischaemic pattern in two different vascular territories, suggestive of multivessel CAD, occurred in 15 of 42 patients with and in 2 of 42 patients without multivessel CAD (sensitivity = 36%, CI 25%–46%; specificity = 95%, CI 91%–100%; accuracy = 65%, CI 55%–76%). The accuracy for the detection of significant stenosis of individual coronary arteries is shown in Table 1. In the 32 patients with previous Q wave myocardial infarction, sensitivity, specificity and accuracy were 68% (CI 52%–84%), 71% (CI 56%–87%) and 69% (CI 53%–85%), respectively. Peri-

Table 2. Accuracy of ischaemic pattern at dobutamine stress echocardiography for the diagnosis of significant coronary artery stenosis in hypertensive patients with and without left ventricular hypertrophy

	LVH 59 pts	No. of patients	No LVH (25 pts)	No. of patients
Overall diagnosis				
Sensitivity	76 (65–87)	35/46	65 (46–84)	13/20
Specificity	85 (75–94)	11/13	80 (64–96)	4/5
Accuracy	78 (67–89)	46/59	68 (50–86)	17/25
LAD stenosis				
Sensitivity	68 (56–80)	19/28	71 (53–89)	12/17
Specificity	84 (74–93)	26/31	88 (75–100)	7/8
Accuracy	76 (65–87)	45/59	76 (59–93)	19/25
LCX stenosis				
Sensitivity	75 (64–86)	18/24	36 (17–55)*	4/11
Specificity	94 (88–100)	33/35	93 (83–103)	13/14
Accuracy	86 (78–95)	51/59	68 (50–86)	17/25
RCA stenosis				
Sensitivity	58 (45–70)	19/33	50 (30–70)	5/10
Specificity	92 (85–99)	24/26	87 (73–100)	13/15
Accuracy	73 (62–84)	43/59	72 (54–90)	18/25
All arteries				
Sensitivity	66 (59–73)	56/85	55 (44–67)	21/38
Specificity	90 (86–95)	83/92	89 (82–96)	33/37
Accuracy	79 (72–85)	139/177	72 (62–82)	54/75

Values are presented as percentage and (95% confidence interval)
LVH, left ventricular hypertrophy
* $P = 0.03$

infarction ischaemia was detected in 11 of 21 patients with and in 2 of 11 patients without significant infarct-related artery stenosis (sensitivity = 52%, CI 35%–70%; specificity = 82%, CI 68%–95%; accuracy = 63%, CI 46%–79%). Sensitivity for infarct-related artery stenosis was 44% (4/9) in patients with an ejection fraction <40%. Sensitivity, specificity and accuracy of MIBI for remote CAD were 62% (CI 45%–78%), 89% (CI 79%–100%) and 78% (64%–92%), respectively (P = NS vs echocardiography). In the 52 patients without previous Q wave myocardial infarction, sensitivity, specificity and accuracy were 66% (CI 53%–79%), 91% (CI 83%–99%) and 71% (CI 59%–83%), respectively. The addition of resting perfusion abnormalities (fixed defects) as a marker of CAD resulted in two true-positive and one false-positive diagnoses. The accuracy increased to 73% (P = NS). The addition of resting perfusion abnormalities for the detection of individual coronary artery stenosis increased sensitivity from 64% (35/55) to 67% (37/55) and accuracy from 83% (130/156) to 84% (131/156), whereas specificity decreased from 94% (95/101) to 93% (94/101). This comprised two true-positive and one false-positive studies.

The influence of left ventricular hypertrophy

Tables 2 and 3 demonstrate that the overall and the regional accuracy of echocardiography and MIBI SPET for the diagnosis of CAD were not different in patients with and without left ventricular hypertrophy. However, there was a small trend towards a higher sensitivity in patients with left ventricular hypertrophy, which reached a statistically significant difference only in the LCx territory.

Comparison of dobutamine stress echocardiography and MIBI SPET

There was no significant difference between echocardiography and SPET with regard to sensitivity, specificity and accuracy for the overall and the regional diagnosis of significant CAD in the presence or absence of left ventricular hypertrophy (Fig. 2, Tables 1–3). There was a fair (71%) overall agreement between the methods in the diagnosis of myocardial ischaemia (60/84, $\kappa = 0.41$). Agreement was not different in patients with [71% (42/59), $\kappa = 0.40$] and patients without left ventricular hypertrophy [72% (18/25), $\kappa = 0.44$]. There was a concomitant diagnosis of ischaemia in two patients without significant CAD. One of them had left ventricular hypertrophy at echocardiography and developed angina during the test. The other developed ST segment depression during the test had no left ventricular hypertrophy. There was no significant difference between echocardiography or MIBI regarding the sensitivity (72%, CI 58%–86 vs 66%, CI 51%–81%), specificity (83%, CI 71%–95% for

Table 3. Accuracy of ischaemic pattern at dobutamine stress MIBI SPET for the diagnosis of significant coronary artery stenosis in hypertensive patients with and without left ventricular hypertrophy

	LVH (59 pts)	No. of patients	No LVH (25 pts)	No. of patients
Overall diagnosis				
Sensitivity	70 (58–81)	32/46	60 (41–79)	12/20
Specificity	85 (75–94)	11/13	80 (64–96)	4/5
Accuracy	73 (62–84)	43/59	64 (45–83)	16/25
LAD stenosis				
Sensitivity	64 (52–77)	18/28	59 (39–78)	10/17
Specificity	90 (83–98)	28/31	88 (75–100)	7/8
Accuracy	78 (67–89)	46/59	68 (50–86)	17/25
LCX stenosis				
Sensitivity	71 (59–82)	17/24	36 (17–55)*	4/11
Specificity	94 (88–100)	33/35	93 (83–103)	13/14
Accuracy	85 (76–94)	50/59	68 (50–86)	17/25
RCA stenosis				
Sensitivity	55 (42–67)	18/33	40 (21–59)	4/10
Specificity	88 (80–97)	23/26	87 (73–100)	13/15
Accuracy	69 (58–81)	41/59	68 (50–86)	17/25
All arteries				
Sensitivity	62 (55–70)	53/85	47 (36–59)	18/38
Specificity	91 (87–95)	84/92	89 (82–96)	33/37
Accuracy	77 (71–84)	137/177	68 (57–79)	51/7

Values are presented as percentage and (95% confidence interval)
LVH, Left ventricular hypertrophy
* $P = 0.05$

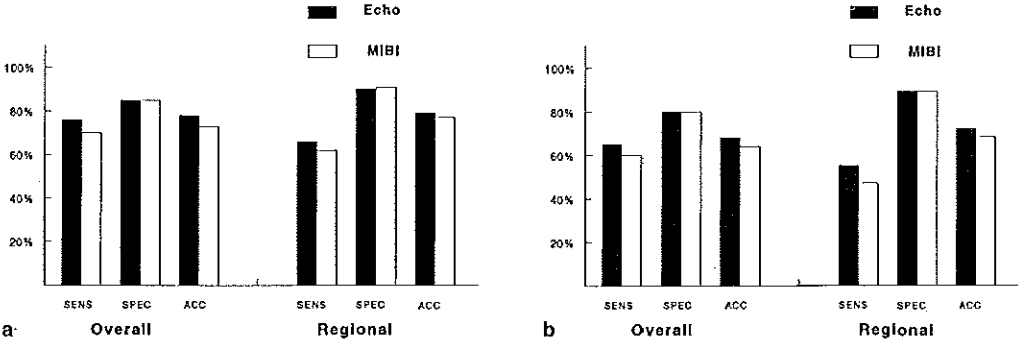


Fig. 2. Sensitivity (*SENS*), specificity (*SPEC*) and accuracy (*ACC*) of dobutamine stress echocardiography (*Echo*) and MIBI SPET (*MIBI*) for the overall and regional diagnosis of coronary artery disease in hypertensive patients with (b) and without (a) left ventricular hypertrophy

both) or accuracy (74%, CI 68%–88% vs 68%, CI 54%–83%) for the diagnosis of CAD in the 38 patients who were receiving beta-blockers.

Discussion

The selection of an accurate non-invasive method for the diagnosis of CAD is important to avoid the risk and expense of unnecessary coronary angiography [2]. Patients with systemic hypertension may develop ST-segment depression without obstructive CAD even in the absence of resting electrocardiographic changes [24]. The accuracy of exercise thallium scintigraphy for detecting obstructive epicardial CAD is superior to that of routine exercise electrocardiographic testing [25]. However, hypertension has been recognized as a cause of false positive perfusion scintigraphic results [1–5]. Conversely, stress echocardiography has been reported to be highly specific for the diagnosis of CAD in hypertensive patients [8, 9] and in patients with left ventricular hypertrophy [10]. Therefore, it has been recommended that in the latter

group of patients, echocardiography should be preferred to myocardial perfusion scintigraphy [10]. However, the diagnostic accuracy of these two imaging modalities has not been compared in hypertensive patients with or without left ventricular hypertrophy.

The present study

To our knowledge, this is the first study to compare the accuracy of stress myocardial perfusion scintigraphy and echocardiography for the diagnosis and localization of CAD in hypertensive patients. Our study shows that in hypertensive patients with limited exercise capacity undergoing dobutamine stress testing for the evaluation of myocardial ischaemia, both echocardiography and MIBI SPET imaging are useful methods for the overall and regional diagnosis of CAD, with a comparably moderate sensitivity and a high specificity. In contrast with the previous reports, left ventricular hypertrophy was not particularly associated with a false-positive diagnosis of CAD using criteria of reversible or fixed perfusion defects at SPET imaging. The results of our study demonstrate that the presence of hypertension with or without left ventricular hypertrophy is compatible with high specificity of stress myocardial perfusion scintigraphy in a population encountered in clinical practice in whom non-invasive evaluation of CAD is required. While echocardiography was as accurate, it did not provide a significant advantage over myocardial perfusion scintigraphy in terms of sensitivity or specificity for the diagnosis of CAD in hypertensive patients in the presence or absence of left ventricular hypertrophy. Furthermore, echocardiography was not feasible in one patient who fulfilled the selection criteria for the population of this study, indicating the advantage of perfusion scintigraphy in this occasional setting.

Comparison with previous studies

Myocardial perfusion abnormalities were reported in hypertensive patients with or without left ventricular hypertrophy in the absence of significant CAD [3]. The mechanisms of myocardial ischaemia in these patients may include impaired vasodilator reserve, increased myocardial oxygen demand due to left ventricular hypertrophy, increased afterload and diastolic dysfunction [26, 27]. While numerous reports have inferred these findings, only a few studies have dealt with the impact of these findings on the utility of myocardial perfusion scintigraphy in the diagnosis of CAD. DePuey et al. [4] reported that fixed perfusion defects in the lateral wall mimicking myocardial infarction occur frequently in hypertensive patients with left ventricular hypertrophy due to end-stage renal disease. Conversely, Cecil et al. [28] found no thallium perfusion abnormalities in 16 hypertensive patients with left ventricular hypertrophy and no renal disease. Unfortunately, none of these studies correlated scintigraphic findings with coronary angiography to exclude the presence of CAD. Schulman et al. [29] compared the results of exercise thallium scintigraphy in patients with and without hypertension. They concluded that hypertension affects the results of thallium-201 exercise stress testing in patients with a low, but not in those with a mid to high likelihood of CAD. These findings have been challenged by Grogan et al. [30], who reported that among patients with a low likelihood of CAD, the prevalence and extent of exercise thallium perfusion abnormalities were similar in those with and those without hypertension. They concluded that hypertension does not cause an increase in false-positive exercise thallium tests. However, the conclusions of these studies were made by the mere comparison of test results in patients with and without hypertension without performing coronary angiography. If hypertension is a major risk of CAD, determination of the pretest likelihood of CAD based only on age, gender and symptoms [31] in these studies may underestimate the prevalence of CAD in the hypertensive group.

Studies on left ventricular function

In normotensive patients, radionuclide left ventricular angiography has been reported to be an excellent indicator of ischaemia due to CAD [32]. However, in the hypertensive population radionuclide angiography has been shown to be a poor method for this purpose [33], owing to the low specificity of the ejection fraction response to exercise and the low sensitivity of new wall motion abnormalities [33, 34]. Marwick et al. [10] reported that in 17 patients with left ventricular hypertrophy and no significant CAD who underwent the dobutamine stress test, echocardiography had a higher specificity than MIBI SPET (94% vs 59%, $P = 0.02$). However, the aetiology of left ventricular hypertrophy was not defined. Left ventricular hypertrophy in these patients may represent non-coronary heart diseases associated with perfusion abnormalities. Our study in 59 patients with left ventricular hypertrophy demonstrated a high overall (85%) and regional (91%) specificity for MIBI SPET imaging, which was comparable to that of echocardiography (85% and 90% respectively). This is not surprising since the mechanisms that may underlie the occurrence of perfusion abnormalities in hypertensive patients with left ventricular hypertrophy in the absence of significant CAD can also result in regional left ventricular dysfunction. Ischaemia due to impaired vasodilator reserve and increased myocardial oxygen demand can readily produce transient myocardial perfusion as well as wall motion abnormalities. Similarly, myocardial fibrosis may manifest as fixed myocardial perfusion and wall motion abnormalities. This is shown in our study by the similar agreement between the two techniques in patients with and without left ventricular hypertrophy. We have previ-

ously reported that in patients with CAD and reversible perfusion defects on dobutamine MIBI SPET, left ventricular hypertrophy was associated with concordant diagnosis of ischaemia on simultaneous echocardiography [18]. In this study, two patients without CAD had transient wall motion and perfusion abnormalities in association with angina or ST-segment depression during dobutamine stress test. This implies the occurrence of true myocardial ischaemia in hypertensive patients without obstructive CAD. Nevertheless, these findings were compatible with a high specificity of both echocardiography and MIBI SPET in the overall and regional diagnosis of CAD in hypertensive patients. The similar accuracy of dobutamine echocardiography and MIBI SPET in this study is in line with the previous reports in unselected patients with [19] and without previous myocardial infarction [35, 36].

Influence of left ventricular hypertrophy on the accuracy of stress echocardiography

Senior et al. [8] reported that dobutamine stress echocardiography had a sensitivity and specificity of 93% and 100% respectively for the diagnosis of CAD in 43 hypertensive patients. However, sensitivity was relatively higher in patients without than in those with left ventricular hypertrophy (100% vs 89%, respectively). Marwick et al. [6] reported that in patients undergoing exercise echocardiography, left ventricular hypertrophy did not influence the sensitivity or specificity. In our study, the trend was even toward a higher sensitivity in patients with than in those without left ventricular hypertrophy (76% vs 65% by echocardiography and 72% vs 60% by MIBI SPET, respectively). This may be explained by the increased myocardial oxygen demand in patients with left ventricular hypertrophy, which may facilitate the induction of ischaemia. The trend towards a higher sensitivity in patients with left ventricular hypertrophy reached a statistically significant value only in the LCx region. This may be explained by possibly better imaging of the lateral wall in the presence of left ventricular hypertrophy, which may improve sensitivity.

Limitations of the study

We studied patients with dobutamine rather than vasodilator stress test, which according to some authors is better than dobutamine in conjunction with myocardial perfusion scintigraphy. However, there are no consistent data in the literature to indicate a superior diagnostic accuracy of vasodilator over dobutamine stress test [37].

Forty-five percent of patients were receiving beta-blockers, which may reduce the sensitivity of both methods. Echocardiography was particularly reported to be more vulnerable to false-negative results at submaximal stress due to the occurrence of wall motion abnormalities later than perfusion abnormalities in the ischaemic cascade. However, we have previously shown that beta-blocker medications do not contribute to false-negative echocardiographic studies in patients with reversible perfusion abnormalities. We could not detect a difference in the diagnostic accuracy between echocardiography and MIBI SPET in patients taking beta-blockers in this study. The results of the test were available to the treating physician and therefore referral bias to coronary angiography might have influenced the diagnostic accuracy of the test. However, such bias, if existent, would affect the accuracy of each technique similarly because both echocardiographic and scintigraphic data were available to the clinicians and the prevalence of an ischaemic pattern was similar with both techniques. Referring a patient with a positive test to coronary angiography may reduce rather than improve specificity. Therefore our conclusion regarding the high specificity of both techniques is unlikely to be limited by the possible referral bias.

Finally, patients with baseline left ventricular dysfunction did not receive nitrates during the injection of MIBI for rest studies, as recently recommended to improve tracer uptake in dyssynergic myocardium [38]. Therefore, the sensitivity of MIBI for the diagnosis of CAD on the basis of reversible hypoperfusion might have been underestimated. This may explain the relatively low sensitivity of MIBI compared to echocardiography for the diagnosis of infarct-related artery stenosis in patients with an ejection fraction <40% in this study. Nevertheless, only 11% of patients in this study had an ejection fraction <40%. Patients with moderate to severe left ventricular dysfunction are usually candidates for dobutamine thallium-201 scintigraphy in our laboratory [39].

Clinical implications

In hypertensive patients with limited exercise capacity, referred for evaluation of myocardial ischaemia, dobutamine stress echocardiography and MIBI SPET imaging have a comparable moderate sensitivity and high specificity for the overall and regional diagnosis of CAD. Hypertensive patients with or without left ventricular hypertrophy should not be considered unsuitable candidates for stress myocardial perfusion scintigraphy.

Acknowledgements. We thank René Frowijn for invaluable technical assistance. This study was supported in part by the Department of Cardiology, Cairo University Hospial, Cairo, Egypt and by a grant from the NUFFIC, The Hague, The Netherlands.

References

1. Frohlich ED, Apstein C, Chobanian AV, et al. The heart in hypertension. *N Engl J Med* 1992;327: 998–1008.
2. Prisant LM, Frank MJ, Carr AA, von Dohlen TW, Abdulla AM. How can we diagnose coronary heart disease in hypertensive patients? *Hypertension* 1987;10: 467–472.

3. Houghton JL, Frank MJ, Carr 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.
4. DePuey EG, Guertler-Krawczynska E, Perkins JV, Robbins WL, Whelchel JD, Clemens SD. Alteration in myocardial thallium-201 distribution in patients with chronic systemic hypertension undergoing single-photon emission computed tomography. *Am J Cardiol* 1988; 62: 234–238.
5. Aguirre JM, Rodriguez E, Ruiz De Azua E, Urrengoetxea J, Faus JM, Iriarte M. Segmentary coronary reserve in hypertensive patients with echocardiographic left ventricular hypertrophy, gammagraphic ischemia and normal coronary angiography. *Eur Heart J* 1993;14 Suppl J: 25–31.
6. Marwick TH, Troelli J, Harjai K, et al. Influence of left ventricular hypertrophy on detection of coronary artery disease using exercise echocardiography. *J Am Coll Cardiol* 1995; 26: 1180–1186.
7. Sawada SG, Segar DS, Ryan T, et al. Echocardiographic detection of coronary artery disease during dobutamine infusion. *Circulation* 1991; 83: 1605–1614.
8. 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.
9. Elhendy A, van Domburg RT, Roelandt JRTC, Geleijnse ML, Ibrahim MM, Fioretti PM. Safety and feasibility of dobutamine-atropine stress testing in hypertensive patients. *Hypertension* 1997; 29: 1232–1239.
10. Marwick TH, D'Hondt AM, Baudhuin T, et al. Optimal use of dobutamine stress for the detection and evaluation of coronary artery disease: combination with echocardiography, scintigraphy or both? *J Am Coll Cardiol* 1993; 22: 159–167.
11. Elhendy A, Geleijnse ML, Roelandt JRTC, et al. Evaluation by quantitative 99m-technetium MIBI SPECT and echocardiography of myocardial perfusion and wall motion abnormalities in patients with dobutamine-induced ST-segment elevation. *Am J Cardiol* 1995; 76: 441–448.
12. Elhendy A, Cornel JH, Roelandt JRTC, van Domburg RT, Fioretti PM. Akinesis becoming dyskinesis during dobutamine stress echocardiography: a predictor of poor functional recovery after surgical revascularization. *Chest* 1996; 110: 155–158.
13. Elhendy A, Cornel JH, Roelandt JRTC, et al. Relation between contractile response of akinetic segments during dobutamine stress echocardiography and ischemia assessed by simultaneous 201 thallium SPECT. *Am J Cardiol* 1996; 77: 955–959.
14. Bellotti P, Fioretti PM, Forster T, et al. Reproducibility of the dobutamine-atropine echocardiography stress test. *Echocardiography* 1993; 10: 93–97.
15. Troy BL, Pombo J, Rackley CE, Measurement of left ventricular thickness and mass by echocardiography. *Circulation* 1972; 45: 602–611.
16. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986; 57: 450–458.
17. Levy D, Savage DD, Garrison RJ, Anderson KM, Kannel WB, Castelli WP. Echocardiographic criteria of left ventricular hypertrophy: the Framingham Heart Study. *Am J Cardiol* 1987; 59: 956–960.
18. Elhendy A, Geleijnse ML, Roelandt JRTC, et al. Dobutamine-induced hypoperfusion without transient wall motion abnormalities. Less severe ischemia or less severe stress? *J Am Coll Cardiol* 1996; 27: 323–329.
19. Elhendy A, Geleijnse ML, Roelandt JRTC, et al. Comparison of dobutamine stress echocardiography and 99m-technetium sestamibi SPECT myocardial perfusion scintigraphy in predicting the extent of coronary artery disease in patients with healed myocardial infarction. *Am J Cardiol* 1997; 79: 7–12.
20. Baptista J, Arnese M, Roelandt JRTC, et al. Quantitative coronary angiography in the estimation of the functional significance of coronary stenosis: correlation with dobutamine-atropine stress test. *J Am Coll Cardiol* 1994; 23: 1434–1439.
21. Pennell DJ, Underwood SR, Swanton RH, Walker JM, Ell PJ. Dobutamine thallium myocardial perfusion tomography. *J Am Coll Cardiol* 1991; 18: 1471–1479.
22. Elhendy A, van Domburg RT, Roelandt JRTC, et al. Accuracy of dobutamine stress echocardiography for the diagnosis of coronary artery stenosis in patients with myocardial infarction: the impact of extent and severity of left ventricular dysfunction. *Heart* 1996; 76: 123–128.
23. Fleiss JL. *Statistical methods for rates and proportions, 2nd edn.* New York: Wiley, 1991.
24. Wroblewski EM, Pearl FJ, Hammer WJ, Bove AA. False positive stress tests due to undetected left ventricular hypertrophy. *Am J Epidemiol* 1982; 115: 412–417.
25. Osbakken MD, Okada RD, Boucher CA, Strauss HW, Pohost GM. Comparison of exercise perfusion and ventricular function imaging: an analysis of factors affecting the diagnostic accuracy of each technique. *J Am Coll Cardiol* 1984; 3: 272–283.
26. Sendon JL. Regional myocardial ischemia and diastolic dysfunction in hypertensive heart disease. *Eur Heart J* 1993; 14 Suppl J: 110–113.
27. Otterstad JE. Ischemia and left ventricular hypertrophy. *Eur Heart J* 1993; 14 Suppl F: 2–6.
28. Cecil MP, Pilcher WC, Eisner RL, Chu TH, Merlino JD, Patterson RE. Absence of defects in SPECT thallium 201 myocardial images in patients with systemic hypertension and left ventricular hypertrophy. *Am J Cardiol* 1994; 74: 43–64.
29. Schulman DS, Francis CK, Black HR, Wackers FJT. Thallium 201 stress imaging in hypertensive patients. *Hypertension* 1987; 10: 16–21.
30. Grogan M, Christian TF, Miller TD, Bailey KR, Gibbons RJ. The effect of systemic hypertension on exercise tomographic thallium-201 imaging in the absence of elctrocardiographic left ventricular hypertrophy. *Am Heart J* 1993;126:327–332.
31. Diamond G, Forrester J. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. *N Engl J Med* 1979;300:1350–1358.
32. Borer JS, Kent KM, Bacharach SL, et al. Sensitivity, specificity and predictive accuracy of radionuclide cineangiography during exercise in patients with coronary artery disease: comparison with exercise electrocardiography. *Circulation* 1979; 60: 572–580.
33. Wasserman AG, Katz RJ, Varghese PJ, et al. Exercise radionuclide ventriculographic responses in hypertensive patients with chest pain. *N Engl J Med* 1984; 311: 1276–1280.
34. Tubau JF, Szlachcic J, Hollenberg M, Massie BM. Usefulness of thallium-201 scintigraphy in predicting the development of angina pectoris in hypertensive patients with left ventricular hypertrophy. *Am J Cardiol* 1989; 64: 45–49.
35. Forster T, McNeill AJ, Salustri A, et al. Simultaneous dobutamine stress echocardiography and 99-m technetium isonitrile single photon emission computed tomography in patients with suspected coronary artery disease. *J Am Coll Cardiol* 1993; 21: 1591–1596.

36. Gunalp B, Dokumaci B, Uyan C, et al. Value of dobutamine technetium-99m-sestamibi SPECT and echocardiography in detection of coronary artery disease compared with coronary angiography. *J Nucl Med* 1993; 34: 889–894.
37. Elhendy A, Geleijnse ML, Roelandt JRTC, et al. Dobutamine 99m-technetium sestamibi SPECT myocardial perfusion scintigraphy in the prediction of restenosis after percutaneous transluminal coronary angioplasty in patients unable to perform exercise stress test. *Nucl Med Comm* 1997; 18: 122–128.
38. Bisi G, Sciagra R, Santoro GM, Fazzini PF. Rest technetium-99m sestamibi tomography in combination with short term adminstration of nitrates: feasibility and reliability for prediction of postrevascularization outcome of asynergic territories. *J Am Coll Cardiol* 1994; 24: 1282–1289.
39. Elhendy A, Cornel JH, Roelandt JRTC, et al. Dobutamine 201-thallium SPECT imaging for the assessment of peri-infarction and remote myocardial ischemia. *J Nucl Med* 1996; 37: 1951–1956.

Chapter 7

Value of dobutamine-atropine stress technetium-99m perfusion imaging in symptomatic patients with left bundle branch block

Geleijnse ML, Elhendy A, Van Domburg RT,
Valkema R, Fioretti PM, Roelandt JRTC

Submitted for publication

ABSTRACT

Aim of the study. To assess the diagnostic and prognostic value of dobutamine-atropine stress-induced reversible perfusion defects in left bundle branch block (LBBB) patients.

Methods. Forty-eight symptomatic LBBB patients underwent dobutamine-atropine technetium-99m scintigraphy. Mean age of the patients was 64 ± 10 years, 23 were men (48%). Scintigraphic results were analysed according to a 20 segments model. Reversible perfusion defects were defined as defects that partially or totally resolved at rest. Significant coronary artery disease (CAD) was quantitatively defined as a diameter stenosis ≥50% in a major epicardial coronary artery.

Results. Dobutamine-atropine increased heart rate from 72 ± 14 bpm to 134 ± 16 bpm. CAD was present in 16 of 29 patients (55%) with available coronary angiography. For the anterior and posterior circulation, respectively, the sensitivity of reversible perfusion defects for the detection of CAD was 56% and 62%, specificity was 80% and 81%, and accuracy was 72% and 72%. Mean follow-up was 27 ± 17 months (range 3 to 77 months). Hard cardiac events (cardiac death or nonfatal myocardial infarction) occurred in 10 of 48 patients (21%). At univariate analysis only a history of prior myocardial infarction or congestive heart failure were associated with hard cardiac events. A history of myocardial infarction was the only independent predictor of hard events.

Conclusions. Dobutamine-atropine stress-induced reversible perfusion defects are useful for the detection of CAD in LBBB patients, both in the anterior and posterior circulation. Their predictive value for hard cardiac events, however, seems limited.

INTRODUCTION

Exercise myocardial perfusion studies often suffer from false positive perfusion defects in the interventricular septum in absence of left anterior descending (LAD) coronary artery stenosis (1-5). One of the mechanisms postulated for these false positive defects is that in left bundle branch block (LBBB) patients septal contraction occurs toward the end of systole, and the compressive effects of the septum restrict blood flow during early diastole, when most of the myocardial perfusion normally occurs (1). With exercise-induced tachycardia and a shortened diastole, septal hypoperfusion may even become more apparent. To overcome the limitations of exercise stress, imaging with pharmacological vasodilation (dipyridamole, adenosine), resulting in only a mild increase in heart rate, was advocated as the preferred test in LBBB patients (3,4). Unfortunately, patients with obstructive airway disease, patients taking medications containing methylxanthines and those with baseline systemic hypotension, sick sinus disease, or advanced atrioventricular node disease are not candidates for vasodilator stress. In such patients stress testing may be done with dobutamine and some studies have shown that dobutamine-induced septal perfusion defects in LBBB patients are both sensitive as well as specific for the detection of LAD disease (5,6), despite a stress mechanism partially based on heart rate increase. The well preserved specificity in these studies was explained by the only moderate increase in heart rate compared to exercise, and it was speculated that the addition of atropine to dobutamine would probably cause specificity to drop. Indeed, in a recently published study using a high-dose dobutamine-atropine protocol mean peak heart rates of 158 bpm were reached and specificity for the detection of LAD disease was dramatically low (7). In our center mean peak heart rates with dobutamine-atropine stress testing are usually around 135 bpm (8), which are just intermediate to those reported in the cited LBBB studies.(5,7) The present study was undertaken to assess the diagnostic accuracy of dobutamine-atropine stress-induced reversible perfusion defects in our LBBB patient population. Additionally, for the first time the prognostic value of these defects was assessed.

METHODS

Patient selection. During a 6-year period, from November 1990 until December 1996, 48 symptomatic patients with permanent, complete LBBB (defined as a notching or slurring QRS ≥120 msec with an initial R wave in I, aVL, and the left precordial leads and displacement of the ST segment, and usually the T wave, in a direction opposite of that of the principal QRS deflection) underwent dobutamine-atropine perfusion scintigraphy for evaluation of suspected myocardial ischemia. None of these patients had known ventricular tachyarrhythmias, unstable angina, or uncontrolled hypertension. Mean age of the patients was 64 ± 10 years (range 43 to 83), 23 were men (48%). Relevant demographic data of all patients are displayed in Table 1.

Table 1. Relevant demographic data for the 48 study patients

	Patients
Age	64 ± 10
Male gender	23 (48)
History	
Myocardial infarction	23 (48)
Congestive heart failure	25 (52)
Aortic valve disease	6 (13)
Typical angina	14 (29)
Medications	
Nitrates	22 (46)
ß-blockers	16 (33)
Calcium antagonists	21 (44)
Digoxin	17 (35)
Diuretics	19 (40)
ACE-inhibitors	25 (52)
Risk factors	
Smoking	12 (25)
Diabetes	5 (10)
Hypertension	32 (67)
Hypercholesterolemia	13 (27)

Data presented are mean value ± SD or number (%) of patients

Dobutamine-atropine stress test. Dobutamine was administered intravenously by an infusion pump with an infusion rate of 10 μg/kg/min for 3 min, increasing by 10 μg/kg/min every 3 min up to a maximum of 40 μg/kg/min. In patients not achieving 85% of their age and gender predicted maximal heart rate (220-age for men and 200-age for women) (9) and without symptoms or signs of myocardial ischemia, atropine was administered, starting with 0.25 mg intravenously and repeated up to a maximum of 1.0 mg within 4 min with continuation of dobutamine infusion. Throughout dobutamine infusion the electrocardiogram (3 leads) was continuously monitored and recorded (12 leads) at one min intervals. Reasons for interruption of the test were: severe angina, symptomatic reduction in systolic blood pressure ≥40 mm Hg from baseline, hypertension (blood pressure ≥240/120 mm Hg), significant tachyarrhythmias and any serious side effect regarded as being due to dobutamine.

Perfusion imaging. At peak stress, 370 MBq of technetium-99m sestamibi (n = 36) or tetrofosmin

(n = 12) was injected intravenously while dobutamine infusion was continued for at least 1 min. Stress scintigraphic images were acquired on average 1 h after the termination of dobutamine infusion. For rest studies, patients were reinjected with 370 MBq of technetium-99m sestamibi or tetrofosmin approximately 24 h after the stress study. Single-photon emission computed tomographic image acquisition was done with a single- (Siemens, Des Plaines, Illinois, USA) or triple-head (Picker, Cleveland, Ohio, USA) camera. Scintigraphic analysis of the left ventricular wall was performed according to the standardized 20-segments model (10). The anterior and septal segment were assigned to the LAD artery (anterior circulation), all other segments were assigned to the right coronary artery and/or left circumflex coronary artery (posterior circulation). Isolated proximal posterior septal defects in continuity with the inferoposterior wall were assigned to the posterior circulation. Isolated apical defects were assigned to the anterior circulation. Myocardial uptake of radiotracer was evaluated visually (with the assistance of circumferential profiles analysis, including the normal values) for each of the 20 segments during both rest and stress with a 4-point scoring method (0 = normal; 1 = equivocal or minimally reduced uptake; 2 = moderately reduced uptake; and 3 = severely reduced uptake). Scan results were considered normal in absence of any defect or the presence of only equivocal defects. Fixed defects were defined as resting perfusion defects >1 in one or more segments, reversible defects were defined as perfusion defects >1 in one or more segments that partially (mixed defects) or totally resolved at rest.

Coronary angiography. Coronary angiography was performed, using the Judkins technique, within 6 months in 29 patients (60%). Significant coronary artery disease (CAD) was defined as a diameter stenosis ≥50% in a major epicardial artery at quantitative coronary angiography (11).

Follow-up. Follow-up data were obtained in all patients until March 1, 1997 by outpatient clinic assessment, review of case notes and contacting the patient, general practitioner or other hospitals when necessary. Mean follow-up was 27 ± 17 months (range 3 to 77 months). Outcome events were hard cardiac events (cardiac death, nonfatal myocardial infarction) and soft cardiac events (coronary artery bypass surgery, percutaneous transluminal coronary angioplasty).

Statistical Analysis. Values were expressed as mean value ± standard deviation, when appropriate. Comparison between variables was performed with the Student's *t* test for continuous variables and chi-square test for discrete variables. Differences of $p < 0.05$ were considered significant. Multivariate logistic regression using the BMDP package (12) was performed to identify factors that were related to cardiac events. A forward and backward stepping algorithm was used with $p < 0.05$ to identify the independent predictors for cardiac events.

RESULTS

Hemodynamic and adverse effects of dobutamine-atropine. Dobutamine-atropine increased

heart rate from 72 ± 14 bpm to 134 ± 16 bpm, systolic blood pressure from 142 ± 27 mm Hg to 145 ± 26 mm Hg, and double (rate-pressure) product from 10,273 ± 2,875 mm Hg x bpm to 19,382 ± 4,090 mm Hg x bpm. Atropine was admistered in 9 of 16 patients (56%) with β-blockers and in 9 of 32 patients (28%) without β-blockers. Test end-points were target heart rate in 41 patients (85%), maximal dose dobutamine-atropine in 2 patients (4%), severe angina in 4 patients (8%) and hypotension in 1 patient (2%). Three patients (6%) had nonsustained (<10 beats) ventricular tachycardia and 2 patients (4%) had nonsustained (<10 beats) supraventricular tachycardia at peak dose or during recovery. Typical angina was induced in 17 patients (35%).

Diagnostic value. CAD was present in 16 of 29 patients (55%) in whom coronary angiography was performed. On the basis of reversible perfusion defects, overall sensitivity for the detection of CAD was 81% (13/16), specificity was 69% (9/13), and accuracy was 76% (22/29). Sensitivity for one, two, and three-vessel CAD was 75% (6/8), 75% (3/4), and 100% (4/4), respectively. As seen in Figure 1, sensitivity for the anterior circulation was 56% (5/9), specificity was 80% (16/20), and accuracy was 72% (21/29). For the posterior circulation sensitivity was 62% (8/13), specificity was 81% (13/16), and accuracy was 72% (21/29). Inclusion of both fixed and/or reversible perfusion defects for the diagnosis of CAD resulted in an overall sensitivity for the detection of CAD of 100% (16/16), a specificity of 15% (2/13), and an accuracy of 62% (18/29).

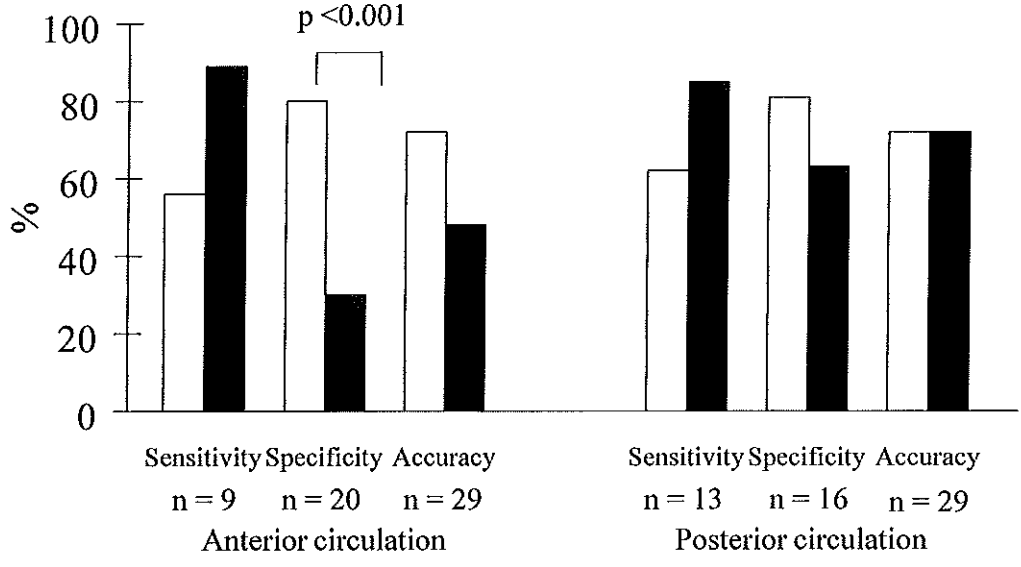


Figure 1. Accuracy of dobutamine-atropine stress perfusion imaging for the detection of coronary artery disease in the anterior (left) and posterior circulation (right) for reversible (white bars) and any perfusion defects (black bars).

As seen in Figure 1, sensitivity for the anterior circulation was 89% (8/9), specificity was 30% (6/20), and accuracy was 48% (14/29). For the posterior circulation sensitivity was 85% (11/13), specificity was 63% (10/16), and accuracy was 72% (21/29). The reversible approach was more specific for CAD, both for overall specificity ($p < 0.001$) and specificity for the anterior circulation ($p < 0.0001$). Fixed defects were more specific for CAD in the posterior circulation than in the anterior circulation ($p < 0.05$). Especially, in patients without known previous myocardial infarction fixed anterior defects tended to be more prevalent than posterior defects (10/25 = 40% versus 4/25 = 16%). The 4 patients with a false negative study for the anterior circulation had (as compared to the 5 patients with a true positive study) comparable peak heart rates (133 versus 142, p = NS) and rate-pressure products (17,949 versus 16,849, p = NS). Three of 4 patients with a false positive study for the anterior circulation had perfusion defects in the septum. Even when patients with reversible septal defects without coronary angiographic data were also considered to be false positive for LAD disease, specificity for the anterior circulation still was 77% (30/39). Both the former 3 and latter 9 patients with a false (or potentially false) positive septal study did not have higher peak heart rates during stress testing compared to patients with a true negative study. Moreover, of 10 patients with a supramaximal peak heart rate (>100%, mean heart rate 143 ± 13 beats/min) only 3 patients had a reversible septal defect. Coronary angiography, available in 2 of the latter patients, showed a normal LAD in 1 patient and a stenosed LAD in 1 patient.

Prognostic value. During follow-up 19 cardiac events occurred in 15 patients (31%). There were 8 cardiac deaths, 2 patients suffered a nonfatal myocardial infarction (1 died later during follow-up), 5 patients underwent coronary artery bypass surgery (2 died later during follow-up), and 4 patients underwent coronary angioplasty (1 died later during follow-up). Patients with normal perfusion, reversible perfusion defects alone, fixed perfusion defects alone, and mixed defects had event rates of 0% (0/6), 13% (1/8), 26% (5/19), and 60% (9/15), respectively. In Table 2 the univariate clinical and stress test data in patients with and without cardiac events are summarized. Clinical variables associated with hard cardiac events were male gender, a history of myocardial infarction, and a history of congestive heart failure. None of the scan variables was significantly associated with hard cardiac events although the presence of any (fixed and/or reversible) perfusion defect or a fixed perfusion defect in both circulations (extensive defects) tended to be more common in patients with hard cardiac events. Clinical variables associated with soft cardiac events were male gender and a history of myocardial infarction. Stress test data associated with soft cardiac events were the presence of stress-induced angina and all abnormal scan patterns, including the presence of reversible perfusion defects. Multivariate analysis revealed prior myocardial infarction (odds ratio [OR] 12.8, 95% confidence interval [CI] 1.4 to 120.0) as the only independent predictor of subsequent hard cardiac events. Dobutamine stress-induced angina (OR 10.1, 95% CI 1.7 to 59.9) was the only independent predictor of subsequent soft cardiac events.

Table 2. Clinical and stress test data for patients with and without cardiac events

	Patients with hard event (n=9)	Patients without hard event (n=39)	P value	Patients with soft event (n=9)	Patients without soft event (n=39)	P value
Age >70 years	1 (11)	12 (31)	0.8817	0 (0%)	13 (33)	0.1828
Male gender	9 (100)	14 (36)	0.0071	7 (78)	16 (41)	0.0490
History						
Myocardial infarction	8 (89)	15 (38)	0.0069	7 (78)	16 (41)	0.0490
Congestive heart failure	8 (89)	17 (44)	0.0153	6 (67)	19 (49)	0.3364
Typical angina	3 (33)	11 (28)	0.7627	5 (56)	9 (23)	0.0559
Stress test data						
Typical angina	3 (33)	14 (36)	0.8859	7 (78)	10 (26)	0.0035
Any defect	9 (100)	33 (85)	0.6077	9 (100)	33 (85)	0.6077
multi-territory	5 (56)	9 (23)	0.0559	6 (67)	8 (21)	0.0066
Fixed defect	9 (100)	25 (64)	0.2389	8 (89)	26 (67)	0.1908
multi-territory	4 (44)	7 (18)	0.0916	5 (56)	6 (15)	0.0105
Reversible defect	5 (56)	18 (46)	0.6146	7 (78)	16 (41)	0.0490
multi-territory	1 (11)	3 (8)	0.7406	2 (22)	2 (5)	0.0979

DISCUSSION

The present study addressed the diagnostic and prognostic value of dobutamine-atropine perfusion imaging in symptomatic LBBB patients. The main finding of the study is that dobutamine-atropine stress-induced reversible perfusion defects are equally moderately sensitive and highly specific for the detection of CAD in the anterior and posterior circulation. The prognostic value of such defects, however, seems limited in a heterogeneous LBBB population.

Etiology of "false-positive" septal perfusion defects. It is well known that in LBBB patients exercise myocardial perfusion studies often show septal defects in absence of LAD disease (1-5). Pacing studies in dogs have indicated that regional myocardial blood flow and thallium-201 uptake during (mid) right ventricular pacing induced LBBB was reduced in the septum compared to the lateral wall, whereas in right atrial pacing and normal ventricular depolarization myocardial blood flow and thallium-201 uptake was equal in the lateral and septal wall (1,13). 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 (13). As heart rate increases and diastole shortens, the relative septal hypoperfusion may even become more apparent. Alternatively, with markedly delayed septal contraction, the myocardium in this region encounters a decreased afterload relative 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 (14). Other proposed mechanisms include coronary spasm or small vessel CAD, septal fibrosis (15), and technical factors, including wall motion artifact (16-18). Because of the suspected major role of heart rate increase in the development of septal defects, vasodilator (dipyridamole, adenosine) perfusion imaging, which causes only a mild increase in heart rate, is advocated as the stress test of choice in LBBB patients to detect CAD (3,4).

Diagnostic value. In accordance to the study of Mairesse *et al.* (6) fixed defects in our study were less specific for CAD in the anterior circulation compared to the posterior circulation and were particularly more common in the anterior circulation in patients without known prior myocardial infarction. In accordance to both Vaduganathan *et al.* (5) and Mairesse *et al.* (6) dobutamine-induced reversible perfusion defects were equally sensitive and specific for the detection of CAD in the anterior and posterior circulation. Even when reversible septal defects in patients without available coronary angiography were considered false positive, specificity for the anterior circulation was well preserved. In contrast to our findings and those of the 2 cited studies, Caner *et al.* (7) recently reported a specificity of only 16% in 19 patients with normal coronary arteries who underwent dobutamine-atropine thallium-201 imaging, with all the false positive septal perfusion defects being reversible. In their study myocardial images were taken 5-7 min after completion of dobutamine-atropine infusion. So, at the moment of imaging heart rate was still raised and wall motion abnormalities could have been still present. It is well known that wall motion abnormalities can influence myocardial images (16-18). Even more importantly, mean peak heart rate in their

study was 158 bpm. Several exercise myocardial perfusion studies have described a relation between peak heart rate and false positive reversible septal defects (2,5,19). In particular heart rates >165 bpm are known to be associated with false positive septal defects (19). Such heart rates are normally uncommon during dobutamine-atropine stress testing. In the present study mean peak heart rate was 134 bpm and only 1 patient had a peak heart rate >165 bpm. The exceptional high peak heart rates in the study of Caner *et al.* may be partially explained by the relatively young age of their patients and their target heart rate criterion for women of 220-age in stead of 200-age as we used (9). Most importantly, for unclear reasons the majority of their patients had despite a target heart rate of 85% of maximal a heart rate of over 95% of maximal. The impact of atropine addition on peak heart rate should always be placed in the context of patient characteristics. In most patients without β-blockers a diagnostic end-point will be achieved without atropine addition. In our study 1 out of every 3 patients was on a β-blocker and, as was shown in other studies (20,21), atropine was particularly useful in these patients to reach their target heart rate. So, whereas atropine addition indeed serves to increase heart rate, a significant increase in heart rate additional to dobutamine is mostly induced in patients on a β-blocker. Future studies should try to assess the optimal percentage heart rate of maximal to detect LAD disease in LBBB patients. Ideally, this should be done by serial studies in individual patients. The 85% of maximal heart rate percentage criterion, which was derived from exercise testing, may potentially be lowered because the threshold for ischemia during dobutamine stress testing seems lower than during exercise (22). Additionally, the sensitivity of perfusion imaging for the detection of CAD is less vulnerable to "submaximal" stress than other markers of ischemia like stress-induced wall motion abnormalities or ST-segment depression (23).

Prognostic value. Most of the revascularization procedures were performed within 3 months from stress testing. Since the results of the test were used by the referring physicians for patient management it is not surprising that reversible perfusion defects were predictive for subsequent revascularization procedures. For hard cardiac events reversible perfusion defects were not predictive at all. It is well known that the probability of suffering from a hard cardiac event relates not only to the quantity of myocardium at risk but also to the quantity of already necrotic myocardium. Therefore, the additional predictive value of reversible perfusion in patients with (extensive) perfusion defects at resting images has often been questioned (24). Due to the underlying causes of LBBB (25), such patients are usually at high risk for hard cardiac events irrespective of reversible perfusion defects. Approximately half of our patients had a previous myocardial infarction and/or a history of congestive heart failure, both reflecting the presence of (extensive) necrotic or nonfunctional (cardiomyopathic) myocardium.

Conclusions. Although dobutamine-atropine stress-induced reversible perfusion defects are useful for the detection of CAD, both in the anterior and posterior circulation, the prognostic value of such defects seems limited in a heterogeneous LBBB population.

REFERENCES

1. 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
2. DePuey AG, Guertler-Krawczynska E, Robbins WL. Thallium-201 SPECT in coronary artery disease patients with left bundle branch block. *J Nucl Med* 1988; 29: 1479-1485
3. Ebersole DG, Heironimus J, Toney MO, Billingsley J. Comparison of exercise and adenosine tecnetium-99m sestamibi myocardial scintigraphy for diagnosis of coronary artery disease in patients with left bundle branch block. *Am J Cardiol* 1993; 71: 450-453
4. O'Keefe J, Bateman TM, Barnhart CS. Adenosine thallium-201 is superior to exercisé thallium-201 for detecting coronary artery disease in patients with left bundle branch block. *J Am Coll Cardiol* 1993; 21: 1332-1338
5. Vaduganathan P, Zuo-Xiang H, Raghavan C, Mahmarian JJ, Verani MS. Detection of left anterior descending coronary artery stenosis in patients with left bundle branch block: exercise, adenosine or dobutamine imaging. *J Am Coll Cardiol* 1996; 28: 543-550
6. Mairesse GH, Marwick TH, Arnese M, Vanoverschelde JLJ, Cornel JH, Detry JMR, Melin JA, Fioretti PM. 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
7. Caner B, Rezaghi C, Uysal U, Tokgozoglu L, Kabakci G, Elahi N, Kes S, Aras T, Ugur O, Bekdik C. Dobutamine thallium-201 myocardial SPECT in patients with left bundle branch block and normal coronary arteries. *J Nucl Med* 1997; 38: 424-427
8. Geleijnse ML, Elhendy A, Van Domburg RT, Cornel JH, Reijs AEM, Roelandt JRTC, Krenning EP, Fioretti PM. Prognostic value of dobutamine-atropine stress technetium-99m sestamibi perfusion scintigraphy in patients with chest pain. *J Am Coll Cardiol* 1996; 28: 447-454
9. Sheffield LT, Maloof JA, Sawayer JA, Roitman D. Maximal heart rate and treadmill performance of healthy women in relation to age. *Circulation* 1978; 57: 79-84
10. Kiat H, Maddahi J, Roy L, Friedman J, Berman DS. Comparison of Tc-99m methoxy isobutyl isonitrile with Tl-201 imaging by planar and SPECT techniques for assessment of coronary disease. *Am Heart J* 1989; 117: 1-11
11. Reiber JHC, Serruys PW, Kooijman CJ Wiins W, Slager CJ, Gerbrands JJ, Suurbiers JC, den Boer A, Hugenholtz PG. Assessment of short-, medium-, and long-term variations in arterial dimensions from computer-assisted quantitation of coronary cineangiograms. *Circulation* 1985; 71: 280-288
12. Dixon WJ. BMDP Statistical Software. Berkeley (CA): University of California Press, 1992: 1105-1144
13. 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
14. Olsson RA, Bunger R. Metabolic control of coronary flow. *Prog Cardiovasc Dis* 1987; 29: 369-387
15. Master AM, Dack S, Jaffe HL. Bundle branch block and intraventricular block in acute coronary artery occlusion. *Am Heart J* 1938; 16: 283-308
16. Gerwitz H, Grotte GJ, Strauss HW, O'Keefe DD, Akins CW, Daggett WM, Pohost GM. The influence of ventricular volume and wall motion on myocardial images. *Circulation* 1979; 59: 1172-1177
17. Parodi O, Schelbert HR, Schwaiger M, Hansen H, Selin C, Hoffman EJ. Cardiac emission computed tomography: underestimation of regional tracer concentration due to wall motion abnormalities. *J Comput Assist Tomogr.* 1984; 8: 1083-1092
18. Sinusas AJ, Shi Q, Vitols PJ, Fetterman RC, Maniawski P, Zaret BL, Wackers FJ. Impact of regional

ventricular function, geometry, and dobutamine stress on quantitative 99mTc-sestamibi defect size. *Circulation* 1993; 88: 2224-2234

19. Matzer L, Kiat H, Friedman JD, Van Train K, Maddahi J, Berman DS. A new approach to the assessment of tomographic thallium-201 scintigraphy in patients with left bundle branch block. *J Am Coll Cardiol* 1991; 17: 1309-1317
20. Fioretti PM, Poldermans D, Salustri A, et al. Atropine increases the accuracy of dobutamine stress echocardiography in patients taking beta-blockers. *Eur Heart J* 1994; 15: 355-60.
21. Lieng LH, Pellikka PA, Mahoney DW, et al. Atropine augmentation in dobutamine stress echocardiography: Role and incremental value in a clinical practice setting. *J Am Coll Cardiol* 1996; 28: 551-7.
22. Cohen JL, Ottenweller JE, George AK, Duvvuri S. Comparison of dobutamine and exercise echocardiography for detecting coronary artery disease. *Am J Cardiol* 1993; 72: 1226-1231
23. Marwick TH, D'Hondt AM, Mairesse GH, et al. Comparative ability of dobutamine and exercise stress in inducing myocardial ischemia in active patients. *Br Heart J* 1994; 72: 31-8.
24. Moss AJ, Goldstein RE, Hall JW, et al. Detection and significance of myocardial ischemia in stable patients after recovery from an acute event. *JAMA* 1993; 269: 2379-2385
25. Schneider JF, Thomas HE, Sorlie P, Kreger BE, McNamara PM, Kannel WB. Comparative features of newly acquired left and right bundle branch block in the general population: the Framingham study. *Am J Cardiol* 1983; 47: 931-940

Chapter 8

Usefulness and limitations of dobutamine-atropine stress echocardiography for the diagnosis of coronary artery disease in patients with left bundle branch block

Geleijnse ML, Vigna C, Kasprzak JD, Rambaldi R,
Elhendy A, Roelandt JRTC, Fioretti PM

Submitted for publication

ABSTRACT

Aim of the study. Patients with left bundle branch block (LBBB) exhibit abnormal septal motion which may limit the interpretation of stress echocardiograms. This study sought to assess the diagnostic value of dobutamine-atropine stress echocardiography (DASE) in LBBB patients.

Methods. Sixty-four LBBB patients (mean age 59 years, 24 men) with suspected coronary artery disease (CAD) underwent DASE and coronary arteriography. Myocardial ischemia was defined as new or worsening wall thickening abnormalities. CAD was quantitatively defined as a diameter stenosis ≥50% in a major epicardial artery.

Results. Rest septal motion was normal (apart from the early systolic septal notch) in 34 patients (53%) and abnormal in 30 patients (47%). Rest septal thickening was normal in 32 patients (50%) and abnormal in 32 patients (50%). All 7 patients with a QRS-duration ≥160 ms and abnormal QRS-axis had abnormal rest septal motion and thickening. Interobserver agreement for ischemia was 88%. In all but one patient disagreement was in the septum. For the anterior and posterior circulation, respectively, sensitivity was 60% (9/15) and 67% (8/12), specificity was 94% (46/49) and 98% (51/52), and accuracy was 86% (55/64) and 92% (59/64). Sensitivity for the anterior circulation tended to be better in patients with normal rest septal thickening (83% vs 44%).

Conclusions. DASE has excellent diagnostic specificity in LBBB patients with suspected CAD. In patients with abnormal rest septal thickening, however, DASE seems to lack good sensitivity for detection of CAD in the anterior circulation. LBBB patients who potentially most benefit from DASE may initially be selected by their resting electrocardiogram.

INTRODUCTION

Left bundle branch block (LBBB) is most commonly associated with atherosclerotic coronary artery disease (CAD) (1). Other etiologic disorders are idiopathic dilated cardiomyopathy, hypertensive heart disease, aortic valvular disease or nonspecific fibrosis of the cardiac conduction system. In a few patients, LBBB may be rate related or idiopathic. Although the presence of LBBB was associated with a three- to fourfold increase in cardiovascular mortality in the Framingham study (1), patients without clinically overt heart disease have an excellent short- and long term prognosis (2,3). Thus, it is important to determine whether LBBB is associated with CAD or other underlying abnormalities. Unfortunately, most noninvasive stress tests have limited value for the detection of CAD in LBBB patients. Exercise-induced ST segment changes are indeterminate for ischemia (4,5) and myocardial perfusion studies, especially exercise perfusion studies, often suffer from false positive perfusion defects in the interventricular septum in the absence of left anterior descending (LAD) coronary artery stenosis (6-9).

Echocardiographically, LBBB is characterized by asynchronous contraction of the ventricles (10), resulting in the (M-mode) echocardiographic hallmark of LBBB, the early systolic posteriorly directed septal notch, first described by McDonald in 1973 (11). After the occurrence of this notch, several types of septal motion have been described. Classically, septal motion is anterior and described as paradoxical (11-13), however, normal posterior motion and several intermediate types may also occur (11-16). Dobutamine-atropine stress echocardiography (DASE) is an established stress modality for the detection of CAD in patients without LBBB (17). It is capable of visualizing septal motion and assessing septal myocardial thickening which might be relatively preserved in LBBB patients, especially in those patients without CAD (16,18,19). To investigate the diagnostic accuracy of DASE for the detection of CAD in LBBB patients and the influence of rest septal motion and thickening on this accuracy we initiated a prospective, multicenter study in which LBBB patients with chest pain and suspected CAD, who were referred for coronary arteriography, underwent DASE.

METHODS

Patient selection. Patients with chest pain and permanent, complete LBBB who where referred for coronary arteriography were eligible for the study if they did not meet any of the following excluding criteria: 1) known ventricular tachyarrhythmias, 2) history of myocardial infarction, 3) unstable angina, 4) uncontrolled hypertension (≥180/110 mm Hg), 5) significant aortic valvular heart disease, or 6) poor quality echocardiogram (n=2). Sixty-four patients gave informed consent and were included in the study. All patients underwent DASE within 1 month of coronary arteriography, without any interceding clinical event. Mean age of the patients was 59 ± 10 years (range 35 to 78), 24 were men (38%). Forty-seven patients (73%) had typical angina, 17 patients (27%) had atypical angina. Mean pre-test probability of CAD, calculated from age, gender and chest pain characteristics (20), was 74% ± 25%. At the time of the study 39 patients (61%) were receiving

antianginal therapy including ß-blockers in 5 (8%). Relevant demographic data of all patients are displayed in Table 1.

Table 1. Pertinent demographic data for 64 the study patients

	CAD (n=19)	No CAD (n=45)	p Value
Age	64 ± 8	58 ± 10	<0.05
Male Gender	8 (42)	16 (36)	NS
Typical Angina	17 (89)	30 (67)	<0.05
Medications			
Nitrates	9 (47)	18 (40)	NS
ß-blockers	2 (11)	3 (7)	NS
Calcium antagonists	8 (42)	13 (29)	NS
Risk Factors			
Smoking	4 (21)	12 (27)	NS
Diabetes	9 (47)	7 (16)	<0.02
Hypertension	14 (74)	23 (51)	NS
Family history of CAD	5 (26)	9 (20)	NS
Hypercholesterolemia	6 (32)	17 (38)	NS

Data are presented as mean value ± SD or number (%) of patients.
CAD = coronary artery disease; NS = nonsignificant.

Electrocardiography. Complete LBBB was defined as a notching or slurring QRS ≥120 ms with an initial R wave in I, aVL, and the left precordial leads and displacement of the ST segment, and usually the T wave, in a direction opposite of that of the principal QRS deflection (21). Electrocardiographic measurements from a standard 12-lead electrocardiogram included QRS-duration, measured to the nearest 10 ms, and frontal QRS-axis, measured to the nearest 15°. A frontal QRS-axis between -30° and +90° was considered normal.

Dobutamine-atropine stress test. Dobutamine was administered intravenously by an infusion pump with an infusion rate of 10 µg/kg/min for 3 minutes, increasing by 10 µg/kg/min every 3 minutes up to a maximum of 40 µg/kg/min. In patients not achieving 85% of their age and gender predicted maximal heart rate and without symptoms or signs of myocardial ischemia, atropine was administered, starting with 0.25 mg intravenously and repeated up to a maximum of 1.0 mg within 4 minutes with continuation of dobutamine infusion. Throughout dobutamine infusion the electrocardiogram (3 leads) was continuously monitored and recorded (12 leads) at one minute intervals. Reasons for interruption of the test were: severe angina, symptomatic reduction in systolic

blood pressure >40 mm Hg from baseline, hypertension (blood pressure >240/120 mm Hg), significant tachyarrhythmias and any serious side effect regarded as being due to dobutamine.

Echocardiographic imaging. Echocardiographic analysis of the left ventricular wall was performed according to the 16-segments model (22). The anterior and septal segments were assigned to the anterior circulation (LAD), all other segments were assigned to the posterior circulation (right coronary artery (RCA) and/or left circumflex (LCx) artery). Isolated apical wall abnormalities were assigned to the anterior circulation. Isolated basal posterior septal wall abnormalities were assigned to the posterior circulation. Systolic wall thickening and/or wall motion were visually evaluated, and each segment was graded on a 5-point scoring system (1 = normal; 2 = mild hypokinesis; 3 = severe hypokinesis; 4 = akinesis; and 5 = dyskinesis). Resting wall motion score index (WMSI) was calculated by summing all individual segment scores and dividing the sum by the total number of segments. A test was considered positive for ischemia in case of new or worsening wall thickening (or motion) abnormalities at any dobutamine (or atropine) stage in ≥1 segment (23). All echocardiograms were scored by two observers (P.M.F. and R.R.) who were blinded for the angiographic data. In case of disagreement, consensus was reached by the two observers or a third observer's (J.D.K) scoring was decisive. Left ventricular end-diastolic diameter (LVEDD) and septal motion were assessed from the baseline M-mode parasternal long axis view. Since it has been documented that septal motion assessment varies with the direction of the ultrasound beam (24), this motion was measured from the cross section in which parts of both mitral valve leaflets were visible. Systolic septal motion after the early notch was visually graded as (relatively) normal (posterior movement ≥3 mm) or abnormal (posterior movement <3 mm, flat [no movement] or paradoxical [anterior movement]). Likewise systolic septal thickening was graded as (relatively) normal (more than 3 mm thickening) or abnormal (less than 3 mm thickening).

Coronary angiography. Coronary angiography was performed, using the Judkins technique, within 1 month from DASE in all patients. Significant coronary artery disease was defined as a diameter stenosis ≥50% in a major epicardial artery at quantitative coronary angiography (25).

Statistical Analysis. Values were expressed as mean value ± standard deviation, when appropriate. Comparison between variables was performed with the Student's *t* test for continuous variables and chi-square test for discrete variables. Differences of $p < 0.05$ were considered significant.

RESULTS

Hemodynamic and adverse effects of dobutamine-atropine. Dobutamine-atropine increased heart rate from 79 ± 13 beats/min to 136 ± 13 beats/min, systolic blood pressure from 135 ± 17 mm Hg to 145 ± 25 mm Hg, and double (rate-pressure) product from 10,704 ± 2,248 mm Hg x beats/min to 19,741 ± 3,915 mm Hg x beats/min. Test end-points were target heart rate in 55

patients (86%), maximal dose dobutamine-atropine in 5 patients (8%), severe angina in 3 patients (5%), and hypotension in 1 patient (2%). None of the patients had a tachyarrhythmia during dobutamine infusion or recovery. Typical angina was induced in 6 patients (9%).

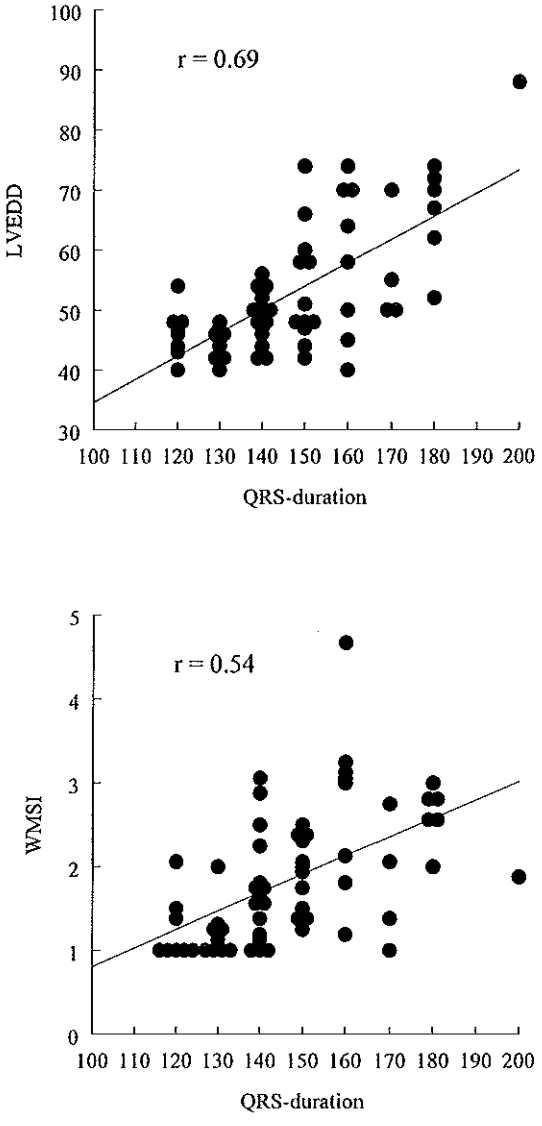


Figure 1. Correlation between QRS-duration and left ventricular end-diastolic diameter (1A, top), and wall motion score index (1B, bottom)

Baseline electrocardiographic and echocardiographic results. QRS-duration was positively correlated with rest LVEDD (r = 0.69, Figure 1A) and rest WMSI (r = 0.54, Figure 1B). Rest septal motion was normal in 34 patients (53%) and abnormal in 30 patients (47%). Abnormal septal motion was severely hypokinetic in 20, flat in 9 and true paradoxical in 1. Rest septal thickening was normal in 32 patients (50%) and abnormal in 32 patients (50%). As shown in Table 2, patients with normal septal thickening had shorter QRS-duration (p <0.001), lower numbers of abnormal frontal QRS-axis (p <0.02), smaller LVEDD (p <0.001), lower WMSI (p <0.001), and more often normal septal motion (p <0.0001). The presence of LAD disease did not differ significantly. Of 30 patients without evidence of CAD or cardiomyopathy (normal coronary arteriography, LVEDD ≤56 mm, and normal resting wall thickening apart from septal wall abnormalities), 26 (87%) had relatively normal septal motion and 25 (83%) had relatively normal septal wall thickening.

Table 2. Characteristics of patients with normal and abnormal septal thickening

	Normal (n=32)	Abnormal (n=32)	p Value
QRS-duration (ms)	137 ± 14	157 ± 17	<0.001
Abnormal QRS-axis	4 (13)	12 (38)	<0.02
WMSI at rest	1.26 ± 0.34	2.43 ± 0.64	<0.001
LVEDD (mm)	47 ± 4	59 ± 12	<0.001
LAD disease	6 (19)	9 (28)	NS
Normal septal motion	32 (100)	2 (6)	<0.0001

Data are presented as mean value ± SD or number (%) of patients. LAD = left anterior descending coronary artery; LVEDD = left ventricular end-diastolic diameter; NS = nonsignificant; WMSI = wall motion score index.

Interobserver agreement for ischemia. Interobserver agreement for myocardial ischemia was 88% (56/64). In all but one patient disagreement was in the septum. Disagreement was present in 9% (3/32) of septums with normal thickening and in 13% (4/32) of septums with abnormal thickening. Myocardial ischemia in the anterior circulation was detected in the septum in 9 patients, in the anterior wall in 1 patient, and in both the septum and the anterior wall in 2 patients.

Diagnostic accuracy. Significant CAD was present in 19 of 64 patients (30%). Of the 45 patients (70%) without significant CAD, 38 patients had normal coronary arteries and 7 patients had non-significant lesions. Overall sensitivity for the detection of CAD was 68% (13/19), specificity was 91% (41/45), and diagnostic accuracy was 84% (54/64). Sensitivity for one, two, and three-vessel CAD was 50% (5/10), 80% (4/5), and 100% (4/4), respectively. For the anterior circulation sensitivity was 60% (9/15), specificity was 94% (46/49), and accuracy was 86% (55/64). For the

posterior circulation sensitivity was 67% (8/12), specificity was 98% (51/52), and accuracy was 92% (59/64).

Analysis of false-negative results. Of 4 patients with a false-negative DASE study for the posterior circulation, 3 patients had one-vessel CAD (LCx stenosis of 55%, 69%, and 75%, respectively), and 1 patient had two-vessel CAD (RCA stenosis of 100% and LCx stenosis of 60%). Achieved heart rates (percentage of "maximal" heart rate) in these 4 patients were 92%, 104%, 117%, and 65%, respectively. Of 6 patients with a false-negative DASE study for the anterior circulation, 1 patient had normal rest septal thickening (LAD stenosis of 53%) and 5 patients had abnormal septal thickening (LAD stenosis of 58%, 63%, 66%, 75%, and 100%, respectively). Achieved heart rates in these 6 patients were 92%, 91%, 102%, 107%, 92% and 75%, respectively. In the 32 patients with normal rest septal thickening sensitivity, specificity and accuracy for the detection of LAD disease was 83% (5/6), 88% (23/26), and 88% (28/32), respectively. In the 32 patients with abnormal rest septal thickening sensitivity, specificity and accuracy for the detection of LAD disease was 44% (4/9), 100% (23/23), and 84% (27/32), respectively. Sensitivity for the detection of LAD disease tended to be better in patients with normal rest septal thickening (5/6 = 83% vs 4/9 = 44%, $p < 0.10$). When only septal ischemia was considered diagnostic for LAD disease this difference was significant (5/6 = 83% vs 3/9 = 33%, $p < 0.05$).

Analysis of false-positive results. The only patient with a false-positive DASE study for the posterior circulation had normal resting wall thickening and mildly impaired basal and mid inferoposterior wall thickening at peak stress. All 3 patients with a false-positive DASE study for the anterior circulation had relatively normal rest septal wall motion and thickening and stress-induced wall thickening abnormalities in the septum. Peak heart rate of the latter 3 patients with a false positive study was comparable to the 46 patients with a true negative study for the anterior circulation (136 ± 7 vs 138 ± 12 beats per minute, p = NS). All patients with a false-positive DASE study had angiographically normal coronary arteries.

DISCUSSION

The present study addressed the diagnostic value of DASE in LBBB patients with chest pain and suspected CAD. The main finding of the study is that DASE is a moderately sensitive and highly specific test for the detection of CAD in LBBB patients, both in the anterior and posterior circulation. Interobserver agreement for detection of CAD in the LAD artery, however, seems somewhat lower compared to patients without LBBB (17). Additionally, sensitivity for the detection of CAD in the LAD artery seems lower in patients with abnormal rest septal thickening.

Echocardiographic characteristics of LBBB. In LBBB patients ventricular activation starts in the right ventricle and the right side of the septum. Transseptal activation from right to left is

transmyocardial and thus slow. Activation of the left ventricle proceeds also from right to left, with the basal and posterolateral wall activated last, although activation of the latter is relatively rapid because of impulse entrance in the distal Purkinje network. Thus, whereas in normal subjects the onset of right and left ventricular contraction occurs nearly simultaneously, in LBBB patients there is asynchronous onset of right and left ventricular contraction. This mechanical asynchrony, resulting in dynamic changes in pressure and volume between the ventricles, continues throughout the cardiac cycle (10). During early systole, right ventricular isovolumic contraction is unopposed by left ventricular contraction, causing the septum to move passively posteriorly (explaining the early systolic septal notch). Abrupt anterior septal motion occurs at the time of normalization of the transseptal pressure gradient by a decrease in right ventricular volume with pulmonic ejection and a rise in left ventricular pressure with isovolumic contraction. During simultaneous right and left ventricular ejection several types of septal motion can be encountered. Classically, septal motion is anterior and described as paradoxical (11-13), however, normal posterior motion and several intermediate types may also occur (11-16). Septal motion seems related to both contraction capability (e.g. presence of septal infarction, cardiomyopathy) as well as activation sequence. Several right ventricular pacing studies, simulating LBBB, have indicated that apical pacing results in an early systolic notch followed by (near) normal posterior septal motion and thickening (18,19), whereas midventricular pacing results in an early systolic notch followed by paradoxical anterior septal motion without thickening (19,26). Likewise, the proximal or more distal site of LBBB may influence septal motion and thickening (15). In contrast to the initial studies describing septal motion (11-13), many LBBB patients in the present study had (apart from the early systolic notch) relatively normal septal motion and thickening. In particular, patients without evidence of CAD or cardiomyopathy usually had normal septal motion and thickening. In the largest (resting) echocardiographic studies in consecutive LBBB patients by Strasberg *et al.* (15) and Curtius *et al.* (16) relatively normal septal motion was also present in the majority of patients. Grines *et al.* (10) described that LBBB patients with more prolonged right/left ventricular filling ratio (interventricular asynchrony) had more abnormal septal motion. In concordance with the studies of Strasberg *et al.* (15) and Curtius *et al.* (16) we found that patients with abnormal septal thickening (and usually motion) had longer QRS-duration, more often an abnormal QRS-axis, and larger LVEDD, findings that were, although not specifically analysed, also present in the classic study of McDonald (11).

Detection of myocardial ischemia. In LBBB patients, exercise-induced ST segment changes are nonspecific for ischemia (4,5) and myocardial perfusion studies, especially when exercise stress is used, often suffer from false positive perfusion defects in the interventricular septum in absence of LAD stenosis (6-9). Pacing studies in dogs have indicated that regional myocardial blood flow and thallium-201 uptake during (mid) right ventricular pacing induced LBBB was reduced in the septum compared to the lateral wall, whereas in right atrial pacing and normal ventricular depolarization myocardial blood flow and thallium-201 uptake was equal in the lateral and septal wall (6,26). True ischemia, as measured by lactate extraction, was not present. 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 (26). As heart rate increases and diastole shortens, the relative septal hypoperfusion may even become more apparent. Alternatively, with markedly delayed septal contraction, the myocardium in this region encounters a decreased afterload relative 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 (27). Other proposed mechanisms include coronary spasm or small vessel CAD, septal fibrosis (28), and technical factors, including wall motion artifact (29). Because of the suspected major role of heart rate increase in the development of septal defects, vasodilator (dipyridamole, adenosine) perfusion imaging, which causes only a moderate increase in heart rate, is advocated as the stress test of choice in LBBB patients to detect CAD (8,9).

Echocardiographically, myocardial ischemia in the LAD territory can be assessed by stress-induced wall thickening abnormalities in the septum or anterior wall. Stress-induced wall thickening abnormalities in the septum are relatively easy to detect because of the well delineated endocardium compared to the anterior wall endocardium and are important because they may reflect proximal or mid LAD stenosis. Our study shows that in LBBB patients septal (and anterior) dobutamine-stress induced wall thickening abnormalities are very specific for the detection of CAD in the LAD. Unfortunately, interobserver agreement for septal ischemia in the present study was relatively low. Additionally, in patients with abnormal rest septal thickening, septal ischemia was detected less frequently and the sensitivity of DASE for the detection of CAD in the LAD seemed lower. The false negative studies could not be explained by less severe LAD stenosis, lower achieved heart rates or double products. Other investigators have shown that in patients without LBBB but with abnormal rest wall thickening or dilated cardiomyopathy, DASE is still an accurate test for the diagnosis of CAD (23,31,32). However, despite the use of the biphasic response (23), the combination of impaired baseline wall thickening and LBBB-induced abnormal wall motion seems to make the assessment of septal ischemia difficult. In this respect, we anticipate that in LBBB patients with septal infarction, who usually have a flat septum without wall thickening (14), assessment of infarct-related artery patency will also be very difficult. Recently, Mairesse *et al.* (33) reported in 8 LBBB patients with prior myocardial infarction and LAD stenosis a sensitivity of DASE for the detection of CAD in the LAD of 88%. However, in their study infarct (or rest wall thickening abnormality) localization was not specified and failure to improve wall thickening during dobutamine infusion was considered an additional criterion for ischemia. Opinions about the use of this latter criterion diverge (34). Application of this criterion to our 32 LBBB patients with abnormal septums would have increased sensitivity for the detection of CAD in the LAD from 44% to 89%, at the sacrifice of a decrease in specificity from 100% to 17%. As mentioned before, vasodilator (dipyridamole, adenosine) perfusion scintigraphy is nowadays considered as the diagnostic stress test of choice in LBBB patients. Unfortunately, there are no studies reported in the literature specifically addressed to the sensitivity of perfusion scintigraphy for the detection of LAD disease in LBBB patients with abnormal rest septal thickening.

Interestingly, the likelihood of having relatively normal rest septal thickening was higher in

patients with shorter QRS-duration and normal QRS-axis. Only 3 of 19 patients (16%) with a QRS-duration ≥160 ms had relatively normal septal thickening, as opposite to 29 of 45 patients (64%) with a QRS-duration ≤150 ms. All 7 patients with a QRS-duration ≥160 ms and abnormal QRS-axis had abnormal rest septal thickening (and motion). If other studies confirm our findings, LBBB patients who potentially most benefit from DASE may initially be selected by their resting electrocardiogram.

Limitations. Despite a mean pre-test probability of CAD of 74% ± 25% only 30% of the patients had significant CAD. Twelve patients (19%) in our study group had evidence of nonischemic dilated cardiomyopathy by LVEDD >56 mm, global hypokinesis and angiographically normal coronary arteries. It is well known that patients with dilated cardiomyopathy can experience typical, exertional angina in absence of epicardial CAD (35). Importantly, the main issue in LBBB patients is the rather low specificity of most noninvasive stress tests. Since 70% of our patients did not have significant CAD, this important issue could adequately be addressed. In fact, our LBBB study population is the largest reported in the literature without angiographic referral bias.

Conclusions. Despite suboptimal interobserver agreement on septal ischemia, we believe that the diagnostic accuracy of DASE establishes this stress modality as one of the stress tests of choice in LBBB patients with relatively normal rest septal thickening. In patients with abnormal rest septal thickening DASE seems to lack good sensitivity for LAD disease detection, although the test remains highly specific. Future studies should confirm our findings and, preferably in head-to-head comparisons, assess whether stress perfusion scintigraphy has better diagnostic accuracy in these latter patients with abnormal rest septal thickening.

REFERENCES

1. Schneider JF, Thomas HE, Sorlie P, Kreger BE, McNamara PM, Kannel WB. Comparative features of newly acquired left and right bundle branch block in the general population: the Framingham study. Am J Cardiol 1983; 47: 931-940
2. Rothbart RM, Beller GA, Watson DD, Nygaard TW, Gibson RS. Diagnostic accuracy and prognostic significance of quantitative thallium-201 scintigraphy in patients with left bundle branch block. *Am J Noninvasive Cardiol* 1987; 1: 197-205
3. Fahy GJ, Pinski SL, Miller DP, McCabe N, Pye C, Walsh MJ, Robinson K. Natural history of isolated bundle branch block. *Am J Cardiol* 1997; 77: 1185-1190
4. Orzan F, Garcia E, Mathur VS, Hall RJ. Is the treadmill exercise test useful for evaluating coronary artery disease in patients with complete left bundle branch block.? *Am J Cardiol* 1978; 42: 36-40
5. Surawicz B, Saito S. Exercise testing for detection of myocardial ischemia in patients with abnormal electrocardiograms at rest. *Am J Cardiol* 1978; 41: 943-951
6. 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
7. DePuey AG, Guertler-Krawczynska E, Robbins WL. Thallium-201 SPECT in coronary artery disease

patients with left bundle branch block. *J Nucl Med* 1988; 29: 1479-1485
8. Ebersole DG, Heironimus J, Toney MO, Billingsley J. Comparison of exercise and adenosine tecnetium-99m sestamibi myocardial scintigraphy for diagnosis of coronary artery disease in patients with left bundle branch block. *Am J Cardiol* 1993; 71: 450-453
9. 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
10. Grines CL, Bashore TM, Boudoulas H, Olson S, Shafer P, Wooley CF. Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony. *Circulation* 1989; 79: 845-853
11. McDonald IG. Echocardiographic demonstration of abnormal motion of the interventricular septum in left bundle branch block. *Circulation* 1973; 48: 272-280
12. Abbasi AS, Eber LM, McAlpin RN, Kattus AA. Paradoxical motion of interventricular septum in left bundle branch block. *Circulation* 1974; 49: 423-427
13. Dillon JC, Chang S, Feigenbaum H. Echocardiographic manifestations of left bundle branch block. *Circulation* 1974; 49: 876-880
14. Fujii J, Watanabe H, Watanabe T, Takahashi N, Ohta A, Kato K. M-mode and cross-sectional echocardiographic study of the left ventricular wall motions in complete left bundle branch block. *Br Heart J* 1979; 42: 255-260
15. Strasberg B, Rich S, Lam W, Swiryn S, Bauernfeind R, Rosen KM. M-mode echocardiography in left bundle branch block: Significance of frontal plane QRS axis. *Am Heart J* 1982;104: 775-779
16. Curtius JM, Nowitzki G, Köhler E, Kuhn H, Loogen F. Left bundle branch block: correlations between interventricular septal motion in the M-mode echocardiogram and left ventricular function. *Z Kardiol* 1983; 72: 635-641
17. Geleijnse ML, Fioretti PM, Roelandt JRTC. Methodology, feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography *J Am Coll Cardiol* 1997; 30: 595-606
18. Xiao HB, Brecker SJD, Gibson DG. Different effects of right ventricular pacing and left bundle branch block on left ventricular function. *Br Heart J* 1993; 69: 166-173
19. Gomes JAC, Damato AN, Akhtar M, Dhatt MS, Calon AH, Pratap Reddy CP, Moran HE. Ventricular septal motion and left ventricular dimensions during abnormal ventricular activation. *Am J Cardiol* 1977; 39: 641-650
20. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. *N Engl J Med* 1979; 300: 1350-8
21. Wilson FN, MacLeod AG, Barker PS. The order of ventricular excitation in human bundle branch block. *Am Heart J* 1932; 7: 305-330
22. American Society of Echocardiography Committee on Standards. Subcommittee on Quantitation of Two-Dimensional Echocardiograms. Recommendations of quantification of the left ventricle by two-dimensional echocardiography. *J Am Soc Echocardiogr* 1989; 2: 358-367.
23. Senior R, Lahiri A. Enhanced detection of myocardial ischemia by stress dobutamine echocardiography utilizing the "biphasic" response of wall thickening during low and high dose dobutamine infusion. *J Am Coll Cardiol* 1995; 26: 26-32.
24. Popp RL, Alderman EL, Brown OR, Harrison DC. Sources of error in calculation of left ventricular volume by echocardiography. *Am J Cardiol* 1973; 31: 152-
25. Reiber JHC, Serruys PW, Kooijman CJ Wiins W, Slager CJ, Gerbrands JJ, Suurbiers JC, den Boer A, Hugenholtz PG. Assessment of short-, medium-, and long-term variations in arterial dimensions from

computer-assisted quantitation of coronary cineangiograms. *Circulation* 1985; 71: 280-288
26. 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
27. Olsson RA, Bunger R. Metabolic control of coronary flow. *Prog Cardiovasc Dis* 1987; 29: 369-387
28. Master AM, Dack S, Jaffe HL. Bundle branch block and intraventricular block in acute coronary artery occlusion. *Am Heart J* 1938; 16: 283-308
29. Gerwitz H, Grotte GJ, Strauss HW, O'Keefe DD, Akins CW, Daggett WM, Pohost GM. The influence of ventricular volume and wall motion on myocardial images. *Circulation* 1979; 59: 1172-1177
30. Arnese M, Fioretti PM, Cornel JH, Postma-Tjoa J, Reijs AE, Roelandt JRTC. Akinesis becoming dyskinesis during high-dose dobutamine stress echocardiography: a marker of myocardial ischemia or a mechanical phenomenon? *Am J Cardiol* 1994; 73: 896-899
31. Elhendy A, Van Domburg RT, Roelandt JRTC, Geleijnse ML, Cornel JH, El-Said GM, Fioretti PM. Accuracy of dobutamine stress echocardiography for the diagnosis of coronary artery stenosis in patients with myocardial infarction: the impact of extent and severity of left ventricular dysfunction. *Heart* 1996; 76: 123-128
32. Sharp SM, Sawada SG, Segar DS, Ryan T, Kovacs R, Fineberg NS, Feigenbaum H. Dobutamine stress echocardiography: detection of coronary artery disease in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 1994; 24: 934-939
33. Mairesse GH, Marwick TH, Arnese M, Vanoverschelde JLJ, Cornel JH, Detry JMR, Melin JA, Fioretti PM. 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
34. Carstensen S, Ali SM, Stensgaard-Hansen FV, et al. Dobutamine-atropine stress echocardiography in asymptomatic healthy individuals. The relativity of stress-induced hyperkinesia. *Circulation* 1995; 92: 3453-63.
35. Cannon RO III, Cunnion RE, Parrillo JE, Palmeri ST, Tucker EE, Schenke WH, Epstein SE. Dynamic limitation of coronary vasodilator reserve in patients with dilated cardiomyopathy and chest pain. *J Am Coll Cardiol* 1987; 10: 1190-1200

Part C – Prognostic merits

Chapter 9

Prognostic value of dobutamine-atropine stress technetium-99m sestamibi perfusion scintigraphy in patients with chest pain

Geleijnse ML, Elhendy A, Van Domburg RT, Cornel JH, Reijs AEM, Roelandt JRTC, Krenning EP, Fioretti PM

J Am Coll Cardiol 1996; 28: 447-454

Prognostic Value of Dobutamine-Atropine Stress Technetium-99m Sestamibi Perfusion Scintigraphy in Patients With Chest Pain

MARCEL L. GELEIJNSE, MD, ABDOU ELHENDY, MD, PHD, RON T. VAN DOMBURG, MSC, JAN H. CORNEL, MD, AMBROOS E. M. REIJS, MSC, JOS R. T. C. ROELANDT, MD, PHD, FACC, ERIC P. KRENNING, MD, PHD, PAOLO M. FIORETTI, MD, PHD, FACC

Rotterdam, The Netherlands

Objectives. This study investigated the prognostic value of dobutamine-atropine technetium-99m (Tc-99m) sestamibi single-photon emission computed tomographic (SPECT) myocardial perfusion imaging.

Background. Dobutamine-atropine Tc-99m sestamibi SPECT imaging is an accurate method for the detection of coronary disease. However, the prognostic value of this stress modality has not been assessed.

Methods. Three hundred ninety-two consecutive patients with chest pain (mean [±SD] age 60 ± 12 years; 220 men, 190 with a previous myocardial infarction) underwent a dobutamine-atropine Tc-99m sestamibi SPECT scintigraphic study. Patients were followed up for 22 ± 13 months to determine the univariate and multivariate variables associated with hard cardiac events (cardiac death, nonfatal myocardial infarction), to define their event-free survival and to determine whether the extent and severity of reversible perfusion defects correlated with events.

Results. Forty-four patients (11%) had hard cardiac events. Multivariate models demonstrated that older age (odds ratio [OR] 2.1, 95% confidence interval [CI] 1.0 to 4.4), history of heart failure (OR 2.6, 95% CI 1.3 to 5.2), abnormal sestamibi scan results (OR 10.0, 95% CI 2.3 to 43.0) and reversible perfusion defects (OR 3.2, 95% CI 1.6 to 6.4) had independent predictive value. Patients without perfusion defects, with fixed defects alone, reversible defects alone and fixed plus reversible defects had annual hard cardiac event rates of 0.8%, 6.8%, 8.1% and 11.6%, respectively. Patients with increasing reversible defect scores had increasing annual event rates of 2.1%, 5.0%, 5.5%, 13.0% and 14.6%, respectively.

Conclusions. Dobutamine-atropine stress Tc-99m sestamibi SPECT imaging provides excellent prognostic information. The single most important independent predictor for future hard cardiac events is an abnormal pattern, and a reversible defect provides additional, independent prognostic information. Moreover, the extent and severity of reversible defects are major determinants for prognosis.

(J Am Coll Cardiol 1996;28:447–54)

Exercise testing provides important diagnostic and prognostic information in patients with known or suspected coronary artery disease (1). Addition of technetium-99m (Tc-99m) sestamibi single-photon emission computed tomographic (SPECT) myocardial perfusion imaging has incremental value for the diagnosis of coronary artery disease (2–4), and a recent study also reported incremental prognostic value (5). However, up to 40% of patients with chest pain are not able to exercise adequately (6), which may significantly reduce the detection of coronary disease. In contrast to exercise stress testing, dobutamine–atropine stress Tc-99m sestamibi SPECT imaging is not dependent on the level of exertion achieved. It is increasingly used as an alternative stress technique (in particular, in patients with contraindications for vasodilator stress), and several investigators have reported that it is an accurate method for the detection of coronary artery disease (7–12). However, to date no study has assessed the prognostic value of this stress modality. Therefore, we studied a large, unselected, consecutive group of patients with chest pain, unable to perform an adequate exercise test, with dobutamine-atropine Tc-99m sestamibi SPECT myocardial perfusion scintigraphy. We hypothesized that abnormal sestamibi scan results carry an increased risk of subsequent cardiac events and that this risk is proportional to the extent of the abnormalities and the presence of reversible perfusion defects.

Methods

Patient selection. Over a 4-year period, between November 1990 and October 1994, 418 consecutive patients with chest pain were referred to the nuclear cardiology laboratory at the Thoraxcentre for the evaluation of suspected myocardial ischemia with dobutamine-atropine Tc-99m sestamibi SPECT imaging. All patients were unable to perform an adequate

From the Thoraxcentre and Department of Nuclear Medicine, University Hospital Rotterdam-Dijkzigt and Erasmus University, Rotterdam, The Netherlands. This study was supported in part by funds from the Dutch Heart Foundation, The Hague, The Netherlands (Grant NHS 94.135) and Cairo University Hospital, Cairo, Egypt, and was presented in part at the 43rd Annual Scientific Session of the American College of Cardiology, Orlando, Florida, March 1996.

Manuscript received September 12, 1995; revised manuscript received March 14, 1996, accepted March 27, 1996.

Address for correspondence: Dr. Paolo M. Fioretti, Thoraxcentre, Ba 302, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

exercise test, and none had undergone prior heart transplantation or had significant congenital or valvular heart disease, primary dilated cardiomyopathy, recent (<3 months) angioplasty or unstable angina. Twenty-six patients with early elective coronary revascularization within 60 days after stress testing were excluded from the analysis. None of these 26 patients sustained a major cardiac event before coronary revascularization. The mean age of the remaining 392 patients was 60 ± 12 years (range 23 to 85), 220 were men (56%), 190 (48%) had a previous myocardial infarction, and 43 (11%) were known to have coronary artery disease without myocardial infarction. Ninety-five patients (24%) had typical angina, 196 (50%) had atypical angina, and 101 (26%) had nonanginal chest pain. At the time of the study, 279 patients (71%) were receiving antianginal therapy, including beta-adrenergic blocking agents in 161 patients (41%), administrated either alone in 43 (11%) or in combination with nitrates or calcium channel blocking agents, or both, in 118 patients (30%).

Dobutamine-atropine stress test. After routine preparation, a rest electrocardiogram (ECG) was obtained, intravenous access was secured and dobutamine was administered intravenously by an infusion pump. The infusion rate was 10 μg/kg body weight per min for 3 min, increasing by 10 μg/kg per min every 3 min up to a maximum of 40 μg/kg per min. In patients not achieving 85% of their predicted maximal heart rate for their age and gender and without symptoms or signs of myocardial ischemia, atropine was administered in addition to the maximal dose of dobutamine, starting with 0.25 mg intravenously and repeated up to a maximum of 1.0 mg within 4 min with continuation of dobutamine infusion. Throughout dobutamine infusion the ECG (3 leads) was continuously monitored and recorded (12 leads) at 1-min intervals. The level of ST segment shift was calculated, after signal averaging, by a computer-assisted system (Cardiovit CSG/12; Schiller, Baar, Switzerland). Blood pressure was measured and recorded by sphygmanometry every 3 min. Reasons for interruption of the test were horizontal or downsloping ST segment depression >0.2 mV at an interval of 80 ms after the J point compared with baseline, ST segment elevation >0.1 mV in patients without previous myocardial infarction, severe angina, a symptomatic reduction in systolic blood pressure (>40 mm Hg from baseline), hypertension (blood pressure >240/120 mm Hg), significant cardiac tachyarrhythmias and any serious side effect regarded as being due to dobutamine. Metoprolol was available and used to reverse the effects of dobutamine if they did not revert spontaneously and quickly.

Perfusion imaging. At peak stress, 370 MBq of Tc-99m sestamibi was injected intravenously while dobutamine infusion was continued for at least 1 min. Stress scintigraphic images were acquired on average 1 h after the termination of the dobutamine infusion. For rest studies, patients were reinjected with 370 MBq of Tc-99m sestamibi at least 24 h after the stress study. Image acquisition was done with a Siemens Gammasonics single-head Orbiter camera. For each study six oblique (short-axis) slices were defined from the apex to the base and three sagittal (vertical long-axis) slices from the septum to the lateral wall. To compare the stress and rest studies, each of the six short-axis slices was divided into eight equal segments. The septal part of the two basal slices (four segments) was not evaluated because this region corresponds to the fibrous portion of the interventricular septum and normally exhibits reduced uptake. The apical region was assessed from the three central sagittal cross sections. A total of 47 segments/patient were analyzed. All tomographic views were reviewed in side-by-side pairs (stress and rest) by two experienced observers who were unaware of the patient's clinical history and other stress results. In case of disagreement, a third investigator reviewed the images and a majority decision was made. Subsequently, the 47 segments were grouped into six major segments: anterior, septum anterior, septum posterior, inferoposterior, lateral and apical. The myocardial uptake of radiotracer was evaluated visually (with the assistance of circumferential profiles analysis, including the normal values) for each of the six major segments during both rest and stress with a four-point scoring method (0 = normal; 1 = equivocal or minimally reduced uptake; 2 = moderately reduced uptake; 3 = severely reduced or absent uptake). Scan results were initially characterized as *abnormal* or *normal*. Scan results were considered normal in the absence of any defect or the presence of only equivocal defects. Abnormal scan results were further classified as demonstrating *fixed defects* (rest perfusion defects) or *reversible defects* (perfusion defects during stress that partially or totally resolved at rest). To measure the influence of the extent and severity of the perfusion defect, a fixed defect score was calculated by summing the fixed perfusion defects, according to a 6 (extent) × 4 (severity) point model (range 0 to 18); similarly, a reversible defect score was calculated by summing the reversible perfusion defect scores. Subsequently, this latter score was corrected for stress level by dividing it by the following correction factor: percent target heart rate reached times peak systolic blood pressure divided by 100. Patients with a zero reversible defect score were classified into a low stress level group (correction factor <1.6) and a high stress level group (correction factor >1.6). This cutoff value was chosen to classify patients with zero scores into two equally sized groups.

Follow-up. Follow-up data were obtained over 22 ± 13 months (range 6 to 54) by outpatient clinic assessment, review of case notes and contacting the patient, general practitioner or other hospitals when necessary. Outcome events were cardiac death, nonfatal myocardial infarction and revascularization (coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty). Cardiac death was defined as a death temporally associated with a known or suspected acute myocardial infarction, life-threatening arrhythmia or pulmonary edema. Unexpected death without an identified noncardiac cause and heart transplantation were also considered as cardiac death. Occurrence of an acute myocardial infarction was confirmed using standard clinical and ECG criteria and when total creatine kinase (CK) enzyme levels exceeded twice normal. Hard cardiac events (cardiac death

Table 1. Clinical and Stress Test Data for 392 Study Patients (hard cardiac events)

	No Cardiac Event (n = 348)	Cardiac Event (n = 44)	p Value
Age >70 yr	64 (18%)	12 (27%)	0.0804
Male	187 (54%)	33 (75%)	0.0037
Risk factors			
Diabetes	50 (14%)	9 (20%)	0.1440
Hypercholesterolemia	89 (26%)	9 (20%)	0.7698
Hypertension	146 (42%)	22 (50%)	0.1551
Smoking	96 (28%)	15 (34%)	0.2958
History			
Myocardial infarction	160 (46%)	30 (68%)	0.0028
Congestive heart failure	59 (17%)	17 (39%)	0.0003
Revascularization	105 (30%)	17 (39%)	0.1269
Typical angina	80 (23%)	15 (34%)	0.0529
Stress test			
Angina during stress	86 (25%)	16 (36%)	0.0487
ST-T wave changes	57 (16%)	11 (25%)	0.0776
MIBI scan pattern			
Abnormal	220 (63%)	42 (95%)	0.0000
Fixed defect	169 (49%)	33 (75%)	0.0005
Reversible defect	130 (37%)	30 (68%)	0.0000

Data presented are number (%) of patients. MIBI = technetium-99m sestamibi.

Table 2. Clinical and Stress Test Data for 392 Study Patients (all cardiac events)

	No Cardiac Events (n = 314)	Cardiac Events (n = 78)	p Value
Age >70 yr	61 (19%)	15 (19%)	0.5156
Male	167 (53%)	53 (68%)	0.0094
Risk factors			
Diabetes	46 (15%)	13 (17%)	0.3281
Hypercholesterolemia	80 (25%)	18 (23%)	0.6692
Hypertension	132 (42%)	36 (46%)	0.2557
Smoking	87 (28%)	24 (31%)	0.2958
History			
Myocardial infarction	138 (44%)	52 (67%)	0.0002
Congestive heart failure	53 (17%)	23 (29%)	0.0059
Revascularization	88 (28%)	34 (44%)	0.0040
Typical angina	61 (19%)	34 (44%)	0.0000
Stress test			
Angina during stress	73 (23%)	29 (37%)	0.0061
ST-T wave changes	47 (15%)	21 (27%)	0.0063
MIBI scan pattern			
Abnormal	190 (61%)	72 (92%)	0.0000
Fixed defect	146 (46%)	56 (72%)	0.0000
Reversible defect	108 (34%)	52 (67%)	0.0000

Format as in Table 1.

and nonfatal myocardial infarction) and all cardiac events (hard events or revascularization) were analyzed as end points.

Statistical analysis. Values were expressed as mean value ± SD, when appropriate. Comparison (two-tailed) of patients with and without cardiac events was performed with the Student *t* test for continuous variables and chi-square test for discrete variables. Differences of $p < 0.05$ were considered significant. Multivariate logistic regression using the BMDP package (13) was performed to identify factors that were related to events. A forward and backward stepping algorithm was used with $p < 0.05$ to identify the independent predictors for both hard and all events. Baseline variables tested were the clinical and stress test variables, as displayed in Tables 1 and 2. Odds ratio and 95% confidence intervals were calculated for variables used in the multivariate model. Kaplan-Meier life-table estimates of infarction-free survival (survival without cardiac death or nonfatal myocardial infarction) and event-free survival (survival without cardiac death, nonfatal myocardial infarction or revascularization) were used to summarize the follow-up experience and to clarify presentation.

Results

Dobutamine-atropine stress test. *Hemodynamic results, end points and side effects.* The maximal dobutamine dose used was 10 μg/kg per min in 1 patient, 20 μg/kg per min in 5 patients, 30 μg/kg per min in 56 patients and 40 μg/kg per min in 330 patients. Atropine was added in 169 patients (43%) and was more often used in patients receiving beta-blockers (108 of 161 with vs. 61 of 231 without beta-blockers, $p < 0.0001$). In the overall group, dobutamine-atropine increased heart rate by 65 ± 15 beats/min to a peak heart rate of 135 ± 17 beats/min, systolic blood pressure by 10 ± 27 mm Hg to a peak pressure of 148 ± 31 mm Hg and rate-pressure product by 10,332 ± 3,764 mm Hg × beats/min to a peak rate-pressure product of 20,025 ± 4,848 mm Hg × beats/min.

Target heart rate (85% of maximum for age and gender) was not reached in 77 tests (20%) either after the maximal dobutamine-atropine dose had been given in 28 patients (7%) or when prematurely stopping the test in 49 patients (14%). The test was prematurely stopped in patients because of angina in 33, ST segment changes in 3, hypertension in 3, symptomatic hypotension in 4, nonsustained ventricular tachycardia in 3, anxiety in 2 and headache in 1. Most patients not reaching their target heart rate because of an insufficient dose of dobutamine-atropine were on beta-blockers (22 of 28 with vs. 6 of 28 without beta-blockers, $p < 0.0001$). Nondiagnostic tests (target heart rate not reached in the absence of reversible perfusion defects) were present in 30 patients (8%). Tachyarrhythmias during dobutamine infusion or recovery were not uncommon; 10 patients (3%) had supraventricular tachycardia, and 17 (4%) had (nonsustained) ventricular tachycardia. Apart from angina (induced in 102 patients [26%]), side effects were unusual and minor (side effects occurring in >5% of patients were chills in 5%, headache in 6% and nausea in 5%). Three hundred twenty-two patients (82%) were free of any side effect (not considering angina).

Distribution of imaging patterns. One hundred thirty patients (33%) had normal (or equivocal in 30) scan results, and 262 (67%) had abnormal results. Scan abnormalities

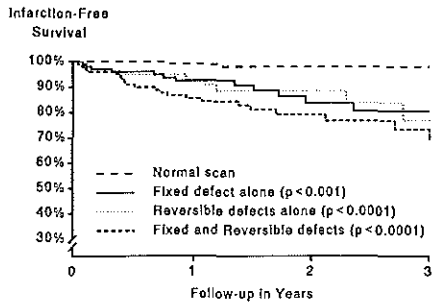


Figure 1. Kaplan-Meier infarction-free survival curves in patients with normal scan results, fixed defects alone, reversible defects alone and mixed defects. Infarction-free survival was significantly lower in patients with fixed defects alone ($p < 0.001$), reversible defects alone ($p < 0.0001$) and mixed defects ($p < 0.0001$) than in those with normal scan results. The number of patients available for follow-up at 0, 1, 2 and 3 years, respectively, was 130, 109, 46 and 28 in the subset with normal scan results; 102, 74, 32 and 17 in the subset with fixed defects alone; 60, 48, 26 and 9 in the subset with reversible defects alone; and 100, 76, 34 and 20 in the subset with mixed defects.

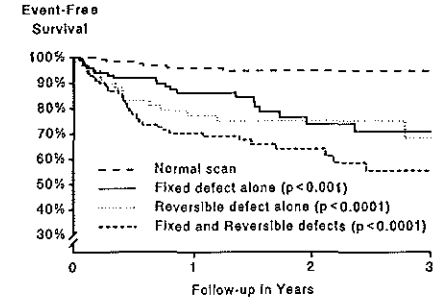


Figure 2. Kaplan-Meier event-free survival curves in patients with normal scan results, fixed defects alone, reversible defects alone and mixed defects. Event-free survival was significantly lower in patients with fixed defects alone ($p < 0.001$), reversible defects alone ($p < 0.0001$) and mixed defects ($p < 0.0001$) than in those with normal scan results. The number of patients available for follow-up at 0, 1, 2 and 3 years, respectively, was 130, 105, 44 and 27 in the subset with normal scan results; 102, 69, 29 and 15 in the subset with fixed defects alone; 60, 39, 23 and 8 in the subset with reversible defects alone; and 100, 62, 25 and 15 in the subset with mixed defects.

included fixed defects alone in 102 patients (26%), reversible perfusion defects alone in 60 (15%) and fixed plus reversible defects (or partially reversible defects) in 100 (26%). In total, 202 patients (52%) had fixed defects, and 160 (41%) had reversible perfusion defects.

Clinical outcome. The mean follow-up period was 22 ± 13 months for patients with and without reversible defects. Eighteen patients (5%) had an "incomplete" follow-up, 13 because of noncardiac death (cancer in 8, pneumonia in 2, acquired immune deficiency syndrome in 1, complicated hip fracture in 1 and myelodysplasia in 1) and 5 because of geographic relocation. Cardiac events occurred in 78 patients, 44 of whom had hard cardiac events (nonfatal myocardial infarction in 17 and cardiac death in 27).

Prediction of events from clinical and stress test results. *Univariate analysis.* In Tables 1 and 2 the clinical and stress test data in patients with and without hard and all cardiac events are summarized. Clinical variables associated with hard cardiac events were male gender, a history of myocardial infarction and a history of congestive heart failure. Clinical variables associated with all cardiac events were male gender and history of myocardial infarction, coronary revascularization, congestive heart failure or typical angina. Apart from peak heart rate in patients with any versus without any event (132 ± 18 vs. 136 ± 17, $p < 0.05$), no hemodynamic variable (rest and peak heart rate, blood pressure and rate-pressure product) was associated with an increased rate of hard or all cardiac events. Of the other stress test variables, stress-induced angina was associated with both hard and all events and ST-T wave changes were only associated with all cardiac events. Sestamibi scan patterns associated with both hard and all cardiac events were the presence of abnormalities on the scan (any perfusion abnormality), fixed perfusion defects and reversible perfusion defects.

The infarction-free and event-free survival curves in patients with normal scan results, fixed defects alone, reversible defects alone and mixed (fixed and reversible) defects are depicted in Figures 1 and 2. Normal scan results were associated with a favorable prognosis over the follow-up period, with an annual event rate of 0.8% for hard events and 2.5% for all events. In contrast, patients with fixed defects alone, reversible defects alone and fixed plus reversible defects had a significantly increased cardiac event rate of 6.8%, 8.1% and 11.6%, respectively, for hard events, and 11.4%, 14.5% and 19.9%, respectively, for all events. Compared with normal scan results, reversible perfusion defects alone increased the risk for future hard events tenfold and for all events sixfold. Compared with fixed defects alone, fixed plus reversible perfusion defects increased the risk for both hard events and all events twofold.

Multivariate analysis, addition of perfusion scintigraphy to clinical data. Tables 3 and 4 summarize the results of univariate and multivariate (stepwise logistic regression) analysis of clinical and stress test data to predict subsequent hard and all cardiac events. Multivariate analysis of clinical variables (Table 3, Clinical Data) revealed male gender (odds ratio [OR] 2.3, 95% confidence interval [CI] 1.1 to 4.7) and a history of congestive heart failure (OR 2.7, 95% CI 1.4 to 5.4) as independent predictors of subsequent hard cardiac events. The addition of scan patterns to this analysis was performed according to two different models. In the first model (Table 3, Model I) the only scan pattern variable entered was the presence of an "abnormal scan" (any abnormality), and in the second model (Table 3, Model II) the presence of a fixed or reversible perfusion defect was separately included. A history of congestive heart failure (OR 2.0, 95% CI 1.0 to 3.9) and

Table 3. Association by Univariate and Multivariate Analysis of Clinical and Stress Test Data With Hard Cardiac Events: Odds Ratios (95% confidence intervals)

		Multivariate Analysis of Clinical and Stress Test Data		
	Univariate Analysis	Clinical Data	Model I	Model II
Clinical data				
Age >70 yr	1.6 (0.8–3.4)*	*	*	2.1 (1.0–4.4)
Male	2.6 (1.3–5.3)	2.3 (1.1–4.7)	*	*
History of infarction	2.5 (1.3–4.9)	*	*	*
History of revascularization	1.5 (0.8–2.8)*	*	*	*
History of heart failure	3.1 (1.6–6.0)	2.7 (1.4–5.4)	2.0 (1.0–3.9)	2.6 (1.3–5.2)
Typical angina	1.7 (0.9–3.4)*	*	*	*
Stress test data				
Angina	1.7 (0.9–3.4)*	—	*	*
ST-T wave changes	1.7 (0.8–3.6)*	—	*	*
Scan abnormalities	12.2 (2.9–51.3)	—	10.0 (2.3–43.0)	—
Fixed defect	3.2 (1.6–6.5)	—	—	*
Reversible defect	3.6 (1.8–7.0)	—	—	3.2 (1.6–6.4)

*p value not significant. In model I, scan variables included scan abnormalities. In model II, pattern variables included fixed defect and reversible defect and excluded scan abnormalities. — = variable excluded.

abnormal scan results (OR 10.0, 95% CI 2.3 to 43.0) in model I were independent predictors of hard cardiac events. In model II, older age (OR 2.1, 95% CI 1.0 to 4.4) and reversible perfusion defects (OR 3.2, 95% CI 1.6 to 6.4) were independent predictors of hard cardiac events.

For all cardiac events (Table 4), the clinical variables history of myocardial infarction (OR 2.9, 95% CI 1.7 to 5.1) and typical angina (OR 3.3, 95% CI 1.9 to 5.7) were independent predictors in the clinical model. In model I, independent predictors were history of typical angina (OR 3.2, 95% CI 1.9 to 5.6) and abnormal scan results (OR 7.9, 95% CI, 3.3 to 18.9). In model II, a history of typical angina (OR 2.9, 95% CI 1.7 to 5.1), fixed perfusion defects (OR 2.5, 95% CI 1.4 to 4.4) and reversible perfusion defects (OR 3.1, 95% CI 1.8 to 5.4) were independent predictors of all cardiac events.

Extent and severity of perfusion defects and prognosis. As described in the legend to Figure 3, 162 patients had a fixed perfusion defect score of zero, 114 had a score of one to three, 70 of four to six, 27 of seven to nine and 19 of ten or higher. At the end of the follow-up period, the annual hard event rate for patients with these fixed perfusion defect scores were 3.3% (mean follow-up 23 months), 5.0% (23 months), 8.1% (21 months), 11.5% (23 months) and 36.4% (12 months), respectively. For all events, these numbers were 5.6%, 13.2%, 13.0%, 17.2% and 36.4%, respectively. As seen in the legend to Figure 4, 100 patients had a stress level corrected reversible perfusion defect zero score with "high stress" (correction factor >1.6), 100 patients had a zero score with "low stress" (correction factor <1.6), 109 had a score of one or two, 62 of three or four and 21 of five or higher. At the end of the follow-up period, the annual hard event rate for the different reversible perfusion defect scores was 2.1% (mean follow-up 21 months), 5.0% (23 months), 5.5% (22 months), 13.0% (22 months) and 14.6% (20 months), respectively. For all events, these numbers were 4.2%, 7.8%, 11.5%, 20.9% and 26.3%, respectively.

Discussion

The present study addressed the prognostic value of dobutamine-atropine stress Tc-99m sestamibi SPECT imaging in patients referred with chest pain and suspected myocardial ischemia. Dobutamine stress is frequently used in conjunction with echocardiography and has been shown to provide important prognostic information (14). However, to our knowledge, no information is available when dobutamine stress is used in conjunction with perfusion imaging. The main finding of this study is that, in patients with chest pain who are unable to perform an adequate exercise test, the test provides useful prognostic information in addition to clinical data.

Stress technique. Dobutamine is a synthetic sympathomimetic amine that stimulates $beta_1$, $beta_2$ and $alpha_1$ receptors. As a result, there is a marked inotropic response (mediated by both $alpha_1$ and $beta_1$ receptors), a modest chronotropic response (mediated by $beta_1$ receptors) and a minor increase in systolic blood pressure (due to $alpha_1$- and $beta_1$-mediated increase in cardiac output and relative stable peripheral vasculature tonus, mediated by $alpha_1$ vasoconstriction and $beta_2$ vasodilation) (15). As a result of this augmentation of myocardial contractility, heart rate, left ventricular pressure and wall stress, more oxygen is required. Normally a dose-related increase in subepicardial and subendocardial blood flow occurs within myocardium supplied by normal coronary arteries (16,17). However, blood flow increases minimally within vascular beds supplied by significantly stenosed arteries, with most of the increase occurring within the subepicardium rather than the subendocardium (16). This heterogeneity in myocardial blood flow between normal and abnormal perfused areas can be visualized by Tc-99m sestamibi myocardial perfusion scintigraphy.

Although direct vasodilators (dipyridamole and adenosine) are believed to be superior in creating blood flow heterogene-

Table 4. Association by Univariate and Multivariate Analysis of Clinical and Stress Test Data With All Cardiac Events: Odds Ratios (95% confidence intervals)

		Multivariate Analysis of Clinical and Stress Test Data		
	Univariate Analysis	Clinical Data	Model I	Model II
Clinical data				
Age >70 yr	1.0 (0.5–1.9)*	*	*	*
Male	1.9 (1.1–3.2)	*	*	*
History of infarction	2.5 (1.5–4.3)	2.7 (1.6–4.5)	*	*
History of revascularization	2.0 (1.2–3.3)	*	*	*
History of heart failure	2.1 (1.2–3.6)	*	*	*
Typical angina	3.2 (1.9–5.4)	3.3 (1.9–5.7)	3.2 (1.9–5.6)	2.9 (1.7–5.1)
Stress test data				
Angina	2.0 (1.2–3.3)	—	*	*
ST-T wave changes	2.1 (1.2–3.8)	—	*	*
Abnormal scan	7.8 (3.3–18.6)	—	7.9 (3.3–18.9)	—
Fixed defect	2.9 (1.7–5.0)	—	—	2.5 (1.4–4.4)
Reversible defect	3.8 (2.3–6.5)	—	—	3.1 (1.8–5.4)

Format as in Table 3.

ity (16), dobutamine Tc-99m sestamibi SPECT imaging has a good accuracy for the detection of coronary artery disease when used in conjunction with perfusion scintigraphic techniques. Pooled data from six published studies in 380 patients (7–12) show a sensitivity of 84% and a specificity of 71% for the detection of coronary artery disease. Moreover, a direct comparison by Marwick et al. (18) between vasodilator and dobutamine for Tc-99m sestamibi myocardial perfusion scintigraphy in 97 patients yielded similar diagnostic accuracies of the two stress agents. Thus, dobutamine can be regarded as an excellent alternative stress agent in patients unable to perform adequate exercise, in particular in those patients with relative contraindications for vasodilator stress (mainly patients with obstructive airway disease) or in patients who have ingested caffeine or aminophylline shortly before undergoing myocardial perfusion stress imaging.

Safety and feasibility. As shown in other (echocardiographic) studies (19–21), dobutamine-atropine stress is a safe and feasible stress method in patients with chest pain. In this study, there were no serious side effects like sustained ventricular tachycardia, ventricular fibrillation, myocardial infarction or death. The feasibility of the test was also high, as only 30 patients (8%) had a nondiagnostic test and 322 patients (82%) were free of any side effect.

Prognostic value. The present study indicates that patients at greater risk for hard or all cardiac events can be identified from a stable chest pain population by virtue of their clinical (older age, male gender and history of myocardial infarction, revascularization procedures, congestive heart failure or typical angina) and scintigraphic (abnormal scan results, fixed or reversible perfusion defects) profile.

The single most important independent predictor of subsequent events was abnormalities on the perfusion study (any abnormality); such an abnormal finding increased the risk for subsequent hard cardiac events tenfold and for all events

Figure 3. Histogram showing the annual event rate for hard events (open bars) and all events (hatched bars) according to extent and severity score of fixed perfusion defects. The number of patients in each category was 162, 114, 70, 27 and 19, respectively.

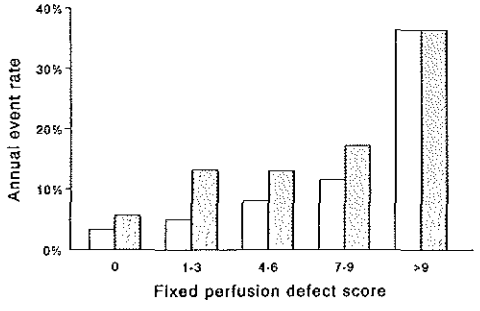
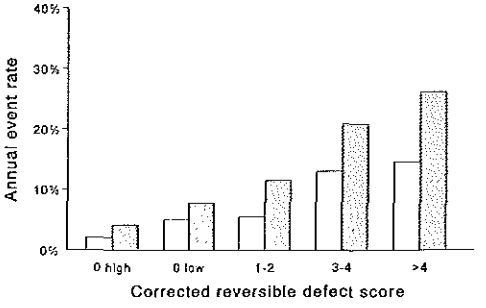


Figure 4. Histogram showing the annual event rate for hard events (open bars) and all events (hatched bars) according to the (stress level [high/low] corrected) extent and severity score of reversible perfusion defects. The number of patients in each category was 100, 100, 109, 62 and 21, respectively.



eightfold. A normal scan conferred a good prognosis and identified 33% of the subgroup that was at a very low risk for hard events (annual event rate 0.8%) and low risk for all events (annual event rate 2.5%). Furthermore, an ischemic pattern provided additional, independent prognostic value. Compared with patients without ischemia, these patients had a threefold increased risk for both hard and all events.

Prognostic value according to extent and severity of perfusion defects. This study clearly shows a direct relation between the extent and severity of the perfusion defects and prognosis. Several other investigators, using mainly exercise planar or SPECT thallium-201 imaging, have described a relation between the extent of the perfusion defect and subsequent coronary events (22–25). In particular, the degree of hypoperfusion on SPECT imaging, with its ability to provide much finer segmental analysis, avoiding the problem of superimposition that occurs with planar imaging, is directly related to the extent of the myocardium either already destroyed by a previous infarct or ischemic but viable and at risk for necrosis. Although the extent of coronary artery disease is an important prognostic indicator (26), sestamibi SPECT imaging represents the functional significance of the stenoses, a factor which may be superior to angiographic data (27).

Comparison with other sestamibi studies. In comparable patient populations, most published data regarding Tc-99m sestamibi in combination with other stress techniques found striking similar results. Stratmann et al. (5) reported the prognostic value of exercise Tc-99m sestamibi imaging in 521 patients. During multivariate analysis, abnormal scan results (OR 11.9, 95% CI 1.6 to 89.4) and reversible defects (OR 2.9, 95% CI 1.2 to 7.0) were the only independent predictors of hard cardiac events. Patients with normal scan results had an annual event rate of 0.4%. In another study by Stratmann et al. (28), comparable prognostic results were reported for dipyridamole Tc-99m sestamibi imaging in 308 patients. Patients with normal scan results had an annual event (unstable angina, nonfatal myocardial infarction or cardiac death) rate of 1.7%. Several studies focused on the predictive value of normal Tc-99m sestamibi imaging for the prediction of hard cardiac events. Both exercise (29,30) and dipyridamole (31) studies found annual event rates <1%.

Study limitations. Although recurrent angina may be a marker of ischemia, the subjective nature of this symptom, as well as influence by medication usage and other factors, makes this a potential unreliable end point of prognostic testing. Furthermore, the decision to perform coronary arteriography and subsequent coronary artery bypass graft surgery is frequently influenced by individual physicians' biases and may also be affected by the presence of abnormal findings on the stress study. Therefore, we excluded patients with early elective revascularizations and we analyzed the "hard" events (nonfatal myocardial infarction and cardiac-related death) separately. Because there is limited angiographic information available, our study does not permit assessment of the specificity and sensitivity of dobutamine stress sestamibi perfusion scintigraphy for the detection of significant coronary artery disease.

Increased lung radiotracer uptake, a prognostic marker in previous scintigraphic studies (32) was also not available in the current Tc-99m sestamibi tomographic investigation. The interpretation of the SPECT images was semiquantitative. This type of analysis, however, is still the most frequently used in daily clinical practice. Antianginal medications were not routinely withheld before stress testing; we believe this also reflects daily clinical practice.

Conclusions. In patients unable to exercise adequately, with chest pain and suspected or known coronary disease, dobutamine-atropine stress Tc-99m sestamibi SPECT perfusion imaging is a safe and feasible stress technique. The test provides useful prognostic information, probably comparable with exercise or dipyridamole stress Tc-99m sestamibi imaging studies. The single most important independent predictor of both hard (nonfatal myocardial infarction or cardiac death) and all (hard events or revascularization procedures) cardiac events is an abnormal perfusion pattern (any abnormality); the presence of a reversible perfusion defect provides additional, independent prognostic information. Moreover, the extent and severity of the perfusion defects are major determinants for prognosis.

We thank Joyce Postma-Tjoa, nuclear medicine technician, for invaluable help in maintaining the data base.

References

1. Chaitman BR. The changing role of the exercise electrocardiogram as a diagnostic and prognostic test for chronic ischemic heart disease. J Am Coll Cardiol 1986;8:1195–1210.
2. Sochor H. Technetium-99m sestamibi in chronic coronary artery disease: the European experience. Am J Cardiol 1990;66:91E–96E.
3. Maddahi J, Kiat H, Van Train KF, et al. Myocardial perfusion imaging with technetium-99m sestamibi SPECT in the evaluation of coronary artery disease. Am J Cardiol 1990;66:55E–62E.
4. Berman DS, Kiat H, Van Train K, Garcia E, Friedman J, Maddahi J. Technetium-99m sestamibi in the assessment of chronic coronary artery disease. Semin Nucl Med 1991;21:190–212.
5. Stratmann HG, Williams GA, Wittry MD, Chaitman BR, Miller DD. Exercise technetium-99m sestamibi tomography for cardiac risk stratification of patients with stable chest pain. Circulation 1994;89:615–22.
6. Marwick TH. Current status of non-invasive techniques for the diagnosis of myocardial ischemia. Acta Clin Belg 1992;47:1–5.
7. Forster T, McNeill AJ, Salustri A, et al. 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;21:1591–6.
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;34:889–94.
9. Marwick T, D'Hondt A, Baudhuin T, et al. 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;22:159–67.
10. Herman SD, Labresh KA, Santos-Ocampo CD, et al. Comparison of dobutamine and exercise using technetium-99m sestamibi imaging for the evaluation of coronary artery disease. Am J Cardiol 1994;73:164–9.
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;128:713–8.
12. Voth E, Baer FM, Theissen P, Schneider CA, Sechtem U, Schicha H. Dobutamine 99m-Tc-MIBI single-photon emission tomography: non-exercise-dependent detection of haemodynamically significant coronary artery stenoses. Eur J Nucl Med 1994;21:537–44.
13. Dixon WJ. BMDP Statistical Software. Berkeley (CA): University of California Press, 1992:1105–44.
14. Mazeika PK, Nadazdin A, Oakley CM. Prognostic value of dobutamine echocardiography in patients with high pretest likelihood of coronary artery disease. Am J Cardiol 1993;71:33–9.
15. Ruffolo RR. The pharmacology of dobutamine. Am J Med 1987;294:244–8.
16. 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;76:943–51.
17. Meyer SL, Curry GC, Donsey MS, Twieg DB, Parkey RW, Willerson JT. Influence of dobutamine on hemodynamics and coronary blood flow in patients with and without coronary artery disease. Am J Cardiol 1976;38: 103–8.
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;87:345–54.
19. Picano E, Mathias W, Pingitore A, Bigi R, Previtali M. Safety and tolerability of dobutamine-atropine stress echocardiography: a prospective, multicentre study. Lancet 1994;344:1190–2.
20. Mertes H, Sawada SG, Ryan T, et al. Symptoms, adverse effects, and complications associated with dobutamine stress echocardiography: experience in 1118 patients. Circulation 1993;88:15–9.
21. Poldermans D, Fioretti PM, Boersma E, et al. Safety of dobutamine-atropine stress echocardiography in patients with suspected or proven coronary artery disease: experience in 650 consecutive examinations. Am J Cardiol 1994;73: 456–9.
22. Machecourt J, Longère P, Fagret D, et al. Prognostic value of thallium-201 SPECT myocardial perfusion imaging according to extent of myocardial defect. J Am Coll Cardiol 1994;23:1096–1106.
23. Brown KA, Boucher CA, Okada RD, et al. Prognostic value of exercise thallium-201 imaging in patients presenting for evaluation of chest pain. J Am Coll Cardiol 1983;1:994–1001.
24. Iskandrian AS, Hakki AH, Kane-Marsch S. Prognostic implications of exercise thallium-201 scintigraphy in patients with suspected or known coronary artery disease. Am Heart J 1985;110:135–43.
25. Ladenheim ML, Pollock BH, Rozanski A, et al. Extent and severity of myocardial hypoperfusion as predictors of prognosis in patients with suspected coronary artery disease. J Am Coll Cardiol 1986;7:464–71.
26. European Coronary Surgery Study Group. Long term results of prospective randomized study of coronary artery bypass surgery in stable angina pectoris. Lancet 1982;2:1173–80.
27. Kaul S, Lilly DR, Gasho JA, et al. Prognostic utility of the exercise thallium-201 test in ambulatory patients with chest pain: comparison with cardiac catheterization. Circulation 1988;77:745–58.
28. Stratmann HG, Tamesis BR, Younis LT, et al. Prognostic value of dipyridamole technetium-99m sestamibi myocardial imaging in >300 consecutive patients with stable chest pain [abstract]. J Am Coll Cardiol 1993;21:68A.
29. Berman DS, Kiat H, Hachamovitch R, et al. Prognosis of 1,178 patients with normal exercise Tc-99m sestamibi myocardial perfusion SPECT [abstract]. Eur J Nucl Med 1994;21 Suppl:S78.
30. Raiker K, Sinusas AJ, Zaret BL, Wackers FJT. One-year prognosis of patients with normal Tc99m-sestamibi stress imaging [abstract]. Circulation 1993;88 Suppl I:I-486.
31. Herman SD, Santos-Ocampo CD, McClellan JR, et al. Dipyridamole Tc-99m sestamibi SPECT myocardial perfusion imaging—prognostic implications [abstract]. J Nucl Med 1993;34:85P.
32. Gill JB, Ruddy TD, Newell JB, Finkelstein DM, Strauss HW, Boucher CA. Prognostic importance of thallium uptake by the lungs during exercise in coronary artery disease. N Engl J Med 1987;317:1486–9.

Chapter 10

Prognostic implications of a normal dobutamine-atropine stress echocardiogram in patients with chest pain

Geleijnse ML, Elhendy A, Van Domburg RT,

Cornel JH, Roelandt JRTC, Fioretti PM

J Am Soc Echocardiogr 1998; 11: 606-611

Prognostic Implications of a Normal Dobutamine-Atropine Stress Echocardiogram in Patients with Chest Pain

Marcel L. Geleijnse, MD, Abdou Elhendy, MD, PhD, Ron T. van Domburg, MSc, PhD, Jan H. Cornel, MD, PhD, Jos R. T. C. Roelandt, MD, PhD, and Paolo M. Fioretti, MD, PhD,
Rotterdam, The Netherlands

To assess the prognostic significance of a normal dobutamine-atropine stress echocardiogram in relation to the pretest probability of coronary artery disease (CAD), 200 consecutive patients (86 men and 114 women, mean [SD] age 59 [13] years) with a stable chest pain syndrome and a normal dobutamine-atropine stress echocardiogram were followed-up for 21 ± 16 months. Outcome events were cardiac death, nonfatal myocardial infarction, and coronary revascularization procedures. Low (<10%), intermediate (10% to 80%), and high (>80%) pretest probabilities of CAD were present in 27 (14%), 108 (54%), and 65 (33%) patients, respectively. During follow-up, 2 patients (annual event rate 0.6%) had cardiac death, none had nonfatal myocardial infarction, and 4 patients (annual event rate 1.1%) underwent a coronary revascularization procedure. All patients with cardiac events had high pretest probabilities of CAD. Patients with cardiac death (but unproven significant CAD) had maximal tests without angina or ischemic electrocardiographic changes. In contrast, all patients with subsequent coronary revascularization had dobutamine-induced angina or ischemic electrocardiographic changes, and all except one study were submaximal. We conclude that patients with a stable chest pain syndrome and normal findings on dobutamine-atropine stress echocardiograms have an excellent cardiac prognosis. However, patients with typical angina, high pretest probabilities of CAD, and stress-induced angina or ischemic electrocardiographic changes, and in particular those with submaximal stress, still appear to be at risk for functionally important CAD despite a normal dobutamine-atropine stress echocardiogram. (J Am Soc Echocardiogr 1998;11:606-11.)

Dobutamine stress echocardiography is increasingly used as a noninvasive diagnostic procedure for the evaluation of patients with a stable chest pain syndrome. The diagnostic accuracy of this stress modality for the detection of coronary artery disease (CAD) has been examined previously, and the results of this test are believed to reflect the functional significance of CAD.[1] A more far-reaching use of the method, however, is in risk stratification. Normal stress echocardiograms may identify a group of patients at low risk for future cardiac events, who would be psychologically reassured and in whom no further tests are required. Previous studies analyzed only small subsets of patients with normal studies,[2,3] included patients with resting wall motion abnormalities,[4,5] and did not take into account the pretest likelihood of CAD.[2-5] Therefore, the purpose of the present study was to evaluate the prognostic significance of normal dobutamine-atropine stress echocardiograms in patients with stable chest pain, in particular in relation to the pretest likelihood of CAD.

From the Thoraxcentre, University Hospital Rotterdam-Dijkzigt and Erasmus University.

Presented in part at the 43rd Annual Scientific Sessions of the American College of Cardiology, Orlando, Fla., March 1996.

Supported by the Dutch Heart Foundation (grant NHS 94.135, M.L. Geleijnse) and by the Department of Cardiology, Cairo University Hospital, Cairo, Egypt (A. Elhendy).

Reprint requests: Marcel L. Geleijnse, MD, Thoraxcentre, Ba 302, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

0894-7317/98 $5.00 + 0 27/1/89946

METHODS

Patient Selection

We reviewed the results of all patients who underwent dobutamine-atropine stress echocardiography for evaluation of stable chest pain between November 1990 and June 1995. After exclusion of patients screened for preoperative risk assessment, reported in a previously published study,[6] those with clinically recognized valvular heart disease, congenital heart disease, previous heart transplantation, asynchronous ventricular contraction (left bundle branch block, electronically paced ventricles), and recent (<3 months) angioplasty, 200 patients were identified with normal rest and stress echocardiograms.

Dobutamine Stress Echocardiography Test

A resting electrocardiogram and echocardiogram were made, intravenous access was secured, and dobutamine was administered intravenously by an infusion pump. Infusion rate was 10 μg/kg per minute for 3 minutes, increasing by 10 μg/kg per minute every 3 minutes up to a maximum of 40 μg/kg per minute. In patients not achieving 85% of their theoretical maximal heart rate (220 minus age for men, 200 minus age for women) and without symptoms or signs of myocardial ischemia, atropine was administered in addition to the maximal dose of dobutamine, starting with 0.25 mg intravenously and repeated up to a maximum of 1.0 mg within 4 minutes with continuation of dobutamine infusion. Throughout dobutamine infusion the electrocardiogram (3 leads) was continuously monitored and recorded (12 leads) at 1-minute intervals. The level of ST-segment shift was calculated, after signal averaging, by a computer-assisted system (Cardiovit CSG/12; Schiller, Baar, Switzerland). Blood pressure was measured and recorded by sphygmomanometry or automatic device every 3 minutes. Reasons for interruption of the test were severe and/or extensive new wall motion abnormalities, horizontal or downsloping ST-segment depression >0.2 mV at an interval of 80 msec after the J point compared with baseline, ST-segment elevation >0.1 mV in patients without previous myocardial infarction, severe angina, a symptomatic reduction in systolic blood pressure >40 mm Hg from baseline, hypertension (blood pressure >240/120 mm Hg), significant cardiac tachyarrhythmias, and any serious side effect regarded as being caused by dobutamine. Metoprolol was available and used to reverse the effects of dobutamine if they did not revert spontaneously and quickly.

For purposes of echocardiographic analysis, the left ventricular wall was analyzed according to the standardized 16-segment model. All patients had a normal dobutamine-atropine echocardiogram, defined as a study in which each segment showed normal systolic wall thickening and inward endocardial motion at baseline and a hyperdynamic response during stress.

Pretest Likelihood of Coronary Disease

The pretest likelihood of CAD was calculated on the basis of age, sex, and chest pain characteristics, by using tables published by Diamond and Forrester.[7] Patients were considered to have typical angina if they complained of substernal discomfort that was precipitated by physical exertion and relieved with rest or nitroglycerin within 10 minutes. They were considered to have atypical angina if their discomfort was either not substernal, not precipitated by exertion, or not relieved by rest or nitroglycerin. If two or more of these characteristics were absent, patients were considered to have nonanginal chest pain. Subsequently, patients were divided into those with low pretest probabilities of CAD (<10%), intermediate pretest probabilities of CAD (10% to 80%), and high pretest probabilities of CAD (>80%). Arbitrary patients with previous myocardial infarction and/or known CAD were considered to have a 100% pretest probability of CAD and were included in the latter probability group.

Table 1 Historical and clinical data of the 200 study patients

	Patients (n = 200)	%
Age	59 ± 13	
Male sex	86	43
Risk factors		
Diabetes	15	8
Hypercholesterolemia	38	19
Hypertension	71	36
Smoking	47	24
History		
Myocardial infarction	22	11
Revascularization	28	14
Chest pain type		
Typical	45	23
Atypical	85	43
Nonanginal	70	35
Medication used		
β-Blocker	69	35
Nitrates	46	23
Calcium antagonists	51	26

Follow-up

Follow-up data were obtained until August 1, 1995, by outpatient clinic assessment and/or contacting the patient, general practitioner, and other hospitals when necessary. Outcome events were cardiac death, nonfatal myocardial infarction, coronary artery bypass surgery, and percutaneous transluminal coronary angioplasty. Cardiac death was defined as a death temporally associated with a known or suspected acute myocardial infarction, life-threatening arrhythmia, or pulmonary edema. Unexpected death without an identified noncardiac cause was also considered as cardiac death. Occurrence of an acute myocardial infarction was confirmed by using standard clinical and electrocardiographic criteria and when total creatine kinase enzyme levels exceeded twice normal. Hard cardiac events were defined as cardiac death or myocardial infarction.

Statistical Analysis

Values are expressed as mean value ± SD, unless specified. Comparison of variables was performed with the Student t test for continuous variables and chi square test for discrete variables. Differences of $p < 0.05$ were considered significant.

RESULTS

Patient Characteristics

The historical and clinical data in the study patients are shown in Table 1. There were 86 men (43%) and 114 women (57%); mean (SD) age was 59 (13) years (range 21 to 84). Of 40 patients (20%) with known

Table 2 Clinical and stress test data of patients with events

Subject	Age, Sex	Chest pain type	Pretest probability (%)	% of Maximal HR	Dobutamine ECG	Stress angina	Event, time*	Angiographic disease
1	79, M	Atypical	91	88	Normal	0	CD, 41 mo	—
2	83, M	Atypical	93	89	Normal	0	CD, 24 mo	—
3	69, M	Typical	96	74‡	Normal	+	CABG, 2 mo	3 vessel
4	52, M	Typical	91	56‡§	Normal	+	CABG, 2 mo	3 vessel
5	71, F	Typical	100†	101	Ischemic	0	CABG, 23 mo	3 vessel
6	46, M	Typical	100†	60#	Ischemic	0	PTCA, 2 mo	1 vessel

CABG, Coronary artery bypass grafting; *CD*, cardiac death; *PTCA*, percutaneous transluminal coronary angioplasty; +, present; 0, absent; —, not done.
*Months after echocardiographic evaluation; †history of myocardial infarction; ‡maximal dose atropine; §stress-induced sinus bradycardia.

CAD, 22 (11%) had history of myocardial infarction and 28 (14%) had history of coronary revascularization (12 patients had both myocardial infarction and revascularization). Typical angina was present in 45 patients (23%), atypical angina in 85 (43%), and nonanginal chest pain in 70 (35%). At the time of stress testing, 69 patients (35%) were using β-blockers, 46 (23%) nitrates, and 51 (26%) calcium antagonists.

Dobutamine-Atropine Stress Results

Atropine was added to dobutamine in 87 patients (44%). During stress, heart rate increased from 71 ± 13 bpm up to 137 ± 15 bpm, systolic blood pressure from 138 ± 22 mm Hg up to 147 ± 28 mm Hg, and double (rate-systolic blood pressure) product from 9823 ± 2539 up to 20,185 ± 4773 beats · mm Hg/min. Target heart rate (85% of maximal) was not reached in 21 tests (11%). In these tests, end points were maximal dose dobutamine-atropine in 15 (14 of these patients were using a β-blocker, $p < 0.0001$ compared with the other patients), angina in 4, symptomatic hypotension in 1, and dobutamine-induced sinus bradycardia in 1 patient. Typical angina was induced in 37 patients (19%) and ischemic electrocardiographic changes in 14 patients (7%). Side effects were unusual and minor.

Clinical Outcome

The mean (SD) follow-up period was 21 (16) months (range 1 to 57 months, median 18 months). Follow-up was incomplete in 7 patients because of noncardiac death after 2 (cancer), 3 (sepsis), 3 (cancer), 3 (pneumonia), 5 (cancer), 10 (cancer), and 13 (ileus) months of follow-up, respectively. These patients had a 90%, 71%, 71%, 100%, 67%, 32%, and 30% pretest likelihood of CAD, respectively. Furthermore, follow-up was incomplete in 3 patients because of geographic relocation after 20, 46, and 47 months, respectively. These patients had a 100%, 33%, and 18% pretest likelihood of CAD, respectively. During the follow-up period, 2 patients (1%) had cardiac death (unexpected death without an identified noncardiac cause), no patient had nonfatal myocardial infarction, 3 patients (1.5%) with unstable angina (necessitating hospitalization) underwent bypass surgery, and 1 patient (0.5%) with crescendo angina underwent coronary angioplasty (Table 2). Apart from these 4 latter patients, 14 additional patients with suspected CAD underwent coronary angiography (none of these patients had unstable angina). Eleven patients had normal coronary arteries, and 3 had single-vessel CAD.

Cardiac Events and Pretest Likelihood of CAD

The mean pretest probability of CAD was 55%, in men it was 65%, and in women 47% ($p < 0.001$). As seen in Figure 1, 27 patients (14%) had a low probability of CAD, 108 (54%) had an intermediate probability of CAD, and 65 (33%) had a high probability of CAD (including 40 patients with previous myocardial infarction and/or known CAD). All cardiac events occurred in patients with a high (>80%) pretest likelihood of CAD. Cardiac death occurred 2 or more years after the test in a 79-year-old man with atypical angina and a 91% probability of CAD and in an 83-year-old man with atypical angina and a 93% probability of CAD (Table 2). Coronary bypass surgery was performed in a 69-year-old man with typical angina and a 96% probability of CAD, in a 52-year-old man with typical angina and a 91% probability of CAD, and in a 71-year-old woman with typical angina and a 100% probability of CAD (history of myocardial infarction). Coronary angioplasty was performed in a 46-year-old man with typical angina and a 100% probability of CAD (history of myocardial infarction). The annual event rate for hard cardiac events was 0.6% for the entire group, 0% for the patients with a low or intermediate probability of CAD, and 1.8% for patients with a high probability of CAD. The annual event rate for all cardiac events was 1.7% for the entire group, 0% for the patients with a low or intermediate probability of CAD, and 5.3% for patients with a high probability of CAD.

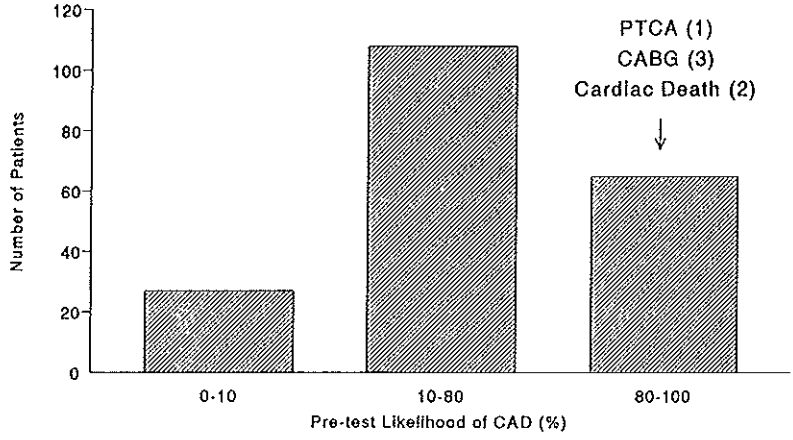


Figure 1 Histogram showing distribution of events according to pretest likelihood of coronary artery disease *(CAD)* in 200 study patients with chest pain and normal dobutamine-atropine stress echocardiogram. *CABG,* Coronary artery bypass grafting; *PTCA,* percutaneous transluminal coronary angioplasty.

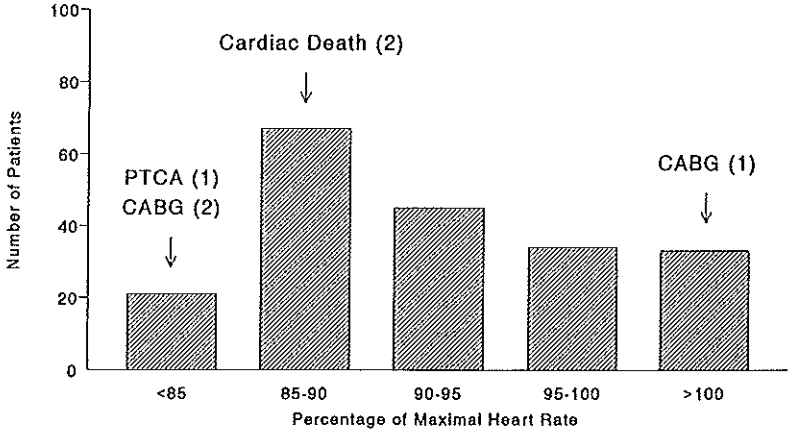


Figure 2 Histogram showing the distribution of events according to percentage of maximal heart rate reached during stress in 200 study patients with chest pain and normal dobutamine-atropine stress echocardiogram. *CABG,* Coronary artery bypass grafting; *PTCA,* percutaneous transluminal coronary angioplasty.

Cardiac Events and Stress Test Variables

As seen in Figure 2, 21 patients (11%) reached <85% of theoretical maximal heart rate, 67 (34%) reached 85% to 90% of maximal, 45 (23%) reached 90% to 95% of maximal, 34 (17%) reached 95% to 100% of maximal, and 33 (17%) reached >100% of maximal. Both patients who had cardiac death had maximal tests (heart rates of 88% and 89% of maximal, respectively), without any sign or symptom of ischemia during stress. In contrast, all except one patient with unstable or crescendo angina and subsequent revascularization procedures had submaximal tests (heart rates of 74%, 56%, and 60% of maximal, respectively), and all had at least one sign or symptom of ischemia during stress (angina in two, ischemic electrocardiographic changes in two, and stress-induced sinus bradycardia in one).[8] All patients with submaximal stress and proven functionally important CAD were receiving β-blockers during the test.

DISCUSSION

Since its clinical introduction in 1986, dobutamine stress echocardiography has been increasingly used for the evaluation of patients with suspected myocardial ischemia. In a recently published review on 28 published studies, including a total of 2246 patients, a mean sensitivity of 80% (95% confidence interval 78% to 82%) and specificity of 84% (95% confidence interval 82% to 86%) were reported.[1] The prognostic significance of abnormal tests has been reported by several authors.[2-5] However, little is known about the clinical significance of normal studies in patients with a stable chest pain syndrome, in particular in relation to the pretest probabilities of CAD.

Our results indicate that the prognosis of patients with a stable chest pain syndrome and a normal dobutamine-atropine stress echocardiogram is excellent. Hard cardiac events were rare (annual event rate 0.6%) and did not occur earlier than 2 years after the stress test. Although both patients with cardiac death had high pretest probabilities of CAD, these events could not be predicted by a history of typical angina, submaximal stress, or stress-induced angina or ischemic electrocardiographic changes. Probably, these patients died after the development of an occlusive thrombus after the rupture of a mild, non-flow-limiting coronary plaque, a coronary embolus, coronary spasm, or idiopathic ventricular fibrillation. These potential fatal mechanisms cannot be excluded by a test screening for ischemia.[9] Furthermore, progression of (initial nonfunctional) CAD could have played a role. Nevertheless, the observed annual hard event rates in the groups of patients with low, intermediate, and high pretest probabilities of disease (0%, 0%, and 1.8%, respectively) were much less than the expected annual event rate of these patient groups, which were reported to be approximately <1%, 3%, and 6%, respectively.[10] Revascularization procedures, performed after the development of unstable or crescendo angina, were also uncommon (annual event rate 1.1%) and occurred exclusively in patients with history of typical angina, high pretest probabilities of CAD, and the presence of stress-induced angina or ischemic electrocardiographic changes. Moreover, in all except one of these patients, stress was submaximal. Because in this subset of patients all submaximal studies were associated with the concomitant use of β-blockers, it should be advised—at least in patients with unknown or relatively benign coronary anatomy—to discontinue these medications several days before the test to achieve optimal results.[11]

Comparisons With Other Studies

The rate of hard cardiac events after normal dobutamine stress echocardiography (studies without rest and stress wall motion abnormalities) was addressed in only two studies. In very small subsets, Mazeika et al.[3] found in 26 high-risk patients an annual event rate of 4% and Afridi et al.[2] found in 40 patients an annual event rate of 5%. The lower event rate reported by our group can be explained by the addition of atropine to dobutamine, a stress combination known to increase the sensitivity of dobutamine stress echocardiography for the detection of CAD.[12] Severi et al.[13] reported for dipyridamole echocardiography an annual event rate of 1.6% for hard cardiac events and 2.9% for all cardiac events. In patients with normal exercise echocardiographic studies, Ismail et al.[14] reported an annual event rate of 1.4% for hard cardiac events and 1.8% for all cardiac events. Sawada et al.[15] reported an annual event rate of 0.6% for hard cardiac events and 1.7% for all cardiac events. This latter group found, in agreement with us, that the majority of patients with events and proven significant CAD had submaximal stress tests. The greater susceptibility of stress echocardiography to submaximal tests compared with stress myocardial perfusion imaging in diagnosing CAD was reported by several authors.[16,17] Notwithstanding these observations, the predictive value of normal stress echocardiograms appears to be comparable to that of normal stress perfusion scintigrams.[18,19]

Limitations

The main limitations of this study are the relatively small number of patients (n = 200) and the short (mean 21 months) follow-up. Additionally, this study was retrospective, and out-of-hospital myocardial infarction could be missed. Prospective studies with larger cohorts of patients and extended follow-up are needed to firmly establish the excellent prognostic value of a normal dobutamine-atropine stress echocardiogram and to clarify the long-term prognosis.

Clinical Implications

Dobutamine-atropine stress echocardiography is currently used in an increasing number of laboratories around the world. Many of the patients studied with a stable chest pain syndrome may have normal echocardiograms, and these patients have an excellent cardiac prognosis. However, patients with typical angina, high pretest probabilities of CAD, and stress-induced angina or ischemic electrocardiographic changes, and in particular those with submaximal stress, still appear to be at risk for functionally important CAD despite a normal dobutamine-atropine stress echocardiogram.

REFERENCES

1. Geleijnse ML, Fioretti PM, Roelandt JRTC. Methodology, feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography. J Am Coll Cardiol 1997;30:595-606.
2. Afridi I, Quinones MA, Zoghbi WA, Cheirif J. Dobutamine stress echocardiography: sensitivity and predictive value for future cardiac events. Am Heart J 1994;127:1510-5.
3. Mazeika PK, Nadazdin A, Oakley CM. Prognostic value of dobutamine echocardiography in patients with high pretest likelihood of coronary artery disease. Am J Cardiol 1993;71:33-9.
4. Poldermans D, Fioretti PM, Boersma E, et al. Dobutamine-atropine stress echocardiography and clinical data for predicting late cardiac events in patients with suspected coronary artery disease. Am J Med 1994;97:119-25.
5. Kamaran M, Teague SM, Finkelhor RS, Dawson N, Bahler RC. Prognostic value of dobutamine stress echocardiography in patients referred because of suspected coronary disease. Am J Cardiol 1995;76:887-91.
6. Poldermans D, Fioretti PM, Forster T, et al. Dobutamine-atropine stress echocardiography for assessment of perioperative and late cardiac risk in patients undergoing major vascular surgery. Eur J Vasc Surg 1994;8:286-93.
7. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. N Engl J Med 1979;300:1350-8.
8. Hopfenspirger MR, Miller TD, Christian TF, Gibbons RJ. Sinus node deceleration during dobutamine perfusion scintigraphy as a marker of inferior ischaemia. Am J Cardiol 1994; 74:817-9.
9. Epstein SE, Quyyumi AA, Bobow RO. Sudden cardiac death without warning: possible mechanisms and implications for screening asymptomatic populations. N Engl J Med 1989; 321:320-4.
10. Harris PJ, Phil D, Lee KL, Harrell FE, Behar VS, Rosati RA. Outcome in medically treated coronary artery disease. Circulation 1980;62:718-26.
11. Fioretti PM, Poldermans D, Salustri A, et al. Atropine increases the accuracy of dobutamine stress echocardiography in patients taking beta-blockers. Eur Heart J 1994;15: 355-60.
12. McNeill AJ, Fioretti PM, El-Said EM, Salustri A, Forster T, Roelandt JRTC. Enhanced sensitivity for detection of coronary artery disease by addition of atropine to dobutamine stress echocardiography. Am J Cardiol 1992;70:41-6.
13. Severi S, Picano E, Michelassi C, et al. Diagnostic and prognostic value of dipyridamole echocardiography in patients with suspected coronary artery disease: comparison with exercise electrocardiography. Circulation 1994;89:1160-73.
14. Ismail G, Lo E, Sada M, Conant RD, Shapiro SM, Ginzton LE. Long-term prognosis of patients with a normal exercise echocardiogram and clinical suspicion of myocardial ischemia. Am J Cardiol 1995;75:934-6.
15. Sawada SG, Ryan T, Conley M, Corya BC, Feigenbaum H, Armstrong WF. Prognostic value of a normal exercise echocardiogram. Am Heart J 1990;120:49-55.
16. Marwick TH, D'Hondt AM, Mairesse GH, et al. Comparative ability of dobutamine and exercise stress in inducing myocardial ischaemia in active patients. Br Heart J 1994;72:31-8.
17. Elhendy A, Geleijnse ML, Roelandt JRTC, et al. Dobutamine-induced hypoperfusion without transient wall motion abnormalities: less severe ischemia or less severe stress? J Am Coll Cardiol 1996;27:323-9.
18. Brown KA. Prognostic value of thallium-201 myocardial perfusion imaging: a diagnostic tool comes of age. Circulation 1991;83:363-81.
19. Wackers FJT, Russo DJ, Russo D, Clements JP. Prognostic significance of normal quantitative planar thallium-201 stress scintigraphy in patients with chest pain. J Am Coll Cardiol 1985;6:27-30.

Chapter 11

Cardiac imaging for risk stratification with dobutamine-atropine stress testing in patients with chest pain. Echocardiography, perfusion scintigraphy, or both?

Geleijnse ML, Elhendy A, Van Domburg RT,
Cornel JH, Rambaldi R, Salustri A,
Reijs AEM, Roelandt JRTC, Fioretti PM

Circulation 1997; 96: 137-147

Cardiac Imaging for Risk Stratification With Dobutamine-Atropine Stress Testing in Patients With Chest Pain

Echocardiography, Perfusion Scintigraphy, or Both?

Marcel L. Geleijnse, MD; Abdou Elhendy, MD, PhD; Ron T. van Domburg, MSc; Jan H. Cornel, MD, PhD; Riccardo Rambaldi, MD; Alessandro Salustri, MD, PhD; Ambroos E.M. Reijs, MSc; Jos R.T.C. Roelandt, MD, PhD; Paolo M. Fioretti, MD, PhD

Background Pharmacological stress echocardiography and myocardial perfusion scintigraphy are used frequently for risk stratification in patients with suspected myocardial ischemia. However, their relative prognostic strength has never been explored.

Methods and Results Two hundred twenty consecutive patients with chest pain (mean age, 60±12 years; 124 men, 115 with previous myocardial infarction) were studied with dobutamine-atropine stress echocardiography (ECHO) and simultaneous ^{99m}Tc sestamibi single photon emission computed tomography imaging (MIBI). Ischemia was defined as deterioration in left ventricular wall motion and reversible perfusion defects, respectively. ECHO was positive for ischemia in 76 and MIBI in 91 patients (agreement, 77%; κ=.51). During follow-up of 31±15 months, 24 patients had hard cardiac events (nonfatal myocardial infarction or cardiac death). By univariate analysis, age, history of congestive heart failure, and any abnormality or ischemia on ECHO or MIBI were associated with cardiac events. Multivariate analysis revealed that age, abnormal ECHO (odds ratio [OR], 18.9; 95% CI, 2.5 to 146.0) or MIBI (OR, 12.8; 95% CI, 1.7 to 98.3), and ischemia on ECHO (OR, 4.0; 95% CI, 1.6 to 9.9) or MIBI (OR, 3.0; 95% CI, 1.2 to 7.4) had independent predictive values. When ECHO was used as a first option, the addition of MIBI to all nonischemic ECHO studies decreased the OR from 4.0 (95% CI, 1.6 to 9.9) to 3.8 (95% CI, 1.4 to 10.2). Addition of MIBI confined to nonischemic ECHO studies in which target heart rate was not attained (nondiagnostic studies) increased the OR to a maximal 5.7 (95% CI, 2.2 to 15.0). In contrast, the addition of ECHO to nondiagnostic MIBI studies was not useful.

Conclusions Dobutamine-atropine ECHO and MIBI provide comparable prognostic information. The addition of MIBI to ECHO may be useful in patients with nondiagnostic ECHO studies. (*Circulation*. 1997;96:137-147.)

Key Words • stress • tests • echocardiography • radioisotopes • prognosis

Risk stratification of patients with known or suspected coronary artery disease is an important goal of clinical cardiology.[1] In daily clinical practice, several modalities of stress testing are used for this purpose, often in conjunction with cardiac imaging.[2-10] Among imaging modalities, myocardial perfusion scintigraphy is currently the most widely used noninvasive technique for the functional and prognostic assessment of patients with known or suspected coronary artery disease,[7-11] in particular in combination with exercise stress. However, since up to 40% of the patients referred for noninvasive evaluation of coronary artery disease are unable to perform adequate exercise,[9] there is a consensus that pharmacological stress tests are first choice in a substantial number of patients. Echocardiography is well suited to be combined with pharmacological stress,[12] and there is a growing body of evidence to indicate that pharmacological stress echocardiography is as feasible and efficient as perfusion scintigraphy for diagnostic purposes.[13,14] However, it is unknown which imaging modality should be preferred for risk stratification. Therefore, the present study was undertaken to assess the relative prognostic value of dobutamine-atropine ECHO, MIBI, and their combination in 220 consecutive patients with chest pain and inability to perform adequate exercise.

Received October 14, 1996; revision received December 17, 1996; accepted January 9, 1997.

From the Thoraxcenter and the Department of Nuclear Medicine, University Hospital, Rotterdam-Dijkzigt and Erasmus University, Rotterdam, Netherlands.

Presented in part at the 67th Annual Scientific Sessions of the American Heart Association, Dallas, Tex, November 1994, and the Second International Conference of Nuclear Cardiology, Cannes, France, April 1995.

Correspondence to Marcel L. Geleijnse, MD, Thoraxcentre, Ba 300, Dr Molewaterplein 40, 3015 GD Rotterdam, Netherlands.

Methods

Study Group

Over a 3-year period, between November 1990 and October 1993, 260 consecutive patients with chest pain underwent a simultaneous dobutamine-atropine stress ECHO and MIBI study. All patients were referred for pharmacological stress testing because of inadequate exercise capacity, either proven by previous nondiagnostic exercise testing or judged by the referring physician. None of these patients had prior heart transplantation, congenital or significant valvular heart disease, known primary dilated cardiomyopathy, or unstable angina. Forty patients were excluded from final analysis: 14 with technically inadequate echocardiograms at rest (11) or peak stress (3), 2 with poor-quality scintigraphic images, 8 with multiple tests (in these patients only the first test was considered), and 16 with early elective coronary revascularization

Selected Abbreviations and Acronyms

CHF = congestive heart failure
ECHO = echocardiography
MI = myocardial infarction
MIBI = ^{99m}Tc sestamibi SPECT imaging
OR = odds ratio
SPECT = single-photon emission computed tomography

within 60 days after stress testing. None of the latter patients sustained MI before coronary revascularization. The mean age of the remaining 220 patients was 60±12 years (range, 23 to 85); 124 were men (56%). One hundred fifteen patients (52%) had a previous MI and 26 patients (12%) had known coronary artery disease without MI. Fifty-two patients (24%) had typical angina, 117 (53%) had atypical angina, and 51 (23%) had nonanginal chest pain. At the time of the study, 156 patients (71%) were receiving antianginal therapy, including β-blockers in 92 (42%), either administered alone in 28 (13%) or in combination with nitrates and/or calcium channel blockers in 64 (29%).

Dobutamine-Atropine Stress Test

After routine preparation, a resting ECG and echocardiogram were made, intravenous access was secured, and dobutamine was administered intravenously by an infusion pump. The initial infusion rate was 10 μg/kg per minute for 3 minutes, increasing by 10 μg/kg per minute every 3 minutes up to a maximum of 40 μg/kg per minute. In patients not achieving 85% of their age- and sex-predicted maximal heart rate and without symptoms or signs of myocardial ischemia, atropine was administered in addition to the maximal dose of dobutamine, starting with 0.25 mg intravenously and repeated up to a maximum of 1.0 mg within 4 minutes with continuation of the dobutamine infusion.[15] Throughout dobutamine infusion the ECG (3 leads) was continuously monitored, and a 12-lead ECG was recorded at 1-minute intervals. The level of ST-segment shift was calculated, after signal averaging, by a computer-assisted system (Cardiovit CSG/12; Schiller). Blood pressure was measured and recorded by sphygmomanometry or automatic device every 3 minutes. Reasons for interruption of the test were horizontal or downsloping ST-segment depression of >0.2 mV at an interval of 80 ms after the J-point compared with baseline, ST-segment elevation of >0.1 mV in patients without previous MI, severe angina, a symptomatic reduction in systolic blood pressure >40 mm Hg from baseline, hypertension (blood pressure >240/120 mm Hg), significant cardiac tachyarrhythmias, and any serious side effect that was regarded to be a result of dobutamine. Metoprolol was available and used to reverse the effects of dobutamine if they did not revert spontaneously and quickly.

Echocardiographic and Perfusion Scintigraphic Imaging

Echocardiographic analysis of the left ventricular wall was performed according to a 16-segment model.[16] Both systolic wall thickening and inward endocardial motion were visually evaluated, and each segment was graded on a 5-point scoring system (1, normal; 2, mild hypokinesis; 3, severe hypokinesis; 4, akinesis; and 5, dyskinesis). For perfusion imaging, 370 mBq of MIBI was injected intravenously at peak stress while dobutamine infusion was continued for 1 minute. Stress scintigraphic images were acquired, on average, 1 hour after termination of the dobutamine infusion. For resting studies, 370 mBq of MIBI was injected at least 24 hours after the stress study. Image acquisition was performed with a Siemens Gammasonics single-head Rota Camera. For each study, 6 short-axis and 3 sagittal long-axis slices were analyzed. To compare the stress and rest studies, each of the 6 short-axis slices was divided into 8 equal segments. The septal part of the 2 basal slices (4 segments) was not evaluated because this region corresponds to the fibrous portion of the interventricular septum and normally exhibits reduced uptake. The apical region was assessed from the 3 sagittal cross sections. A total of 47 segments per patient were analyzed. All tomographic views were reviewed in side-by-side pairs (stress and rest) and the myocardial uptake of radiotracer was evaluated visually, with the assistance of circumferential profile analysis including the normal values, also with the use of a 5-point scoring method (1, normal; 2, minimally reduced uptake; 3, moderately reduced uptake; 4, severely reduced uptake; and 5, absence of uptake).

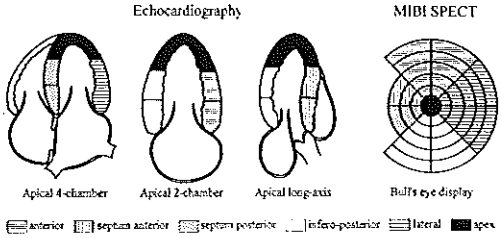


FIG 1. Representation of the 16 echocardiographic and the 47 scintigraphic segments (bull's-eye display from short-axis and sagittal long-axis for apex) that were regrouped to 6 major myocardial regions.

As depicted in Fig 1, the echocardiographic and scintigraphic images were subsequently matched by regrouping the 16 echocardiographic and the 47 scintigraphic segments in 6 major myocardial regions (anterior, anterior septum, posterior septum, inferoposterior, lateral, and apical).[17] A region was classified as infarcted in the case of a resting score >2 in one or more segments on ECHO[18] and >2 in two or more adjacent segments on MIBI. A region was classified as ischemic on ECHO in the case of an increase in score between rest and stress in one or more segments unless an akinetic segment showed no improvement during low-dose dobutamine and became dyskinetic during high-dose dobutamine.[19] On MIBI, ischemia was defined as a perfusion defect during stress that partially or totally resolved at rest in at least two contiguous segments or slices. An ECHO or MIBI study was classified as abnormal in the presence of either infarction or ischemia. All studies were reviewed by two experienced observers (A.S. and R.R. for ECHO; J.H.C. and A.R. for MIBI) unaware of all other stress test results. In cases of disagreement, a third reviewer (P.M.F.) decided on the grading of each study. Pattern (normal, ischemia alone, infarction alone, or both infarction and ischemia [mixed]) interobserver agreement, as assessed in 200 patients, was 89% for ECHO and 92% for MIBI. Interobserver agreement on ischemia was 92% for ECHO and 95% for MIBI.

Follow-up

Follow-up data were obtained over a 31±15-month period (range, 12 to 48 months) by outpatient clinic assessment, review of case notes, and contact with the patient, general practitioner, or other hospitals when necessary. Outcome events were cardiac death, nonfatal MI, and revascularization (coronary bypass surgery or percutaneous transluminal coronary angioplasty). Cardiac death was defined as a death temporally associated with a known or suspected acute MI, life-threatening arrhythmia, or pulmonary edema. Unexpected death without an identified noncardiac cause also was considered to be cardiac death. Occurrence of an acute MI was confirmed with the use of standard clinical and ECG criteria and when total creatine kinase enzyme levels exceeded twice the normal values. Hard cardiac events (cardiac death and nonfatal MI) and all cardiac events (hard events or revascularization) were separately analyzed as end points. Patients with revasculariza-

tion procedures were censored at the time of intervention, so only the first event in each patient was considered.

Statistical Analysis

Values were expressed as mean±SD unless specified. Comparison of patients with and without cardiac events was performed with the Student's t test for continuous variables and χ^2 test for discrete variables. Differences of $P<.05$ were considered significant. Variables correlated with cardiac events at a significance level of $P<.10$ by univariate analysis and selected variables with $P=.10$ to .20 were further analyzed with the use of stepwise logistic regression. ORs and 95% CIs were calculated for variables used in the multivariate model. Kaplan-Meier life table estimates of infarction-free survival (survival without cardiac death or nonfatal MI) and event-free survival (survival without cardiac death, nonfatal MI, or revascularizations) were used to summarize the follow-up results. Comparison of life tables was performed with the use of the log-rank test.

Results

Dobutamine-Atropine Stress Test

Hemodynamic Results, End Points, and Side Effects

The maximal dobutamine dose used was 10 μg/kg per minute in 1 patient, 20 μg/kg per minute in 4 patients, 30 μg/kg per minute in 30 patients, and 40 μg/kg per minute in 185 patients. Atropine was added in 83 patients (38%) and was more often used in patients on β-blockers (58 of 92 on versus 25 of 128 off β-blockers, $P<.0001$). Heart rate increased by 63±15 bpm up to 134±17 bpm at peak stress, systolic blood pressure by 13±27 mm Hg up to 151±31 mm Hg, and the double product (heart rate times systolic blood pressure) by 10 382±3809 up to 20 108±4825 beats×mm Hg per minute.

Target heart rate (85% of maximum for age and sex) was not reached in 46 tests (21%) either after maximal-dose dobutamine-atropine had been given in 18 patients (8%) or premature stopping of the test in 28 patients (13%). The test was prematurely stopped because of angina in 19 patients, ST-segment changes in 2, hypertension in 1, symptomatic hypotension in 4, nonsustained ventricular tachycardia in 1, and anxiety in 1. Most patients not reaching their target heart rate despite maximal-dose dobutamine-atropine were on β-blockers (15 of 18 on versus 3 of 18 off β-blockers, $P<.001$). Side effects usually were minor, and significant tachyarrhythmias (paroxysmal supraventricular or nonsustained ventricular) were encountered during dobutamine infusion or recovery in 14 patients (6%).

Distribution of Imaging Patterns

As shown in Fig 2, the distributions of ECHO and MIBI patterns were, respectively, normal in 86 (39%) and 70 (32%), infarction alone in 58 (26%) and 59 (27%), ischemia alone in 31 (14%) and 32 (15%), and both ischemia and infarction in 45 (20%) and 59 (27%). Therefore, abnormal patterns were present in 134 (61%) and 150 (68%) patients, infarction patterns in 103 (47%) and 118 (54%), and ischemic patterns in 76 (35%) and 91 (41%), respectively. Pattern agreement (normal, ischemia alone, infarction alone, and mixed patterns) between ECHO and MIBI was 66% ($\kappa=.53$). The agreement for ischemia was 77% ($\kappa=.51$).

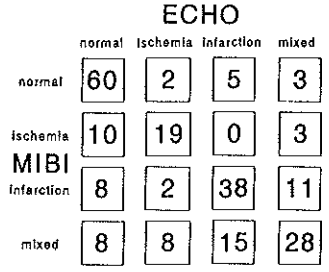


FIG 2. Distribution of the different imaging patterns for ECHO and MIBI. Patterns were divided into normal, infarction alone, ischemia alone, and both infarction and ischemia (mixed). Pattern agreement was 66% ($\kappa=.53$). The agreement for ischemia was 77% ($\kappa=.51$).

Clinical Outcome

Twelve patients (5%) had "incomplete" follow-up, 7 because of noncardiac death (cancer in 3, pneumonia in 2, AIDS in 1, and myelodysplasia in 1) and 5 because of geographic relocation. During follow-up, 11 patients had a nonfatal MI and 13 died as the result of a cardiac event. Thirty patients underwent a late or nonelective revascularization procedure. In total, 24 patients had a "hard" cardiac event (cardiac death or nonfatal MI) and 54 patients had "any" cardiac event (cardiac death, nonfatal MI, or revascularization).

Prediction of Events From Clinical and Stress Test Results

Univariate Analysis

The clinical and the stress test variables in patients with and without hard cardiac events are summarized in Tables 1 and 3. Clinical variables associated with hard cardiac events were age and history of CHF. Of the stress test variables, peak systolic blood pressure and double product were lower in patients with subsequent events. However, peak heart rate, angina, or ST-segment changes during the test were not associated with increased rate of hard cardiac events. Imaging patterns associated with hard cardiac events were the presence of any abnormality on ECHO or MIBI, infarction on MIBI, and ischemia on ECHO or MIBI. Associated with all cardiac events were the clinical variables of male sex, a

TABLE 1. Clinical Characteristics of the Study Patients With and Without Hard Events

	No Cardiac Event (n=196)	%	Cardiac Event (n=24)	%	P
Age >70 y	31	16	8	33	.0343
Male sex	106	54	18	75	.0517
Risk factors					
Diabetes	21	11	4	17	.3869
Hypercholesterolemia	42	21	4	17	.5890
Hypertension	84	43	9	38	.6169
Smoking	50	26	8	33	.4127
History					
MI	99	51	16	67	.1356
CHF	34	17	9	38	.0190
Revascularization	55	28	9	38	.3377
Typical angina	48	24	4	17	.3956

TABLE 2. Clinical Characteristics of the Study Patients With and Without Any Event

	No Cardiac Event (n=166)	%	Cardiac Event (n=54)	%	P
Age >70 y	26	16	13	24	.1607
Male sex	87	52	37	69	.0386
Risk factors					
Diabetes	19	11	6	11	.9465
Hypercholesterolemia	37	22	9	17	.3786
Hypertension	70	42	23	43	.9564
Smoking	45	27	13	24	.6610
History					
MI	77	46	38	70	.0022
CHF	29	17	14	26	.1744
Revascularization	39	23	25	46	.0014
Typical angina	30	18	22	41	.0007

history of typical angina, MI, or revascularization, and all abnormal imaging patterns on ECHO or MIBI (Tables 2 and 4).

Infarction-Free Survival Curves

The infarction-free survival curves in patients with the different ECHO and MIBI patterns are depicted in Fig 3A and 3B. A normal study was associated with a favorable prognosis over the follow-up period, with a negligible annual cardiac event rate of 0.4% by ECHO and 0.5% by MIBI. In contrast, patients with infarction alone, ischemia alone, and mixed patterns had significantly increased cardiac event rates of, for ECHO versus MIBI, respectively, 7.2% ($P<.0005$) versus 6.4% ($P<.005$), 10.8% ($P<.0001$) versus 6.1% ($P<.005$), and 7.2% ($P<.0005$) versus 7.5% ($P<.005$). For event-free survival (Fig 4A and 4B), annual event rates were, for the different patterns on ECHO versus MIBI, respectively, 1.8% versus 1.8%, 14.3% ($P<.0001$) versus 11.3% ($P<.005$), 10.8% ($P<.0001$) versus 13.3% ($P<.0005$), and 26.7% ($P<.0001$) versus 18.6% ($P<.0001$).

Annual Hard Event Rates According to Extent of Abnormalities

As seen in Fig 5A, patients with normal segments only had annual event rates of 0.4% (n=86) for ECHO and 0.5% (n=70) for MIBI. For patients with one or two and more than two abnormal segments, annual event rates were, for ECHO and MIBI, respectively, 4.9% (n=74) versus 5.7% (n=98) and 13.6% (n=60) versus 9.6% (n=52). As seen in Fig 5B, patients without infarcted segments had annual event rates of 2.6% (n=117) for ECHO and 2.0% (n=102) for MIBI. For patients with one and more than one infarcted segment, annual event rates were, for ECHO and MIBI, respectively, 2.5% (n=35) versus 5.6% (n=56) and 10.4% (n=68) versus 8.9% (n=62). As seen in Fig 5C, patients without ischemic segments had annual event rates of 2.3% (n=144) for ECHO and 2.6% (n=129) for MIBI. For patients with one and more than one ischemic segment, annual event rates were, for ECHO and MIBI, respectively, 6.0% (n=35) versus 5.6% (n=51) and 12.3% (n=41) versus 9.3% (n=40).

Annual Event Rates According to Combination of ECHO and MIBI Results

As seen in Fig 6A, patients with both a negative ECHO study and a negative MIBI study had annual hard event rates of 0% (n=60) if any abnormality was considered and 2.0% (n=111) if ischemia was considered. For patients with a negative ECHO study and a positive MIBI study, these numbers were 1.3% (n=10) and 3.7% (n=18); for patients with a positive ECHO study and a negative MIBI study, these numbers were 3.0% (n=26)

TABLE 3. Stress Test Results in the Study Patients With and Without Hard Events

	No Cardiac Event (n=196)	%	Cardiac Event (n=24)	%	P
Rest					
Heart rate	70±14		72±15		.5856
Systolic blood pressure	137±22		138±24		.8812
Diastolic blood pressure	81±11		74±12		.0026
Double product	9708±2849		9854±2322		.8117
Peak stress					
Heart rate	134±17		132±17		.6058
Systolic blood pressure	152±32		137±27		.0261
Diastolic blood pressure	77±13		72±15		.0918
Double product	20 369±4905		17 972±3515		.0213
Angina during stress	45	23	7	29	.5003
ST changes	30	15	4	17	.8621
ECHO pattern					
Abnormal	111	57	23	96	.0002
Infarction	88	45	15	63	.1036
Ischemia	61	31	15	63	.0023
MIBI pattern					
Abnormal	127	65	23	96	.0021
Infarction	100	51	18	75	.0265
Ischemia	76	39	15	63	.0263

TABLE 4. Stress Test Results in the Study Patients With and Without Any Event

	No Cardiac Event (n=166)	%	Cardiac Event (n=54)	%	P
Rest					
Heart rate	70±14		72±14		.4174
Systolic blood pressure	137±22		139±24		.5799
Diastolic blood pressure	81±11		79±11		.1725
Double product	9649±2844		9961±2640		.4767
Peak stress					
Heart rate	135±16		130±18		.0579
Systolic blood pressure	151±30		150±36		.8331
Diastolic blood pressure	77±13		76±15		.8221
Double product	20 382±4942		19 264±4381		.1393
Angina during stress	35	21	17	32	.1191
ST changes	20	12	14	26	.0145
ECHO pattern					
Abnormal	85	51	49	91	.0000
Infarction	67	40	36	67	.0008
Ischemia	43	26	33	61	.0000
MIBI pattern					
Abnormal	100	60	50	93	.0000
Infarction	79	48	39	72	.0017
Ischemia	55	33	36	67	.0000

and 8.2% (n=33); and for patients with both a positive ECHO study and a positive and MIBI study, these numbers were 9.2% (n=124) and 9.9% (n=58), respectively. Similarly, for all cardiac events, the respective numbers were 0.5% and 4.5%, 5.5% and 10.9%, 16.5% and 14.3%, and 23.4% and 31.8% (Fig 6B).

Multivariate Analysis: Addition of ECHO or MIBI to Clinical Data

Table 5 summarizes the results of univariate and multivariate (stepwise logistic regression) analyses of clinical data and stress test imaging results as predictors of subsequent cardiac events. The results of the addition of ECHO or MIBI to clinical data were analyzed separately (clinical data + ECHO and clinical data + MIBI). Furthermore, each analysis was performed twice; in the first model (Table 5, model I) the only imaging pattern variable entered was the presence of an abnormal pattern (any abnormality), and in the second model (Table 5, model II) the presence of an ischemic or infarcted pattern was separately included. As shown in Table 5, age and an abnormal pattern on ECHO (OR, 18.9; 95% CI, 2.5 to 146.0) or MIBI (OR, 12.8; 95% CI, 1.7 to 98.3) in model I and an ischemic pattern on ECHO (OR, 4.0; 95% CI, 1.6 to 9.9) or MIBI (OR, 3.0; 95% CI, 1.2 to 7.4) in model II were independent predictors of subsequent hard cardiac events. Infarcted patterns on ECHO or MIBI were not independent predictors for hard cardiac events. However, when the presence of an infarcted pattern in 3 or more segments was forced into multivariate model II, independent predictors were age, an infarcted pattern on ECHO (OR, 6.2; 95% CI, 2.3 to 16.7) or MIBI (OR, 3.9; 95% CI, 1.4 to 10.7), and an ischemic pattern on ECHO (OR,

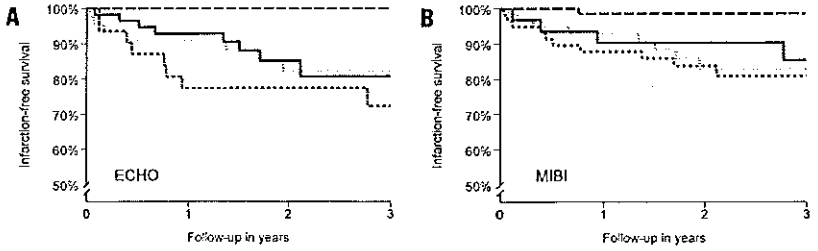


FIG 3. A, Kaplan-Meier infarction-free survival curves for patients with normal (line of heavy, long dashes), infarction alone (solid, heavy line), ischemia alone (line of short, heavy dashes), and mixed (line of light, vertical dashes) ECHO studies. The numbers of patients available for follow-up at 0, 1, 2, and 3 years were, respectively, 86, 83, 76, and 53; 58, 50, 21, and 11; 31, 25, 20, and 11; and 45, 39, 26, and 13. Probability values compared with the normal patients were, respectively, <.0005, <.0001, and <.0005. B, Kaplan-Meier infarction-free survival curves for patients with normal, infarction alone, ischemia alone, and mixed MIBI studies. The numbers of patients available for follow-up at 0, 1, 2, and 3 years were, respectively, 70, 68, 61, and 39; 59, 49, 28, and 14; 32, 29, 22, and 14; and 59, 51, 32, and 19. Probability values compared with the normal patients were <.005 for all.

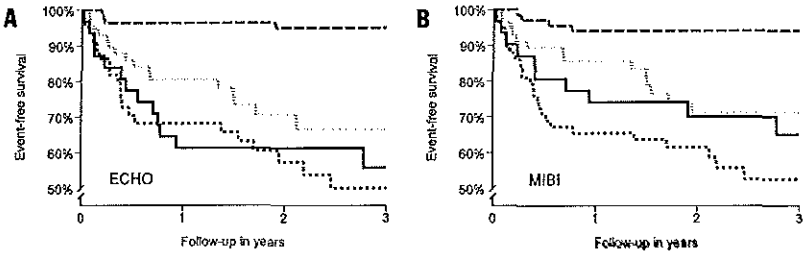


FIG 4. A, Kaplan-Meier event-free survival curves for patients with normal (line of long, heavy dashes), infarction alone (line of light, vertical dashes), ischemia alone (solid, heavy line), and mixed (line of short, heavy dashes) ECHO studies. The numbers of patients available for follow-up at 0, 1, 2, and 3 years were, respectively, 86, 80, 72, and 51; 58, 43, 18, and 9; 31, 20, 16, and 8; and 45, 30, 19, and 9. Probability values compared with normal patients were <.0001 for all. B, Kaplan-Meier event-free survival curves for patients with normal, infarction alone, ischemia alone, and mixed MIBI studies. The numbers of patients available for follow-up at 0, 1, 2, and 3 years were, respectively, 70, 65, 59, and 38; 59, 45, 25, and 12; 32, 24, 18, and 12; and 59, 39, 23, and 13. Probability values compared with the normal patients were, respectively, <.0005, <.005, and <.0001.

4.8; 95% CI, 1.8 to 12.5) or MIBI (OR, 3.1; 95% CI, 1.2 to 7.8). For all cardiac events (Table 6), age, typical angina, a history of MI or revascularization, and an abnormal pattern on ECHO (OR, 8.9; 95% CI, 3.3 to 23.8) or MIBI (OR, 8.8; 95% CI, 2.9 to 26.6) in model I and an ischemic pattern on ECHO (OR, 4.0; 95% CI, 2.0 to 7.9) or MIBI (OR, 3.9; 95% CI, 1.9 to 7.8) in model II were independent predictors of events.

Multivariate Analysis: Different Additions of MIBI to Clinical and ECHO Data

Since MIBI is thought to be slightly more sensitive (but less specific) for the detection of ischemia[20,21] and more informative in submaximal stress[22] than ECHO, we tried to assess if, to what extent, and in which patients MIBI could provide additional prognostic information in addition to ECHO. In this multivariate regression analysis, MIBI was added to nonischemic ECHO studies according to four different strategies (Table 7). In each strategy, a patient was considered to be at risk for future events when either one of the two techniques revealed ischemia.

In the first strategy (A), all 220 patients underwent only an ECHO study. On the basis of an ischemic response, 76 patients were considered to be at risk, and 15 of them had a hard cardiac event. The predictive OR for cardiac events was 4.0 (95% CI, 1.6 to 9.9) (as reported in Table 5, model II).

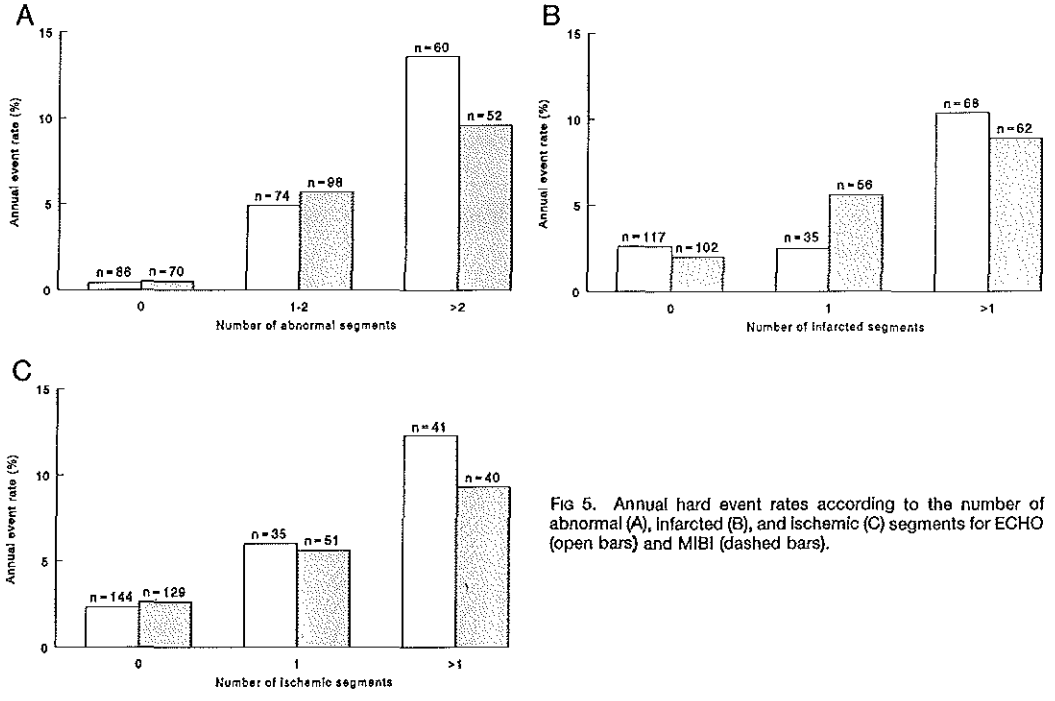


FIG 5. Annual hard event rates according to the number of abnormal (A), infarcted (B), and ischemic (C) segments for ECHO (open bars) and MIBI (dashed bars).

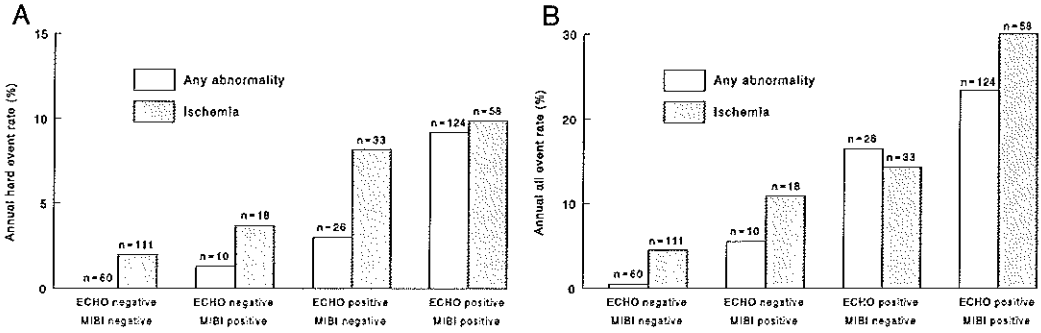


FIG 6. Annual hard event rate (A) and all events rate (B) according to the different combinations of ECHO and MIBI outcomes. Positive indicates abnormal (open bars) or ischemic (dashed bars); negative indicates normal (open bars) or nonischemic (dashed bars).

In the second strategy (B), MIBI was added to all patients without ischemia on ECHO. This strategy required 144 MIBI scans, and, by definition, yielded a higher number of patients at risk compared with strategy A (109 versus 76 patients). Eighteen of the patients at risk had a hard cardiac event. Because of a decrease in specificity, the OR of an ischemic response for the prediction of events was lower compared with ECHO used alone (3.8; 95% CI, 1.4 to 10.2).

In the third strategy (C), MIBI was added to ECHO only in patients with a nondiagnostic ECHO study (a submaximal test, without ischemia on ECHO). This strategy required 28 MIBI studies; myocardial ischemia was detected in 85 patients, and a hard cardiac event occurred in 17 of them. This strategy resulted in an OR of 5.3 (95% CI, 2.0 to 14.0).

In the last strategy (D), the addition of MIBI was limited to the 12 patients with a nondiagnostic study in which the ECHO test was interrupted prematurely because of other potential signs or symptoms of ischemia such as angina, ST-segment changes, or ventricular tachyarrhythmias but without ischemia on ECHO (studies in which the probability of a false-negative ECHO study is highest). By this strategy, 81 patients at risk could be identified; 17 had a hard cardiac event, and, with the use of the least additional MIBI studies, the OR was improved to 5.7 (95% CI, 2.2 to 15.0). By considering all patients in this last strategy to be at risk without addition of any MIBI study, 88 patients were classified to be at risk, 17 had a hard cardiac event, and the OR was 5.1 (95% CI, 2.0 to 13.5). In a similar fashion, for the prediction of any event, the addition of MIBI was also most useful in strategy D (Table 7, bottom). A similar analysis with reversed strategies (addition of ECHO to MIBI) is presented in Table 8. The results of this analysis show that the addition of ECHO to nondiag-

TABLE 5. Association by Univariate and Multivariate Analyses of Clinical and Stress Test Variables With Late Hard Cardiac Events

		Multivariate Analysis of Clinical Data and Imaging Patterns			
		Model I		Model II	
	Univariate Analysis	Clinical Data + ECHO	Clinical Data + MIBI	Clinical Data + ECHO	Clinical Data + MIBI
Clinical data					
Age >70 y	2.6 (1.0-6.8)	3.1 (1.1-8.3)	2.8 (1.1-7.3)	3.0 (1.1-8.1)	3.1 (1.2-8.3)
Male sex	2.5 (1.0-6.7)	*	*	*	*
History of MI	2.0 (0.8-4.8)*	*	*	*	*
History of revascularization	1.5 (0.6-3.7)*	*	*	*	*
History of CHF	2.9 (1.2-7.1)	*	*	*	2.4 (1.0-5.6)
Typical angina	0.6 (0.2-1.9)*	*	*	*	*
Stress test data					
Angina	1.4 (0.5-3.5)*	*	*	*	*
ST-segment changes	1.1 (0.4-3.5)*	*	*	*	*
ECHO					
Abnormal	17.6 (2.3-133.1)	18.9 (2.5-146.0)	...	...	...
Infarction	2.0 (0.9-4.9)*	...	...	*	...
Ischemia	3.7 (1.5-8.9)	...	...	4.0 (1.6-9.9)	...
MIBI					
Abnormal	12.5 (1.7-94.6)	...	12.8 (1.7-98.3)	...	...
Infarction	2.9 (1.1-7.6)	...	...	...	*
Ischemia	2.6 (1.1-6.3)	...	...	...	3.0 (1.2-7.4)

ORs are shown with 95% CIs in parentheses. In model I, pattern variable included "abnormal." In model II, pattern variables included were "infarction" and "ischemia"; "abnormal" was excluded.
*Probability value not significant.

TABLE 6. Association by Univariate and Multivariate Analyses of Clinical and Stress Test Variables With Any Late Cardiac Event

		Multivariate Analysis of Clinical Data and Imaging Patterns			
		Model I		Model II	
	Univariate Analysis	Clinical Data + ECHO	Clinical Data + MIBI	Clinical Data + ECHO	Clinical Data + MIBI
Clinical data					
Age >70 y	1.7 (0.8-3.6)*	*	*	2.3 (1.0-5.4)	2.4 (1.0-5.6)
Male sex	2.0 (1.0-3.8)	*	*	*	*
History of MI	2.7 (1.4-5.3)	*	*	2.8 (1.3-5.7)	3.0 (1.4-6.2)
History of revascularization	2.8 (1.5-5.3)	*	2.1 (1.0-4.3)	*	*
History of CHF	1.6 (0.8-3.4)*	*	*	*	*
Typical angina	3.1 (1.6-6.1)	2.9 (1.4-5.9)	3.2 (1.5-7.0)	3.0 (1.4-6.3)	3.0 (1.4-6.3)
Stress test data					
Angina	1.7 (0.9-3.4)*	*	*	*	*
ST-segment changes	2.6 (1.2-5.5)	*	*	*	*
ECHO					
Abnormal	9.3 (3.5-24.6)	8.9 (3.3-23.8)	...	...	...
Infarction	3.0 (1.6-5.6)	...	...	*	...
Ischemia	4.5 (2.4-8.6)	...	...	4.0 (2.0-7.9)	...
MIBI					
Abnormal	8.3 (2.8-23.9)	...	8.8 (2.9-26.6)	...	...
Infarction	2.9 (1.5-5.6)	...	...	...	*
Ischemia	4.0 (2.1-7.7)	...	...	...	3.9 (1.9-7.8)

See Table 5 legend.

nostic MIBI did not add to the information provided by MIBI alone.

Discussion

In daily clinical practice, stress-induced transient perfusion defects and wall motion abnormalities are used as myocardial ischemia markers.[7-14] However, their relative prognostic information in a heterogeneous population, such as that referred to a busy cardiac stress imaging laboratory, is unknown. Therefore, we initiated this study to make a head-to-head comparison between the prognostic value of these different ischemic markers from high-dose dobutamine-atropine stress testing in 220 patients unable to perform an adequate exercise test. The main findings of our study are (1) an ischemic pattern on dobutamine-atropine stress ECHO or MIBI provides comparable, independent prognostic information in addition to clinical data, (2) an increased number of ischemic segments is directly related to a worse prognosis for both ECHO and MIBI, and (3) if ECHO is selected as the imaging modality of first choice, the addition of MIBI to clinical and ECHO data can be useful but should be limited to the minority of patients with a nondiagnostic ECHO study, whereas the reverse addition of ECHO to MIBI seems less useful, certainly from a cost-effective point of view.

Stress Test Technique

In the present study, high-dose dobutamine-atropine was used as the stressing agent. High-dose dobutamine, up to 40 μg/kg per minute, eventually in combination with atropine, has been used widely for the diagnosis of coronary artery disease in conjunction with echocardiography and, although less frequently, also with perfusion scintigraphy.[11,13,14,20] Dobutamine is a predominant β_1-agonist that causes an increase of myocardial oxygen demand mainly resulting from increased contractility and heart rate, providing hemodynamic changes partially similar to exercise.[23] In the case of significant coronary stenoses, dobutamine induces a maldistribution of flow and eventually a worsening of regional wall thickening that can be detected by perfusion SPECT imaging and echocardiography, respectively. In echocardiographic studies, the addition of atropine to dobutamine has been shown to improve its diagnostic accuracy, especially in patients receiving β-blockers.[15,24]

As shown in other studies,[25-27] dobutamine-atropine stress is a safe and feasible stress method. Consistently, in the present series there were no major side effects such as sustained ventricular tachycardia, ventricular fibrillation, MI, or death. The feasibility of the test was also high, since in only 18 tests (7%) the maximal dose of dobutamine-atropine was insufficient to attain 85% of predicted maximal heart rate and there were only a few nonischemia-related, limiting side effects. Apart from 14 patients (5%) with inadequate acoustic echocardiographic windows for the assessment of all ventricular regions and 2 patients (1%) with scintigraphic images that could not be interpreted completely, only 28 of all ECHO studies (13%) and 23 of all MIBI studies (10%) were nondiagnostic.

Image Pattern Distribution

Ischemic segments were relatively more common on MIBI than on ECHO. Of note, ischemia was especially more frequently detected in patients with infarct patterns. These findings are not surprising, since it is known that according to the "ischemic cascade" theory,[28] perfusion abnormalities are expected to precede the development of true ischemia, eventually resulting in wall motion abnormalities. Furthermore, in segments with resting myocardial dysfunction, the detection of ischemia on ECHO can be problematic.[29] Abnormal echocardiographic images in the presence of normal perfusion

TABLE 7. Predictive Value of an Ischemic Response for Future Hard Events and All Cardiac Events According to Different Additions of MIBI to the 220 ECHO Studies

Diagnostic Strategy	No. of MIBI Studies Added to ECHO	No. of Patients at Risk	Hard Events Correctly Predicted	OR (95% CI)	All Events Correctly Predicted	OR (95% CI)
A	0	76/220	15/24	4.0 (1.6-9.9)	33/54	4.0 (2.0-7.9)
B	144	109/220	18/24	3.8 (1.4-10.2)	41/54	3.9 (1.9-7.9)
C	28	85/220	17/24	5.3 (2.0-14.0)	37/54	4.6 (2.2-9.4)
D	12	81/220	17/24	5.7 (2.2-15.0)	36/54	4.6 (2.3-9.3)

In all strategies, ECHO was performed in all 220 patients. Strategy A was confined to ECHO used alone. In the other strategies, MIBI was added to nonischemic ECHO (B), nondiagnostic ECHO (C), and nondiagnostic ECHO studies interrupted because of angina, ST-segment deviation, or ventricular tachyarrhythmia (D). A patient was considered at risk when either of the imaging techniques revealed ischemia.

images are hard to explain according to a pathophysiological mechanism. In these 10 patients, 2 had a moderately dilated left ventricle with diffuse hypokinesis but "normal" perfusion, possibly the result of cardiomyopathy. Unfortunately, coronary angiography was not available in these patients. The other 8 patients all had their echocardiographic wall motion abnormalities in basal inferoposterior segments, although in most patients the mid part of the wall was also involved. These regions of the myocardium are known for their tendency to cause false-positive results.[30]

Prognostic Value

This is the first study conducted as a head-to-head comparison of the prognostic information of stress echocardiography and perfusion scintigraphy in patients with known or suspected coronary artery disease and suspected myocardial ischemia. Univariate and multivariate analyses, in which clinical and stress test variables were incorporated, confirmed the prognostic value of well-known parameters such as age, a history of CHF, and any abnormality detected by stress ECHO and MIBI.[9,10] Dobutamine-atropine stress–induced myocardial ischemia (whether detected by ECHO or MIBI) also carried independent prognostic information in addition to clinical data. This was not as strong as that of any perfusion or wall motion abnormalities, including fixed defects corresponding to myocardial scarring. However, the additional prognostic value of stress-induced ischemia is clinically relevant for its potential to be relieved by medical treatment or revascularization procedures.

Several reports on comparable populations have been published on the individual prognostic value of stress echocardiography and myocardial perfusion scintigraphy.[4,7,10] Although different stress modalities were used, these studies reported similar figures in terms of follow-up results and predictive value of the tests. Therefore, our findings on the prognostic value of dobutamine-atropine ECHO and MIBI are not very surprising. However, this study is unique in the assessment of the relative prognostic value of stress echocardiography and myocardial perfusion scintigraphy applied simultaneously in the same population.

Because both imaging modalities seem to have similar prognostic values, the choice should be made on the basis of cost aspects, availability, and (most importantly) local experience and skill. Dobutamine-atropine perfusion scintigraphy also could be considered a useful alternative in patients with a poor acoustic window and additive to echocardiography in patients with nondiagnostic echocardiographic studies (strategies C and D, Table 7), especially in patients with contraindications for vasodilator stress. Theoretically, MIBI could be injected in these patients during the same stress test, conditional to on-line interpretation of the echocardiographic images and availability of the radiotracer and the gamma camera. This strategy seems reasonable and financially convenient in a laboratory with well-balanced experience in stress echocardiography and myocardial perfusion imaging. Addition of stress echocardiography to perfusion scintigraphy, however, provided little to no additional information and requires two separate tests because ischemia at MIBI can only be assessed off-line. Therefore, such a strategy does not seem cost-effective.

Limitations of the Study

Both animal[31] and clinical studies[21] have suggested that dobutamine is an appropriate stress agent to demonstrate abnormal wall motion caused by ischemia. However, vasodilators (adenosine or dipyridamole) might be more suitable to create blood flow heterogeneity detected by perfusion scintigraphy. Indeed, in the same animal model[31] dipyridamole caused the most blood flow heterogeneity, making it particularly suited

TABLE 8. Predictive Value of an Ischemic Response for Future Hard Events and All Cardiac Events According to Different Additions of ECHO to the 220 MIBI Studies

Diagnostic Strategy	No. of ECHO Studies Added to MIBI	No. of Patients at Risk	Hard Events Correctly Predicted	OR (95% CI)	All Events Correctly Predicted	OR (95% CI)
A	0	91/220	15/24	3.0 (1.2-7.4)	36/54	3.9 (1.9-7.8)
B	129	109/220	18/24	3.8 (1.4-10.2)	41/54	3.9 (1.9-7.9)
C	23	96/220	15/24	2.3 (0.9-5.8)	37/54	3.7 (1.8-7.5)
D	8	94/220	15/24	2.4 (1.0-6.0)	37/54	3.9 (1.9-7.9)

See Table 7 legend for explanation of strategies. ECHO and MIBI strategies are reversed in this table.

for myocardial perfusion studies. Published clinical data, however, conflict concerning the superiority of vasodilators to dobutamine for perfusion scintigraphy. Kumar et al[32] found that dipyridamole thallium scintigraphy correlated better with coronary score. However, these results were based on a small group of patients and the dobutamine dose used was very low (20 μg/kg per minute). Marwick et al[13] found in a larger series of 97 patients—using high-dose dobutamine—that the accuracy of dobutamine MIBI was comparable with adenosine MIBI (accuracies of 77% and 80%, respectively). Recently, these findings were confirmed by others.[33] Although none of the aforementioned studies provides evidence for a superiority of vasodilator over dobutamine perfusion imaging for prognosis, the former stress modality is more routinely used in clinical cardiology. Future studies should provide information on the relative prognostic value of vasodilator versus dobutamine perfusion imaging and eventually versus dobutamine stress echocardiography.

The decision to perform coronary arteriography and subsequent coronary artery angioplasty or bypass graft surgery is influenced frequently by individual physicians' biases and may be affected by the presence of abnormal findings on the stress study. Therefore, we excluded patients with early elective revascularizations, and "hard" cardiac events (nonfatal MI and cardiac-related death) were analyzed separately.

The scintigrams were scored with the use of a semiquantitative method. Quantitative methods may improve diagnostic accuracy[34]; however, such an improvement is usually marginal. In an in-depth prospective analysis of patients referred for ^{201}Tl SPECT, Mahmarian et al[34] reported that visual and quantitative methods were comparably sensitive for identifying patients with single, double, and triple coronary disease; however, quantitative tomography tended to be more specific. In contrast, in a prior study from our center, we reported similar sensitivity and a trend toward better specificity for semiquantitative analysis versus quantitative analysis of dipyridamole–exercise ^{201}Tl scintigrams.[35] Finally, the interobserver agreement on ischemia for the semiquantitative analysis in the present study was excellent (95%).

Conclusions

In a population unable to perform adequate exercise with suspected or known coronary artery disease and stable chest pain, probably reflecting the continuous spectrum of disease in the total population, dobutamine-atropine stress is a safe and feasible stress technique. Combined with either imaging modality—echocardiography or ^{99m}Tc sestamibi myocardial perfusion scintigraphy—it provides useful prognostic information additional to clinical data. For both imaging modalities, the single most important independent predictor for future nonfatal MI or cardiac death is any abnormal pattern, while an ischemic pattern provides additional, independent prognostic information. If a stress laboratory chooses to use echocardiography as the routine pharmacological stress test, the addition of perfusion scintigraphy could be useful but should be limited to patients with nondiagnostic echocardiographic studies. If a center prefers perfusion imaging as the first choice, the addition of stress echocardiography does not seem cost-effective.

Acknowledgments

Dr Geleijnse is supported by the Dutch Heart Foundation (grant NHS 94.135) and Dr Elhendy by the Department of Cardiology, Cairo University Hospital, Cairo, Egypt. The authors would like to acknowledge Joyce Postma-Tjoa, nuclear technician, for her invaluable help in maintaining the database and Jeroen Vos, MD, for statistical advice.

References

1. Chaitman BR. The changing role of the exercise electrocardiogram as a diagnostic and prognostic test for chronic ischemic heart disease. *J Am Coll Cardiol.* 1986;8:1195-1210.
2. Severi S, Picano E, Michelassi C, Lattanzi F, Landi P, Distante A, L'Abbate A. Diagnostic and prognostic value of dipyridamole echocardiography in patients with suspected coronary artery disease: comparison with exercise electrocardiography. *Circulation.* 1994;89:1160-1173.
3. Ryan T, Armstrong WF, O'Donnel JA, Feigenbaum H. Risk stratification after acute myocardial infarction by means of exercise two-dimensional echocardiography. *Circulation.* 1991;83(suppl III):III-32-III-37.
4. Picano E, Severi S, Michelassi C, Lattanzi F, Masini M, Orsini E, Distante A, L'Abbate A. Prognostic importance of dipyridamole-echocardiography test in coronary artery disease. *Circulation.* 1989;80:450-457.
5. Picano E, Landi P, Bolognese L, Chiaranda G, Chiarella F, Seveso G, Sclavo MG, Gandolfo N, Previtali M, Orlandini A. Prognostic value of dipyridamole echocardiography early after uncomplicated myocardial infarction: a large-scale, multicenter trial. *Am J Med.* 1993;95:608-618.
6. Mazeika PK, Nadazdin A, Oakley CM. Prognostic value of dobutamine echocardiography in patients with high pretest likelihood of coronary artery disease. *Am J Cardiol.* 1993;71:33-39.
7. Stratmann HG, Williams GA, Wittry MD, Chaitman BR, Miller DD. Exercise technetium-99m sestamibi tomography for cardiac risk stratification of patients with stable chest pain. *Circulation.* 1994;89:615-622.
8. Machecourt J, Longère P, Fagret D, Vanzetto G, Wolf JE, Polidori C, Comet M, Denis B. Prognostic value of thallium-201 SPECT myocardial perfusion imaging according to extent of myocardial defect. *J Am Coll Cardiol.* 1994;23:1096-1106.
9. Iskandrian AS, Chae SC, Jaekyeong H, Stanberry CD, Wasserleben V, Cave V. Independent and incremental prognostic value of exercise single-photon emission computed tomographic (SPECT) thallium imaging in coronary artery disease. *J Am Coll Cardiol.* 1993;22:665-670.
10. Hendel RC, Layden JJ, Leppo JA. Prognostic value of dipyridamole thallium scintigraphy for evaluation of ischemic heart disease. *J Am Coll Cardiol.* 1990;15:109-116.
11. Hays JT, Mahmarian JJ, Cochran AJ, Verani MS. Dobutamine thallium-201 tomography for evaluating patients with suspected coronary artery disease unable to undergo exercise or vasodilator pharmacologic stress testing. *J Am Coll Cardiol.* 1993;21:1583-1590.
12. Picano E. Stress echocardiography: from pathophysiological toy to diagnostic tool. *Circulation.* 1992;85:1604-1612.
13. Marwick T, Willemart B, D'Hondt AM, Willemart B, Wijns W, Detry JM, Melin J. 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.
14. Günalp B, Dokumaci B, Uyan C, Vardareli E, Isik E, Bayhan H, Özgüven M, Öztürk E. 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.
15. McNeill AJ, Fioretti PM, El-Said EM, Salustri A, Forster T, 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.
16. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereaux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I, Silverman NH, Tajik AJ. Recommendations for quantification of the left ventricle by two-dimensional echocardiography: American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr.* 1989;2:358-367.

17. Forster T, McNeill AJ, Salustri A, Reijs AEM, El-Said EM, Roelandt JRTC, Fioretti PM. Simultaneous dobutamine stress echocardiography and 99-m technetium isonitrile single photon emission computed tomography in patients with suspected coronary artery disease. *J Am Coll Cardiol.* 1993;21:1591-1596.
18. Pandian NG, Skorton DJ, Collins SM, Falsetti HL, Burke ER, Kerber RE. Heterogeneity of left ventricular segmental wall thickening and excursion in 2-dimensional echocardiograms of normal human subjects. *Am J Cardiol.* 1983;51:1667-1673.
19. Arnese M, Fioretti PM, Cornel JH, Postma-Tjoa J, Reijs AEM, Roelandt JRTC. Akinesis becoming dyskinesis during high-dose dobutamine stress echocardiography: a marker of myocardial ischemia or a mechanical phenomenon? *Am J Cardiol.* 1994;73:896-899.
20. Marwick T, D'Hondt A, Baudhuin T, Willemart B, Wijns W, Detry JM, Melin JA. 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.
21. 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.
22. 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.
23. Ruffolo RR. The pharmacology of dobutamine. *Am J Med.* 1987; 294:244-248.
24. Ling LH, Pellekka PA, Mahoney DW, Oh JK, McCully RB, Roger VL, Seward JB. Atropine augmentation in dobutamine stress echocardiography: role and incremental value in a clinical practice setting. *J Am Coll Cardiol.* 1996;28:551-557.
25. Picano E, Mathias W, Pingitore A, Bigi R, Previtali M. Safety and tolerability of dobutamine-atropine stress echocardiography: a prospective, multicentre study. *Lancet.* 1994;344:1190-1192.
26. Mertes H, Sawada SG, Ryan T, Segar DS, Kovacs R, Foltz J, Feigenbaum H. Symptoms, adverse effects, and complications associated with dobutamine stress echocardiography: experience in 1118 patients. *Circulation.* 1993;88:15-19.
27. Poldermans D, Fioretti PM, Boersma E, Forster T, van Urk H, Cornel JH, Arnese M, Roelandt JRTC. Safety of dobutamine-atropine stress echocardiography in patients with suspected or proven coronary artery disease: experience in 650 consecutive examinations. *Am J Cardiol.* 1994;73:456-459.
28. Nesto RW, Kowalchuck GJ. The ischemic cascade: temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. *Am J Cardiol.* 1987;57:23C-27C.
29. Senior R, Lahiri A. Enhanced detection of myocardial ischemia by stress dobutamine echocardiography utilizing the 'biphasic' response of wall thickening during low and high dose dobutamine infusion. *J Am Coll Cardiol.* 1995;26:26-32.
30. Bach DS, Muller DWM, Gros BJ, Armstrong WF. False positive dobutamine stress echocardiograms: characterization of clinical, echocardiographic and angiographic findings. *J Am Coll Cardiol.* 1994;24:928-933.
31. 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.
32. Kumar EB, Steel SA, Howey S, Caplin JL, Aber CP. Dipyridamole is superior to dobutamine for thallium stress imaging: a randomised crossover study. *Br Heart J.* 1994;71:129-134.
33. Vaduganathan P, He ZX, Raghavan C, Mahmarian JJ, Verani MS. Detection of left anterior descending coronary artery stenosis in patients with left bundle branch block: exercise, adenosine or dobutamine imaging? *J Am Coll Cardiol.* 1996;28:543-550.
34. Mahmarian JJ, Boyce TM, Goldberg RK, Cocanougher MK, Roberts R, Verani MS. Quantitative exercise thallium-201 single photon emission computed tomography for the enhanced diagnosis of ischemic heart disease. *J Am Coll Cardiol.* 1990;15: 318-329.
35. Laarman GJ, Bruschke AVG, Verzijlbergen JF, Go TL, Bal ET, Van der Wal EE, Ascoop CAPL. Thallium-201 scintigraphy after dipyridamole infusion with low exercise: quantitative analysis vs visual analysis. *Eur Heart J.* 1990;11:162-172.

Chapter 12

Safety and prognostic value of early dobutamine-atropine stress echocardiography in patients with spontaneous chest pain and a nondiagnostic electrocardiogram

Geleijnse ML, Elhendy A, Kasprzak JD, Rambaldi R,
Van Domburg RT, Cornel JH, Klootwijk APJ,
Fioretti PM, Simoons ML, Roelandt JRTC

Submitted for publication

ABSTRACT

Aim of the study. To risk stratify and shorten hospital stay in patients with spontaneous chest pain and a nondiagnostic electrocardiogram (ECG).

Methods. The study comprised 102 patients (mean age 58 ± 12 years, 67 men) with spontaneous chest pain and a nondiagnostic ECG. Forty-three patients had suspected coronary artery disease (CAD) and 59 patients had known (but of unknown actual significance) CAD. All patients underwent serial creatine kinase (CK) enzyme measurement, continuous ECG monitoring for at least 12 h and early dobutamine-atropine stress echocardiography (DASE) in case of negative CK enzymes and normal findings at ECG monitoring. DASE was considered positive in case of new or worsening wall thickening abnormalities. Patients with negative DASE were discharged within 24 h of DASE (usually the same day). In-hospital and 6 months follow-up events noted were cardiac death, nonfatal myocardial infarction (MI), unstable angina (UA), and coronary artery bypass surgery or angioplasty.

Results. Thirteen patients had evidence of evolving MI by elevated CK enzymes or UA by ECG monitoring. In the remaining 89 patients DASE was performed after a median observation period of 31 h (range 12 - 68 h). During DASE no serious complications (death, nonfatal MI, sustained ventricular tachycardia or fibrillation) occurred. All patients with signs or symptoms of severe myocardial ischemia and/or supraventricular tachyarrhythmias responded well to intravenous injection of metoprolol. DASE results were of low quality in 3, nondiagnostic in 6, negative in 44 and positive in 36 patients. In the 80 patients with diagnostic DASE, variables associated with in-hospital events (n=7) were exertional angina ($p < 0.005$), stress-induced angina ($p < 0.001$) and positive DASE ($p < 0.005$). Variables associated with follow-up events (n=11) were history of exertional angina ($p < 0.05$), stress-induced angina ($p < 0.01$) and positive DASE ($p < 0.01$). At multivariate analysis the only significant predictor of events was positive DASE ($p < 0.01$).

Conclusions. Our results show that early DASE can safely discriminate patients with spontaneous chest pain and a nondiagnostic ECG into low- and high-risk subsets for subsequent cardiac events.

INTRODUCTION

The emergency room evaluation of patients with spontaneous chest pain and a nondiagnostic electrocardiogram (ECG) remains a challenge for the physician. Especially, in this time of financial constrains physicians are under pressure to reduce the frequency, intensity and length of hospital stay. To improve risk assessment several approaches have been proposed using decision algorithms (1,2), resting two-dimensional echocardiography (3), and resting perfusion imaging with thallium-201 or technetium-99m (4-6). All these approaches aimed at identification of low-risk patients who could be sent home immediately. The consequences of inappropriate emergency room discharge of patients with true acute myocardial ischemia, however, may be serious (7,8) Therefore, in daily clinical practice these sophisticated techniques are seldom used in the emergency room. Most physicians practice a conservative admission policy that results in a high level of admissions of patients with noncardiac chest pain (9). In-hospital observation, usually followed by some form of stress testing, may take several days, especially in patients initially considered at relatively high-risk. To shorten hospital stay and improve risk stratification we investigated the value of a structured protocol including serial creatine kinase (CK) enzyme measurements, continuous 12-lead ECG monitoring and early dobutamine-atropine stress echocardiography (DASE) followed by discharge of patients without inducible myocardial ischemia. In patients with stable chest pain DASE has shown to safely provide excellent diagnostic and prognostic information (10,11). The safety and predictive value of DASE in patients with acute, spontaneous chest pain and a nondiagnostic ECG, however, is still relatively unknown (12). This report addresses these issues.

METHODS

Protocol. Patients with spontaneous chest pain within 12 h of admission, unexplained by trauma, radiographic abnormality or extracardiac conditions that may induce myocardial ischemia (Braunwald type IIIA angina) (13), and without evidence of myocardial infarction (MI) or unstable angina (UA) by initial CK enzyme level and admission ECG were eligible for the study if they did not meet any of the following excluding criteria: 1) known ventricular tachyarrhythmias, 2) uncontrolled hypertension (≥180/110 mm Hg), 3) significant valvular heart disease, or 4) known significant coronary artery disease (CAD). Apart from a chest x-ray, ECG and CK enzyme measurement, emergency room evaluation comprised patient history (including previous cardiac disease, chest pain characteristics [see appendix I] and coronary risk factors [see appendix II]) and physical examination (see appendix III). After hospitalization the 12-lead ECG was continuously monitored with a MIDA 1000 (Ortivus Medical, Täby, Sweden) or Mortara ST-100 (Mortara Instrument, Milwaukee, USA) system (14). CK enzyme measurement, including the MB isoform, was repeated at 6 h and 12 h. DASE was not performed in patients with myocardial necrosis, evidenced by CK >220 U/L (or >110 and MB isoform >10%) and in patients with ECG changes during observation, conclusive for myocardial ischemia (>0.1 mV ST-segment change, T wave

inversion). In these patients the diagnosis MI or UA was established, respectively. In absence of conclusive CK enzymes or ECG changes DASE was performed between 12 and 48 h after admission (in patients with suspected CAD after 12 h, in patients with known CAD, but of unknown actual significance, after 24h). Patients who reached their target heart rate without inducible myocardial ischemia were discharged within 24 h of the study (usually the same day of stress testing).

All patients were followed-up for 6 months. In-hospital and follow-up events noted were cardiac death, nonfatal MI, UA (defined as chest pain necessitating rehospitalization), coronary artery bypass surgery (CABG) and percutaneous transluminal coronary angioplasty (PTCA). Cardiac events were presented individually and in a cumulative fashion in which only the worst event in each patient was considered. If a patient underwent coronary angiography this was also noted. Significant CAD was defined as a diameter stenosis ≥50% in a major epicardial artery, scored by two observers blinded to the clinical data. In case of disagreement quantitative coronary angiography was decisive (15). The study protocol was approved by the hospital ethics committee.

Dobutamine-atropine stress echocardiography. Dobutamine was administered intravenously by an infusion pump with an infusion rate of 10 μg/kg/min for 3 minutes, increasing by 10 μg/kg/min every 3 minutes up to a maximum of 40 μg/kg/min. In patients not achieving 85% of their age and gender predicted maximal heart rate and without symptoms or signs of myocardial ischemia, atropine was administered, starting with 0.25 mg intravenously and repeated up to a maximum of 1.0 mg within 4 minutes with continuation of dobutamine infusion. Throughout dobutamine infusion the ECG was continuously monitored (3 leads) and recorded (12 leads) at one minute intervals. Reasons for interruption of the test were: severe angina, severe and/or extensive wall thickening abnormalities, symptomatic reduction in systolic blood pressure >40 mm Hg from baseline, hypertension (blood pressure >240/120 mm Hg), significant tachyarrhythmias, horizontal or downsloping ST-segment depression more than 0.2 mV at an interval of 80 ms after the J point compared with baseline, ST-segment elevation more than 0.1 mV in patients without previous MI, and any serious side effect regarded as being due to dobutamine. Metoprolol was available to reverse the effects of dobutamine if they did not revert spontaneously and quickly. The echocardiograms were recorded on videotape and digitized on optical disk. Echocardiographic analysis of the left ventricular wall was performed according to the standardized 16-segments model (10). Systolic wall thickening (and/or wall motion) was visually evaluated, and each segment was graded with a 5-point scoring model (1 = normal; 2 = mild hypokinesis; 3 = severe hypokinesis; 4 = akinesis; and 5 = dyskinesis) during any dobutamine (or atropine) stage. DASE was considered nondiagnostic when peak heart rate was <85% of maximal in absence of new or worsening wall thickening abnormalities. DASE was considered positive in case of new or worsening wall thickening abnormalities at any dobutamine (or atropine) stage in ≥1 segment. Positive DASE studies were further stratified into high-risk and low-risk studies. High-risk studies were defined as studies in which new or worsening wall thickening abnormalities occurred at a heart rate <70% of maximal or when they occurred in >1 vascular territory (10).

Table 1. Baseline characteristics of the 102 study patients

	Patients (n=102)
Age	58 ± 12
Male gender	67 (66)
History of CAD	59 (58)
Myocardial infarction	43 (42)
Coronary bypass surgery	14 (14)
Coronary angioplasty	30 (29)
Medications	
Nitrates	23 (23)
ß-blockers	41 (40)
Calcium antagonists	36 (35)
ACE-inhibitors	19 (19)
Diuretics	16 (16)
Risk Factors	
Smoking	47 (46)
Diabetes	14 (14)
Hypertension	43 (42)
Family history of CAD	48 (47)
Hypercholesterolemia	30 (29)
Exertional Angina	37 (36)
Chest pain >60 min	35 (34)
Chest pain at admission	48 (47)
Normal electrocardiogram	41 (40)

Data are presented as mean value ± SD or number (%) of patients.
CAD = coronary artery disease.

Statistical Analysis. Values were expressed as mean value ± standard deviation, when appropriate. Comparison between variables was performed with the Student's *t* test for continuous variables and chi-square test for discrete variables. Differences of $p < 0.05$ were considered significant. To identify independent predictors for cardiac events, multivariate logistic regression analysis with a forward and backward stepping algorithm was used (BMDP package) (16). Variables included in this analysis were gender, age, history of CAD, history of exertional angina, admission ECG, need for intravenous nitroglycerine, dobutamine stress-induced angina and DASE results.

RESULTS

Patient characteristics. One-hundred and two consecutive patients gave informed consent and were included in the study. Mean age of the patients was 58 ± 12 years (range 22 to 83), 67 were men (66%). There were 43 patients (42%) with suspected CAD and 59 patients (58%) with known CAD, but of unknown actual significance. All patients with suspected CAD had a chest pain score ≥6 (see appendix I). Forty-eight patients (47%) had chest pain at admission, in the other 54 patients (53%) median time between last chest pain attack and admission was 2 h (range 1 - 12 h). Forty-one patients (40%) had a normal electrocardiogram (defined as sinus rhythm without pathologic Q-waves, conduction disturbances, high QRS voltage, and any ST-segment deviation or negative T-waves in leads I, II, aVL, aVF, and V3-V6). The other 61 patients (60%) had an abnormal, but nondiagnostic electrocardiogram (defined as absence of >0.1 mV new ST-segment change or new T-wave inversion). Relevant data of the 102 study patients are displayed in Table 1.

Identification of patients with MI or unstable angina. During observation the diagnosis evolving MI was confirmed in 4 patients (4%) and the diagnosis UA was established in 9 patients (9%). Compared to the other 89 study patients, these 13 patients were older (64 ± 11 vs. 57 ± 12, p <0.05), had higher chest pain scores (12.6 ± 3.2 vs. 9.6 ± 3.5, p <0.05), had more frequently a history of exertional angina (10 of 13 [77%] vs. 27 of 89 [30%], p <0.005), and received more frequently intravenous nitroglycerine therapy (13 of 13 [100%] vs. 39 of 89 [44%], p <0.0005).

Hemodynamic and adverse effects of DASE. The remaining 89 patients without a definite diagnosis of either evolving MI or UA were referred for early DASE for the evaluation of myocardial ischemia. Mean time from hospitalization to DASE was 33 ± 12 h. In 3 patients (3%) with a poor echocardiographic window DASE was not performed. In the remaining 86 patients dobutamine-atropine stress increased heart rate from 66 ± 12 bpm to 134 ± 16 bpm and systolic blood pressure from 136 ± 19 mm Hg to 145 ± 26 mm Hg. Test end-points were target heart rate in 59 patients (69%), maximal dose dobutamine-atropine in 6 patients (7%), severe and/or extensive wall thickening abnormalities in 7 patients (8%), severe angina in 6 patients (7%), ST-segment changes in 2 patients (2%), ventricular tachyarrhythmia in 2 patients (2%), supraventricular tachyarrhythmia in 1 patient (1%), bradycardia with hypotension in 1 patient (1%), and nausea in 2 patients (2%). Most important arrhythmias during dobutamine infusion or recovery were non-sustained ventricular tachyarrhythmia in 2 patients (2%) and supraventricular tachyarrhythmia in 4 patients (5%). One additional patient developed sustained atrial flutter. The ventricular rate of this atrial flutter was well controlled with intravenous injection of 5 mg metoprolol. Typical angina was induced in 27 patients (31%). All responded well to intravenous injection of metoprolol (3-8 mg). Other side effects were nausea in 11 patients (13%), headache in 4 patients (5%) and anxiety in 1 patient (1%).

Predictors of positive DASE. In the 86 patients who underwent DASE, stress echocardiographic

results were nondiagnostic in 6 patients (7%), negative in 44 patients (51%) and positive in 36 patients (42%). Nineteen of the latter 36 patients (53%) had high-risk DASE. Clinical variables associated with positive DASE were male gender ($p < 0.005$), higher chest pain score ($p < 0.0001$), a history of exertional angina ($p < 0.005$), a history of CAD ($p < 0.0005$), and an abnormal admission ECG ($p < 0.05$) (Table 2).

Table 2. Predictors of a positive stress echocardiogram

	Positive DASE (n=36)	Negative DASE (n=44)	p Value
Age	56 ± 12	58 ± 12	0.4257
Male gender	29 (81)	22 (50)	0.0047
History of CAD	28 (78)	17 (39)	0.0004
Exertional angina	18 (50)	7 (16)	0.0011
Risk factor score	2.0 ± 1.0	1.7 ± 1.2	0.2276
Chest pain score	11.2 ± 3.7	8.2 ± 2.9	0.0001
Physical examination score	0.3 ± 0.6	0.1 ± 0.6	0.1756
Normal ECG	11 (31)	23 (52)	0.0500
Normal ECG with pain	3 (8)	12 (27)	0.0308
Need for nitroglycerine	20 (56)	15 (34)	0.0542

Data are presented as mean value ± SD or number (%) of patients. CAD = coronary artery disease. ECG = electrocardiogram.

Hospital stay and cardiac events in patients with poor or nondiagnostic DASE. The 3 patients with a poor echocardiographic window had hospital stays of 48, 122 and 360 h, respectively. None of these patients had an in-hospital event. During follow-up 1 patient returned with UA. The 6 patients with a nondiagnostic study had a median hospital stay of 72 h (range 27 - 381 h). Three patients underwent in-hospital coronary angiography, in 2 patients coronary arteries were normal, 1 patient had one-vessel CAD and subsequently underwent PTCA. During follow-up another patient underwent coronary angiography which showed one-vessel CAD, treated with PTCA.

Hospital stay in patients with diagnostic DASE studies. The 44 patients with negative DASE were discharged early after a median hospital stay of 39 h (range 15 - 203 h). Three of these patients had a prolonged hospital stay despite negative DASE. Two patients underwent coronary angiography, 1 because of clinically suspected significant CAD despite negative DASE and 1 because of dilated cardiomyopathy. As seen in Fig. 1A, both patients were found to have normal coronary arteries. The third patient with prolonged hospital stay despite negative DASE underwent electrical cardioversion for non-DASE related atrial fibrillation. When these 3 patients were

excluded from analysis median hospital stay was 37 h (range 15 - 104 h). The 36 patients with positive DASE had a median hospital stay of 186 h (range 13 - 552 h). Hospital stay was significantly shorter in patients with low-risk DASE than in patients with high-risk DASE (median 126 h [range 44 - 447 h] vs. median 204 h [range 13 - 552 h], $p < 0.05$).

Prediction of in-hospital events by clinical and stress test data. As seen in Fig. 1A, 7 of 80 patients (9%) with diagnostic DASE had an in-hospital cardiac event (CABG in 2, PTCA in 5). Clinical predictors of in-hospital events were (see Table 3) a history of exertional angina ($p < 0.005$) and higher chest pain score ($p < 0.005$). Stress test data associated with in-hospital events were positive DASE ($p < 0.005$), high-risk DASE ($p < 0.0001$) and stress-induced angina ($p < 0.001$). Patients with high-risk DASE had, as compared to patients with low-risk DASE, more multi-vessel CAD at CAG (5 of 12 [42%] vs. 0 of 6 [0%], $p < 0.005$) and underwent more frequently PTCA ($p < 0.05$).

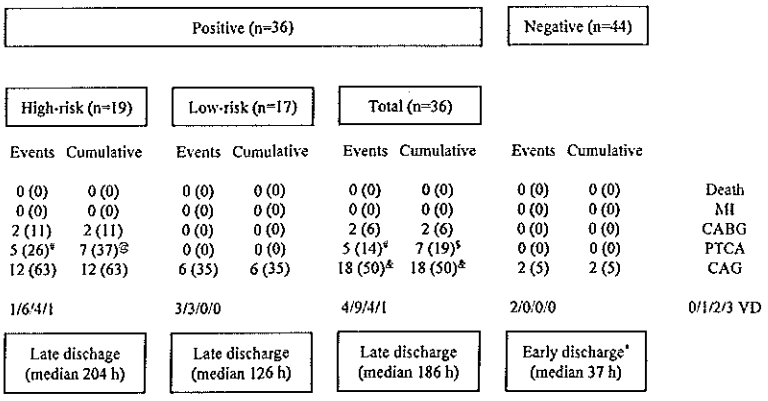
Table 3. Predictors of in-hospital cardiac events

	Cardiac Event (n=7)	No Cardiac Event (n=73)	p Value
Age	54 ± 13	57 ± 12	0.4332
Male gender	5 (71)	46 (63)	0.6582
History of CAD	5 (71)	40 (55)	0.3967
Exertional angina	6 (86)	19 (26)	0.0011
Risk factor score	2.0 ± 1.4	1.8 ± 1.1	0.6808
Chest pain score	13.4 ± 3.0	9.2 ± 3.4	0.0023
Physical examination score	0.3 ± 0.5	0.2 ± 0.6	0.6192
Normal ECG	2 (29)	32 (44)	0.4352
Normal ECG with pain	0 (0)	15 (21)	0.1833
Need for nitroglycerine	4 (57)	31 (43)	0.4546
Abnormal resting DASE	3 (43)	20 (27)	0.3880
Positive DASE	7 (100)	29 (40)	0.0022
High-risk DASE	7 (100)	12 (16)	0.0000
Stress-induced angina	6 (86)	18 (25)	0.0008
Stress-induced ST changes	2 (29)	9 (12)	0.2332

Data are presented as mean value ± SD or number (%) of patients. CAD = coronary artery disease. DASE = dobutamine-atropine stress echocardiography. ECG = electrocardiogram.

Prediction of follow-up events by clinical and stress test data. As seen in Fig. 1B, 11 of 80 patients (14%) with diagnostic DASE had a cardiac event during follow-up (MI in 1, UA in 10,

DASE Results and In-Hospital Cardiac Events



DASE Results and 6-Months Follow-Up

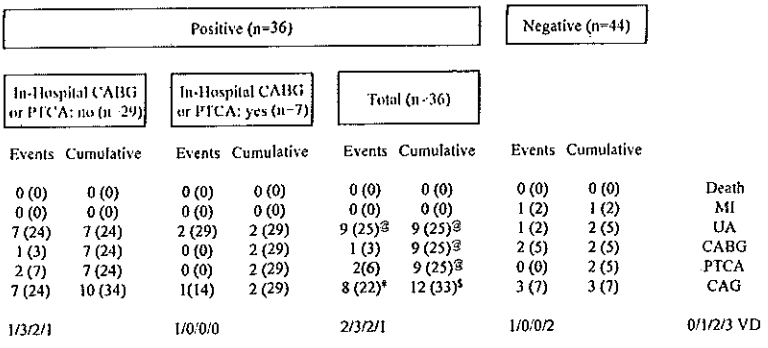


Figure 1. In-hospital (Fig. 1A, top) and 6-months follow-up (Fig. 1B, bottom) events according to the dobutamine-atropine stress echocardiographic results. In the "cumulative" column only the worst event in each patient was considered. For high-risk vs. low-risk studies or positive vs. negative studies: # = $p < 0.05$; @ = $p < 0.01$; $ = $p < 0.005$; & = $p < 0.001$. * = excluding 2 patients with in-hospital coronary angiography and 1 patient who underwent cardioversion for non-DASE related supraventricular tachycardia. CABG = coronary artery bypass surgery; CAG = coronary angiography; DASE = dobutamine-atropine stress echocardiography; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplast; UA = unstable angina.

CABG in 3 and PTCA in 2; 5 patients had more than 1 event). Clinical predictors of follow-up events were (see Table 4) a history of exertional angina ($p < 0.05$) and higher chest pain score ($p < 0.001$). Stress test data associated with events were positive DASE ($p < 0.01$), high-risk DASE ($p < 0.01$) and stress-induced angina ($p < 0.01$). There were no significant differences in follow-up events in patients with and without in-hospital revascularization. At multivariate analysis the only significant predictor of events was positive DASE (odds ratio 7.0; 95% confidence interval 1.4-35.8, $p < 0.01$)

Table 4. Predictors of 6-months follow-up events

	Cardiac Event (n=11)	No Cardiac Event (n=69)	p Value
Age	56 ± 12	57 ± 12	0.8069
Male gender	8 (73)	43 (62)	0.5048
History of CAD	8 (73)	37 (54)	0.2355
Exertional angina	7 (64)	18 (26)	0.0126
Risk factor score	2.2 ± 0.9	1.8 ± 1.1	0.2594
Chest pain score	12.9 ± 2.9	9.0 ± 3.4	0.0006
Physical examination score	0.1 ± 0.7	0.2 ± 0.6	0.6265
Normal ECG	4 (36)	30 (44)	0.6575
Normal ECG with pain	1 (9)	14 (20)	0.3768
Need for nitroglycerine	6 (55)	29 (42)	0.4371
Abnormal resting DASE	4 (36)	19 (28)	0.5480
Positive DASE	9 (82)	27 (39)	0.0082
High-risk DASE	6 (55)	13 (19)	0.0098
Stress-induced angina	7 (64)	17 (25)	0.0088
Stress-induced ST changes	2 (18)	9 (13)	0.6458

See Table 3 for abbreviations.

DISCUSSION

Every day, emergency physicians are faced with the challenge of accurately diagnosing the cause of spontaneous chest pain in patients with a nondiagnostic ECG. Despite many vigorous efforts to identify patients with and without a true acute ischemic coronary syndrome (1-6) it is well known that a small percentage of patients is inadvertently released home, sometimes with serious (fatal) consequences (7,8). Therefore, in daily clinical practice most physicians practice a conservative admission policy which, in some patients with a final diagnosis of noncardiac chest pain, may require

long in-hospital observation, especially in those patients initially considered at relatively high-risk.

Our protocol provides a rapid and structured approach for each patient that includes testing for evolving MI with serial CK enzyme measurements, observation for resting ischemia with continuous ST-segment trend monitoring, and DASE to detect inducible myocardial ischemia. Previous studies have shown that in patients with a nondiagnostic ECG the diagnosis of evolving MI can be effectively established through measurement of CK enzyme within 12 hours after symptom onset (2,17). Continuous ST-segment trend monitoring provides observational data which reflect ischemic status both in symptomatic and asymptomatic patients (18,19). If serial CK enzyme determination and continuous ST-segment trend monitoring demonstrate no evidence of resting ischemia over a 12-hour period, DASE is performed. Although resting wall thickening abnormalities may reflect ischemia, we did not use these abnormalities as a contra-indication to DASE because in a heterogeneous patient population resting wall thickening abnormalities usually represent either a variant of normal, cardiomyopathy, or scar (20). Indeed, in our patient population an abnormal resting echocardiogram was not predictive for cardiac events. Moreover, in case of true resting ischemia further worsening of wall thickening will be seen directly (on-line) during low-dose dobutamine infusion (21).

Previous studies have demonstrated the safety and prognostic value of DASE in patients with stable chest pain (10,11). In experienced hands, this stress modility offers many advantages over the usually performed exercise ECG test such as increased accuracy for the detection of CAD (10), independence of exercise capacity or resting ECG abnormalities, on-line monitoring of new wall thickening abnormalities (one of the earliest signs of ischemia) (22), detection of other cardiac causes of chest pain (valvular dysfunction, cardiomyopathy, pericarditis), and - in case of ischemia - the possibility to neutralize the effects of dobutamine immediately with intravenous injection of a beta-blocker. All these characteristics make us believe that DASE is a saver and better risk stratificating stress modality compared to exercise ECG testing in patients who are potentially ischemic at rest.

Safety and feasibility. In accordance to previously published reports (10) DASE could not be performed due to poor echocardiographic window quality only in a small minority of patients. Additionally, a few DASE studies were nondiagnostic (peak heart rate <85% of maximal in absence of new or worsening wall thickening abnormalities). So, in approximately 90% of patients DASE could be performed and yielded a diagnostic result. Although we noticed more often severe and/or extensive myocardial thickening abnormalities compared to prior studies in patients with stable chest pain, ventricular arrhythmias did not occur more frequently (10). Importantly, all patients with signs or symptoms of severe myocardial ischemia responded well to the injection of metoprolol, as did all patients with supraventricular tachyarrhythmias.

Clinical outcome. Patients with positive DASE had (by protocol definition) a significantly higher in-hospital event rate than patients with negative DASE. Despite intensive medical or invasive treatment of patients with positive DASE, such a study carried also a significantly increased risk of cardiac events during follow-up. Negative DASE was associated with a 6 months cardiac event rate of 5% while patients with positive DASE had an event rate of 25%. The predictive value of high-

risk DASE was even more striking. Patients with such a study had more often multi-vessel CAD compared to patients with low-risk DASE and most of the events, both in-hospital as well as during 6 months follow-up, occurred in patients with high-risk DASE. Of great importance is that DASE more accurately characterized the risk of cardiac events than clinical data.

Like all other stress modalities, negative DASE does not completely rule out the possibility of functionally important CAD. One 60-year-old male with a history of atypical angina and negative DASE underwent exercise ECG testing 2 weeks after discharge. Although this patient showed excellent exercise tolerance with adequate blood pressure response and absence of angina, arrhythmias or ST-segment changes, he suffered an inferoposterior MI 2 weeks later. Subsequent CAG revealed a significantly stenosed proximal right coronary artery (RCA) and mid left anterior descending (LAD) coronary artery and an occluded left circumflex (LCx) coronary artery. The LCx and RCA were retrogradely filled by collaterals from the LAD. The other patient with false negative DASE was a 73-year-old male with a history of typical, exertional angina. During DASE 0.05 mV inferolateral ST-segment elevation occurred without angina. DASE results were scored as normal although there was some doubt about the inferior wall, in particular because of relatively poor quality of the 2-chamber view during peak dobutamine stress. One week after discharge this patient returned to the hospital with chest pain accompanied by significant inferolateral ST-segment elevation. CK enzymes were negative, subsequent CAG revealed a severe stenosis with thrombus of the proximal RCA and significant stenosis of the LAD and LCx. Clearly, this last patient was misdiagnosed as not having functionally important CAD. Nevertheless, the number of events in patients with negative DASE look favorable to the 7% hard event rate previously published from our center in comparable patients with the final diagnosis noncardiac chest pain (23). Importantly, in this latter publication hospital stay was more intensive, both in duration (in 10% of patients hospital stay was >5 days) as in number and type of diagnostic procedures (sometimes including CAG).

A specific benefit of DASE was demonstrated in a patient without a history of CAD. His resting echocardiogram showed global hypokinesis of the left ventricular wall. During dobutamine stress all myocardial segments showed sustained improvement in thickening. Subsequent CAG revealed, as predicted by DASE results, normal coronary arteries. Laboratory results showed elevated levels of thyroid hormone (24).

Comparison with other studies. Early risk stratification of patients with spontaneous chest pain has mainly involved resting nuclear perfusion imaging and exercise ECG testing. Several reports have shown the usefulness of thallium-201 or technetium-99m injection during or even after a spontaneous chest pain episode (4-6). Although this technique has the advantage of not stressing a potentially unstable patient there are also some disadvantages such as radiation exposure, perfusion artifacts, costs and most importantly limited availability. Resting perfusion imaging obviously only recognizes patients at the highest risk, who in our study were partly identified by serial CK enzyme measurements and continuous ECG monitoring.

Usually, however, risk stratification is done by exercise ECG testing. Guidelines for exercise

ECG testing state that this stress modality is contra-indicated in patients with (serious) chest pain at rest within the previous 48 h (25). Nevertheless, several studies have shown evidence of the safety and efficacy of early exercise ECG testing in patients presenting with spontaneous chest pain to the emergency department (26-28). However, these studies usually included patients with a very low pre-test probability of CAD, evidenced by the very low numbers of patients with positive tests, which were not uncommonly false positive. Most of the patients included in these studies probably required no cardiac workup in the first place. In contrast, in our study over half of the included patients had evidence of myocardial ischemia by serial CK enzymes, ECG monitoring or DASE.

Recently, DASE was proposed as a screening tool on an emergency room basis to risk stratify patients with spontaneous chest pain (12). However, as with the published exercise ECG studies, the included patients were at very low risk, evidenced by the low numbers of patients with positive DASE. Apart from logistic problems of performing DASE in the emergency room department, the major drawback of this emergency room approach is that patients with a true acute coronary syndrome are not given a second chance to show their myocardial ischemia by means of CK enzyme rise or ECG monitoring. Moreover, DASE was not performed in patients with resting wall thickening abnormalities. By not performing DASE in patients with resting wall thickening abnormalities patients in whom the wall thickening abnormalities represent actual myocardial ischemia are protected against potential harmful DASE. Unfortunately, this implies that all patients with actually nonischemic wall thickening abnormalities (in our study over a third of the patients) are not suitable for such a protocol and will be hospitalised for prolonged observation.

Limitations. Inherent to the study protocol was the availability of DASE results to all physicians treating the patients. Knowledge of these results obviously affected management decisions regarding the aggressiveness of medical therapy or performance of coronary artery revascularization. As a result the predictive value of positive DASE, and in particular of high-risk DASE, for cardiac events such as PTCA or CABG could be anticipated. The number of patients with a hard cardiac event (death or MI) was surprisingly low. Patients with spontaneous chest pain without evidence of ischemia on the resting ECG constitute a relatively low-risk group, as opposed to high-risk unstable patients with ECG evidence of ischemia (29). On the other hand, the overall predictive value of positive DASE for cardiac events during follow-up may have been underestimated because of the intensive medical and invasive treatment of patients with positive DASE. The number of patients included in our study was relatively small. Therefore, conclusions, especially regarding safety, should be interpreted with caution.

Conclusions. Our results show that DASE can safely discriminate patients with spontaneous chest pain and a nondiagnostic ECG into low- and high-risk subsets for cardiac events. Other, larger studies are needed to confirm our findings and to assess the relative value and cost-effectiveness of this protocol in comparison to other protocols, involving other stress modalities. A study using troponin T as chemical marker of myocardial injury (30) and comparing early DASE with early exercise stress testing or a more conservative strategy is currently in progress in Europe.

Appendix I. Chest pain score

Location	
Substernal	+3
Precordial	+2
Neck, jaw, epigastrium	+1
Apical	-1
Radiation	
Either arm	+2
Shoulder, back, neck, jaw	+1
Character	
Crushing, pressing, squeezing	+3
Heaviness, tightness	+2
Sticking, stabbing, pinprick catching	-1
Severity	
Severe	+2
Moderate	+1
Influenced by	
Nitroglycerine	+1
Stature	-1
Breathing	-1
Associated symptoms	
Dyspnea	+2
Nausea or vomiting	+2
Diaphoresis	+2
Previous history of exertional angina	+3

Appendix II. Risk factor score

Hypertension	+1
Smoker	+1
Diabetes	+1
Family history of coronary disease	+1
Hypercholesterolemia	+1

Appendix III. Physical examination score

Pulmonary rales	+1
Increased central venous pressure	+1
Pain at local pressure	-1
Third heart sound	+1
Mitral regurgitation murmur	+1
Pericardial friction rub	-1
Vascular bruits	+1
Peripheral edema	+1

REFERENCES

1. Pozen MW, D'Agostino RB, Selker HP, Sytkowski PA, Hood WB. A predictive instrument to improve coronary-care-unit admission practices in acute ischemic heart disease. *N Engl J Med* 1984; 310:1273-1278
2. Lee TH, Juarez G, Cook FE, Weisberg MC, Rouan GW, Brand DA, Goldman L. Ruling out acute myocardial infarction. A prospective multicenter validation of a 12-hour strategy for patients at low risk. *N Engl J Med* 1991; 324: 1239-1246
3. Sabia P, Abbott RD, Afrookteh A, Keller MW, Touchstone DA, Kaul S. Importance of two-dimensional echocardiographic assessment of left ventricular systolic function in patients presenting to the emergency room with cardiac-related symptoms. *Circulation* 1991; 84: 1615-1624
4. Wackers FJ, Lie KI, Liem KL, Buseman Sokole E, Samson, van der Schoot JB, Durrer D. Thallium-201 Scintigraphy in unstable angina pectoris. *Circulation* 1978; 57: 738-743
5. Varetto T, Cantalupi D, Altieri A, Orlandi C. Emergency room technetium-99m sestamibi imaging to rule out acute myocardial ischemic events in patients with nondiagnostic electrocardiograms. *J Am Coll Cardiol* 1993; 22: 1804-1808
6. Hilton TC, Thompson RC, Williams HJ, Saylors R, Fulmer H, Stowers SA. Technetium-99m sestamibi myocardial perfusion imaging in the emergency room evaluation of chest pain. *J Am Coll Cardiol* 1994; 23: 1016-1022
7. McCarthy BD, Beshansky JR, D'Agostino RB, Selker HP. Missed diagnosis of acute myocardial infarction in the emergency department: results from a multicenter study. *Ann Emerg Med* 1993; 22: 579-582
8. Lee TH, Rouan GW, Weisberg MC, Brand DA, Acampora D, Stasiulewicz C, Walshon J, Terranova G, Gottlieb L, Goldstein-Wayne B. Clinical characteristics and natural history of patients with acute myocardial infarction sent home from the emergency room. *Am J Cardiol* 1987; 60: 219-224
9. Lee TH, Goodman L. The coronary care unit turns 25: historical trends and future directions. *Ann Intern Med* 1988; 108: 887-894
10. Geleijnse ML, Fioretti PM, Roelandt JRTC. Methodology, feasibility, safety, and diagnostic accuracy of dobutamine stress echocardiography: A review. *J Am Coll Cardiol.* 1997; 30: 595-606
11. Geleijnse ML, Elhendy A, Cornel JH, Rambaldi R, Van Domburg RT, Salustri A, Reijs AEM, Roelandt

JRTC, Fioretti PM. 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

12. Trippi JA, Lee KS, Kopp G, Nelson DR, Yee KG, Cordell WH. Dobutamine stress tele-echocardiography for evaluation of emergency patients with chest pain. *J Am Coll Cardiol* 1997; 30: 627-632
13. Braunwald E. Unstable angina. A classification. *Circulation* 1989; 80: 410-414
14. Klootwijk P, Langer A, Meij S, Green C, Veldkamp RF, Ross OM, Armstrong PW, Simoons ML. Non-invasive prediction of reperfusion and coronary artery patency by continuous ST segment monitoring in the GUSTO-I trial. *Eur Heart J* 1996; 17: 689-698
15. Reiber JHC, Serruys PW, Kooijman CJ Wiins W, Slager CJ, Gerbrands JJ, Suurbiers JC, den Boer A, Hugenholtz PG. Assessment of short-, medium-, and long-term variations in arterial dimensions from computer-assisted quantitation of coronary cineangiograms. *Circulation.* 1985; 71: 280-288
16. Dixon WJ, BMDP Statistical Software. Berkeley (CA): University of California Press, 1992: 1105-1144
17. Gibler WB, Young GP, Hedges JR, Lewis LM, Smith MS, Carleton SC, Aghababian RV, Jorden RO, Allison EJ, Otten EJ, Makens PK, Hamilton C. Acute myocardial infarction in chest pain patients with nondiagnostic ECGs: Serial CK-MB sampling in the emergency department. *Ann Emerg Med* 1992; 21: 504-512
18. Krucoff MW, Green CE, Satler LF, Miller FC, Pallas RS, Kent KM, Del Negro AA, Pearle DC, Fletcher RD, Rackley LE. Noninvasive detection of coronary artery patency using continuous ST-segment monitoring. *Am J Cardiol* 1986; 57: 916-922
19. Gibler WB, Sayre MR, Levy RC, Runyon JP, Kacich R, Hamilton C, Walsh RA. Serial 12-lead electrocardiographic monitoring in patients presenting to the emergency department with chest pain. *J Electrocardiol* 1994; 26 (suppl): 238-243
20. Pandian NG, Skorton DJ, Collins SM, Falsetti HL, Burke ER, Kerber RE. Heterogeneity of left ventricular segmental wall thickening and excursion in 2-dimensional echocardiograms of normal human subjects. *Am J Cardiol* 1983; 51: 1667-1673
21. Panza JA, Curiel RV, Laurienzo JM, Quyyumi AA, Dilsizian V. Relation between ischemic threshold measured during dobutamine stress echocardiography and known indices of poor prognosis in patients with CAD. *Circulation* 1995; 92: 2095-101.
22. Nesto RW, Kowalchuck GJ. The ischemic cascade: temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. *Am J Cardiol* 1987; 57: 23C-7C.
23. van Miltenburg AJM. Management policies and prognosis in unstable angina pectoris. Dissertation. Erasmus University Rotterdam, 1992.
24. Polikar R, Burger AG, Scherrer U, Nicod P. The thyroid and the heart. *Circulation* 1993; 87: 1435-1441
25. Dargie HJ for the ESC working group on exercise physiology, physiopathology and electrocardiography. Guidelines for cardiac exercise testing. *Eur Heart J* 1993; 14: 969-988
26. Lewis WR, Amsterdam EA. Utility and safety of immediate exercise testing of low-risk patients admitted to the hospital for suspected acute myocardial infarction *Am J Cardiol* 1994; 74: 987-990
27. Kerns JR, Shaub TF, Fontanarosa PB. Emergency cardiac stress testing in the evaluation of emergency department patients with atypical chest pain. *Ann Emerg Med* 1993; 22: 36-40
28. Gibler WB, Runyon JP, Levy RC, Sayre MS, Kacich R, Hattemer CR, Hamilton C, Gerlach JW, Walsh RA. A rapid diagnostic and treatment center for patients with chest pain in the emergency department. *Ann Emerg Med* 1995; 25: 1-8
29. Lee TH, Cook EF, Weisberg M, Sargent RK, Wilson C, Goldman L. Acute chest pain in the emergency

room. Identification and examination of low-risk patients. *Arch Intern Med* 1985; 145: 65-69

30. Hamm CW, Goldmann BU, Heeschen C, Kreymann G, Berger J, Meinertz T. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. *N Engl J Med* 1997; 337: 1648-1653

APPENDIX

The data presented in this thesis were derived from 6 prospectively defined databases:

1. A multicenter database on 223 patients who underwent simultaneous dobutamine ECHO and MIBI and coronary angiography within 3 months (chapter 4)

2. A multicenter database on 64 left bundle branch block patients without prior myocardial infarction who underwent dobutamine ECHO and coronary angiography within 1 month (chapter 8)

3. A singlecenter database on 418 patients who underwent dobutamine MIBI (chapter 9)

4. A singlecenter database on 260 of the above-described patients who underwent simultaneous dobutamine ECHO and MIBI (chapter 11)

5. A singlecenter database on 200 patients with normal dobutamine ECHO results (chapter 10)

6. A singlecenter database on 102 patients with suspected unstable angina who underwent dobutamine ECHO (chapter 12)

The data used in the retrospective studies presented in chapters 3 and 5 to 7 were derived from the third database

SUMMARY AND CONCLUSIONS

In this thesis the methodology of dobutamine stress testing and the relative diagnostic and prognostic merits of imaging myocardial ischemia with two-dimensional echocardiography (ECHO) and technetium-99m single-photon emission computed tomographic scintigraphy (MIBI) in patients with chest pain and known or suspected coronary artery disease (CAD) were described.

Test methodology

Dobutamine is a synthetic catecholamine with a relatively short plasma half-life of approximately 2 minutes due to rapid metabolization in the liver to inactive metabolites. It has strong β_1-receptor and mild α_1- and β_2-receptor agonist activity. This activity results in marked positive chronotropic (mediated by β_1-receptor stimulation) and inotropic (mediated by both β_1-receptor and α_1-receptor stimulation) effects. Systemic blood pressure increases only minimally due to an increase in cardiac output and a decrease in systemic vascular resistance because of peripheral vasoconstrictive effects (mediated by α_1-receptor stimulation) overwhelmed by vasodilative effects (mediated by β_2-receptor stimulation). In patients without sufficient rise in heart rate, the addition of atropine can further increase heart rate by its vagolytic effects. As a result of the hemodynamic changes there is an increase in oxygen demand and as a consequence in coronary artery blood flow. In myocardial regions supplied by a coronary artery with a critical stenosis, the increase in oxygen demand cannot be met by an adequate increase in blood flow. The resultant heterogeneity in blood flow can be detected by a decrease in technetium-99m uptake in the malperfused myocardium. If regional malperfusion is severe enough, wall thickening abnormalities develop which can be detected by two-dimensional echocardiography.

Each imaging modality has its specific benefits. Echocardiography machines are smaller in size, portable and widespread available at relatively low cost. Echocardiography is capable of accurately defining systolic and diastolic function, chamber dimensions, volumes and wall thickness. Non-ischemic explanations for patient symptoms may be apparent from visualization of valve anatomy and gradients or pericardial effusion. Myocardial ischemia, including the ischemic threshold, may be observed on-line during stress echocardiography, which may be attractive in patients in whom safety is a major concern. Nuclear perfusion images, however, are sometimes of better quality, easier to interpret and can be analyzed quantitatively by a computer, whereas the interpretation of stress echocardiograms is always subjective.

Diagnostic merits

- Patients with suspected CAD

Despite the fact that sensitivity (probability of an abnormal test result, given the presence of disease) and specificity (probability of a normal test result, given the absence of disease) define the

strength of a stress test, the final result of dobutamine ECHO or MIBI cannot be satisfactorily interpreted unless the pre-test probability of CAD is considered. According to Bayes' theorem post-test probability can be calculated according to pre-test probability (based on gender, age and chest pain characteristics) and the sensitivity and specificity of the test. In a prospective, multicenter study in 223 patients with suspected CAD, 15 patients were, according to the pre-test probabilities, in the low-risk group (CAD probability <10%), 53 patients were in the high-risk group (probability >80%), and the remaining 155 patients were in the intermediate-risk group (probability 10-80%) for having CAD. Sensitivity and specificity for the detection of CAD (defined as a ≥50% diameter stenosis at quantitative coronary angiography) were, for dobutamine ECHO versus MIBI respectively, 72% versus 76% and 79% versus 63%. Dobutamine ECHO was more specific than MIBI. Both dobutamine ECHO and MIBI significantly reduced the number of patients in the intermediate-risk group (from 155 to 102 and 126, respectively) The reduction of patients in this intermediate-risk group was better for dobutamine ECHO than for MIBI. Most importantly, dobutamine stress testing did not only identify absolutely more patients with post-test 'diagnostic' low- or high-risk probabilities but the relative number of patients in the low-risk group with true absence of CAD and the number of patients in the high-risk group with true presence of CAD tended to be higher, both for dobutamine ECHO (105/121, 87%) and for MIBI (88/97, 91%) compared to patients with pre-test 'diagnostic' low- or high-risk probabilities (56/68, 82%).

- Patients with a history of myocardial infarction

The major goals of dobutamine stress testing in patients with a history of myocardial infarction are to assess infarct-related coronary artery stenosis and to identify patients with multivessel CAD in whom coronary angiography and eventually myocardial revascularization may be indicated. In a retrospective study in 72 patients with a history of myocardial infarction and known coronary anatomy, sensitivity and specificity for the detection of infarct-related CAD were, for ECHO versus MIBI respectively, 56% versus 44% and 82% versus 82%. The sensitivity and specificity for the detection of multivessel CAD (as assessed by a multivessel ischemic pattern) were, for ECHO versus MIBI respectively, 40% versus 36% and 96% versus 96%. It should be emphasized that the echocardiographic "biphasic" response to detect myocardial ischemia in patients with resting wall thickening abnormalities was not used in this study.

- Patients with left ventricular hypertrophy

Hypertension is a major risk factor for the development of CAD and a frequent finding in patients undergoing dobutamine stress testing. Patients with hypertension often have left ventricular hypertrophy, a condition that is presumed to potentially cause false positive perfusion defects in the absence of CAD due to impairment of coronary flow reserve. To investigate the relative role of

dobutamine ECHO and MIBI in this patient subset we retrospectively studied 84 hypertensive patients (59 with left ventricular hypertrophy and 25 without left ventricular hypertrophy) with known coronary anatomy. Sensitivity and specificity for the detection of CAD were, for ECHO versus MIBI respectively, 73% versus 67% and 83% versus 83%. A subanalysis in patients with versus without left ventricular hypertrophy did not show a difference in diagnostic accuracy for the detection of CAD, both for dobutamine ECHO and MIBI.

- Patients with left bundle branch block

In patients with left bundle branch block, exercise myocardial perfusion studies often suffer from false positive perfusion defects in the interventricular septum despite a normal left anterior descending coronary artery. Several mechanisms have been proposed to explain these perfusion defects. In left bundle branch block 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. As heart rate increases and diastole shortens, the relative septal hypoperfusion may even become more apparent. During dobutamine stress, the attained heart rate is usually lower than during exercise which could potentially preserve the specificity of the test. In a retrospective dobutamine MIBI study in 20 patients without left anterior descending stenosis, specificity for CAD in this artery was 80%.

In a prospective, multicenter dobutamine ECHO study in left bundle branch block patients without a history of myocardial infarction we found that in 49 patients without left anterior descending stenosis specificity for CAD in this artery was 97%. In the 15 patients with CAD in the left descending coronary artery sensitivity for the detection of CAD, however, was quit low in patients with abnormal rest septal thickening (44%) as opposite to patients with normal rest septal thickening (83%). Interestingly, the likelihood of having relatively normal rest septal thickening was higher in patients with shorter QRS-duration and normal QRS-axis. So, patients who potentially most benefit from dobutamine ECHO may initially be selected by their resting electrocardiogram.

Prognostic merits

- Patients with stable chest pain

The prognostic value of dobutamine MIBI was assessed in 392 patients with stable chest pain. This study indicated that patients at greater risk for hard (cardiac death or myocardial infarction) or all cardiac events (hard events or late revascularization procedures) can be identified by virtue of their clinical and MIBI scintigraphic profile. The single most important independent predictor of subsequent events was abnormalities on the perfusion study (any abnormality); such an abnormal finding increased the risk for subsequent hard cardiac events tenfold and for all events eightfold. A

normal scan conferred a good prognosis and identified 33% of the patients that were at a very low risk for hard events (annual event rate 0.8%) and low risk for all events (annual event rate 2.5%). An ischemic pattern provided additional, independent prognostic value. Compared to patients without ischemia, these patients had a threefold increased risk for both hard and all events. Most importantly, this study clearly showed a direct relation between the extent and severity of dobutamine-induced perfusion defects and prognosis.

In another study the relative prognostic value of dobutamine ECHO and MIBI was assessed in 220 of the 392 above-described patients. No significant differences where found in the prognostic value of the two imaging modalities although the positive predictive value of an ischemic dobutamine ECHO study tended to be somewhat better. After analyzing different strategies of adding dobutamine ECHO to MIBI or dobutamine MIBI to ECHO, it was speculated that addition of dobutamine MIBI to a nonischemic submaximal dobutamine ECHO study may be a reasonable and financially convenient strategy to optimize the predictive value of dobutamine stress testing.

In a third study in 200 patients with stable chest pain it was shown that patients with low or intermediate pre-test probabilities of CAD and a normal dobutamine ECHO study had a negligible event rate during a 2-year follow-up. Patients with high pre-test probabilities of CAD and a submaximal normal dobutamine ECHO study, and in particular those patients with other signs or symptoms of myocardial ischemia during dobutamine stress (angina or ischemic electrocardiographic changes) still appear to be at some risk for functionally important CAD.

- Patients with suspected unstable chest pain

To shorten hospital stay and to study the predictive value of early dobutamine ECHO in patients with suspected unstable angina we prospectively studied 102 patients with spontaneous chest pain and a nondiagnostic ECG. All patients underwent serial creatine kinase enzyme measurement, continuous ECG monitoring for at least 12 h and dobutamine ECHO in case of negative creatine kinase enzymes and normal findings at ECG monitoring. Patients with negative dobutamine ECHO were discharged within 24 h of the test (usually the same day). Six months follow-up events noted were cardiac death, nonfatal myocardial infarction, unstable angina, and coronary revascularization. Thirteen patients had evidence of evolving myocardial infarction by elevated creatine kinase enzymes or unstable angina by ECG monitoring. In the remaining 89 patients, dobutamine ECHO was performed after a median observation period of 31 hours. During the test no serious complications occurred. Dobutamine ECHO results were of poor quality in 3, nondiagnostic in 6, negative in 44 and positive in 36 patients. In the 80 patients with a diagnostic dobutamine ECHO study, variables associated with events during follow-up were history of exertional angina, stress-induced angina and a positive dobutamine ECHO study. At multivariate analysis the only significant predictor of events was a positive dobutamine ECHO study.

Our results in perspective of other published data

In general, our diagnostic dobutamine ECHO and MIBI results are within the range of those reported by others (see Tables 1-3 and Tables 1-2 in Chapter 1), although the available data in specific patient populations are scarce. However, a comparison of our results with those reported in the literature is not that relevant since patient characteristics, stress protocols, criteria for a positive test and the golden standard for CAD are so different. More important than individual study results are the respective values of dobutamine ECHO and MIBI, studied in head-to-head comparisons. Some nuclear orientated physicians have concluded that stress myocardial perfusion scintigraphy is [1] more sensitive for the detection of overall CAD, especially for the detection of single-vessel CAD, [2] superior in the localization of disease in a specific vessel, and [3] superior in the identification of multivessel CAD (25). The authors included in their analysis both head-to-head comparisons and indirect comparisons between the imaging modalities, did not analyse all available studies and did not take into account the earlier discussed limitations of published studies. Only in our dobutamine study in patients with suspected CAD we found a tendency towards better identification of CAD by dobutamine MIBI. Of note, in this study the relatively mild stress level (atropine was not used in this study) was not favoring the echocardiographic detection of myocardial ischemia. On the other hand, dobutamine ECHO may be the more specific test.

More important than diagnostic results (or knowing the coronary anatomy of a patient) is to know if a positive test denotes worse outcome (and ultimately if medical or invasive interventions improve outcome). Clearly, coronary anatomy has predictive power (26). Several studies, however, have indicated that functional tests are better capable of predicting future events (27). So, how do stress echocardiography and perfusion imaging perform in this respect? In a recent publication, Kenneth A. Brown concluded that the ability to define a low-risk cohort is not the same for stress echocardiography (estimated annual hard event rate 6%) and stress myocardial perfusion imaging (estimated rate <1%) and the use of stress echocardiography may therefore not be appropriate for cardiac risk stratification (28). Again, such a conclusion seems inappropriate, not only because of the earlier mentioned limitations in comparing studies, but also by defining stress echo studies with resting wall motion abnormalities as normal.

Our excellent prognostic dobutamine ECHO results were recently confirmed by a larger study from the Mayo Clinic (29). In this study, 860 patients (with comparable baseline characteristics, undergoing a similar stress protocol) were followed-up for a mean of 24 months. Hard annual events rates for patients with a normal versus an abnormal stress echocardiogram were 2.0% versus 6.6% (in our study 0.4% versus 6.6%). Event rates for nonischemic versus ischemic stress echocardiograms were 3.9% versus 6.9% (in our study 2.4% versus 7.6%). For all cardiac events these numbers were, respectively, 2.3% versus 12.9% and 5.8% versus15.0% (in our study these numbers were 2.3% versus 14.2% and 5.6% versus 16.8%). Preliminary, extended data in 1,737 patients from our center by Poldermans *et al.* (30) also confirm our data. An annual hard event rate less than 2.0% for patients with a normal stress echocardiogram was also reported by authors describing the value of exercise (31-33) or dipyridamole (34) stress echocardiography.

Table 1. Diagnostic Accuracy of Dobutamine Stress Myocardial Perfusion Imaging As Reported in 20 Studies

Year	Author	Protocol		Tracer	Analysis	Patients	Mean age	Men	MI	ß-Blocker	CAG	Defect	Sensitivity	Specificity	Accuracy
1984	Mason (1)	20	- 5 min	Tl-201	Planar	24	59	NA	0%	48 h stop	>50, V	Rev	94%	88%	92%
1991	Pennell (2)	20	- 5 min	Tl-201	Planar	50	54	84%	30%	48 h stop	>50, V	Rev	98%	80%	94%
1993	Günalp (3)	30	- 5 min	Tc-99	SPECT	27	47	85%	0%	48 h stop	>50, V	Rev	94%	89%	93%
	Forster (4)	40+A	- 3 min	Tc-99	SPECT	21	62	55%	0%	52%	>50, V	Rev	83%	89%	86%
	Marwick (5)	40	- 3 min	Tc-99	SPECT	217	58	72%	0%	19%	>50, Q	Any	76%	67%	73%
	Pennell (6)	40	- 3 min	Tl-201	Planar	20	63	60%	0%	0%	>50, V	Rev	91%	78%	85%
	Hays (7)	40	- 3 min	Tl-201	SPECT	67	65	50%	29%	10%	>50, Q	Any	86%	90%	87%
	Warner (8)	50	- 3 min	Tl-201	SPECT	16	61	44%	56%	24 h stop	>50, Q	Any	93%	100%	94%
1994	Senior (9)	40	- 3 min	Tc-99	SPECT	61	63	72%	21%	72 h stop	>50, V	Any	95%	71%	89%
	Herman (10)	30	- 5 min	Tc-99	SPECT	20	57	92%	29%	42%	>50, V	Any	100%	100%	100%
1995	**This thesis**	**40**	**- 3 min**	**Tc-99**	**SPECT**	**223**	**58**	**69%**	**0%**	**23%**	**>50, Q**	**Any**	**76%**	**63%**	**71%**
	Thorley (11)	40+A	- 4 min	Tc-99	SPECT	23	57	69%	48%	48 h stop	>50, V	Any	95%	100%	96%
	Henzlova (12)	40	- 3 min	Tl-201	SPECT	15	48	65%	0%	+	>50, V	Rev	100%	36%	53%
1996	Di Bello (13)	40+A	- 3 min	Tc-99	SPECT	45	53	73%	0%	stopped	>50, V	Rev	87%	86%	87%
	Kisacik (14)	40+A	- 3 min	Tc-99	SPECT	69	51	84%	30%	48 h stop	>50, V	Rev	96%	64%	86%
	Iftikhar (15)	40	- 3 min	Tc-99	SPECT	38	55	57%	33%	9%	>50, V	Any	79%	90%	82%
1997	Huang (16)	40+A	- 3 min	Tl-201	SPECT	93	61	77%	39%	58%	>50, Q	Rev	90%	81%	87%
	Caner (17)	40+A	- 3 min	Both	SPECT	29	NA	52%	38%	48 h stop	>50, V	Rev	84%	70%	79%
1998	Santoro (18)	40+A	- 3 min	Tc-99	SPECT	60	NA	NA	0%	NA	>70, Q	Any	91%	81%	87%
	San Román (19	40+A	- 3 min	Tc-99	SPECT	92	64	49%	0%	9%	>50, Q	Any	87%	70%	82%

A = atropine; CAG = coronary angiography; MI = myocardial infarction; NA = not available; Rev = reversible defect; SPECT = single-photon emission computed tomography; Q = (semi)quantitative; V = visual

Table 2. Dobutamine stress testing in patients with hypertension and/or left ventricular hypertrophy

Year	Author	Dob dose		Echocardiografie				Perfusie scintigrafie			
				Sensitivity		Specificity		Sensitivity		Specificity	
1993	Marwick (5)	40	HT	-	-	-	-	-	-	-	-
			LVH	27/37	(73%)	16/17	(94%)	29/37	(78%)	10/17	(59%)
1996	Senior 20)	40	HT	27/29	(93%)	14/14	(100%)	-	-	-	-
			LVH	17/19	(89%)	9/9	(100%)	-	-	-	-
1998	Ho (21)	40[A]	HT	26/29	(90%)	23/27	(85%)	-	-	-	-
			LVH	16/17	(93%)	12/14	(84%)	-	-	-	-
1998	**This thesis**	**40[A]**	**HT**	**48/66**	**(73%)**	**15/18**	**(83%)**	**44/66**	**(67%)**	**15/18**	**(83%)**
			LVH	**35/46**	**(76%)**	**11/13**	**(85%)**	**32/46**	**(70%)**	**11/13**	**(85%)**

A = Atropine, Dob dose = Dobutamine dose in μg/kg/min, HT = Hypertension, LVH = Left ventricular hypertrophy.

Table 3. Dobutamine stress testing in patients with left bundle branch block

Year	Author	Dob dose		Echocardiografie				Perfusie scintigrafie			
				Sensitivity		Specificity		Sensitivity		Specificity	
1995	Mairesse (22)	40	Overall	14/15	(93%)	7/9	(78%)	10/15	(67%)	8/9	(89%)
			Anterior	10/12	(83%)	11/12	(92%)	9/12	(75%)	11/12	(92%)
			Posterior	11/13	(85%)	8/11	(73%)	1/13	(8%)	9/11	(82%)
1996	Vaduganathan (23)	40	Overall	-	-	-	-	23/25	(92%)	1/2	(50%)
			Anterior	-	-	-	-	17/17	(100%)	8/10	(80%)
			Posterior	-	-	-	-	-	-	-	-
1997	Caner (24)	40[A]	Overall	-	-	-	-	-	-	3/19	(16%)
			Anterior	-	-	-	-	-	-	3/19	(16%)
			Posterior	-	-	-	-	-	-	16/19	(84%)
1999	**This thesis**	**40[A]**	**Overall**	**13/19**	**(68%)**	**41/45**	**(91%)**	-	-	-	-
			Anterior	**9/15**	**(60%)**	**46/49**	**(94%)**	-	-	-	-
			Posterior	**8/12**	**(67%)**	**51/52**	**(98%)**	-	-	-	-
1999	**This thesis**	**40[A]**	**Overall**	-	-	-	-	**13/16**	**(81%)**	**9/13**	**(69%)**
			Anterior	-	-	-	-	**5/9**	**(56%)**	**16/20**	**(80%)**
			Posterior	-	-	-	-	**8/13**	**(62%)**	**13/16**	**(81%)**

A = Atropine, Dob dose = Dobutamine dose in μg/kg/min, LBBB = Left bundle branch block. Anterior and posterior refer to the respective circulations.

Despite some theoretical limitations of dobutamine as a stressor used in conjunction with perfusion imaging, our prognostic dobutamine MIBI results were comparable to previously published exercise (35) and dipyridamole (36) MIBI results. The comparable prognostic value of stress echocardiography and myocardial perfusion imaging, described in our dobutamine study, was recently confirmed by authors describing the respective values of dobutamine (37), exercise (38), and dipyridamole (39) stress.

Which test for whom?

Several stress modalities are available to the clinician for the detection of myocardial ischemia and risk assessment. This section will discuss the choice for a stress modality in a particular patient. The discussion will be focused on today's most popular stressors exercise (bicycle or treadmill) and pharmacological stress testing with a vasodilator (adenosine, dipyridamole) or dobutamine and the imaging modalities two-dimensional echocardiography and perfusion scintigraphy. Other, more expensive and/or less available imaging modalities such as magnetic resonance imaging, electron-beam computed tomography, positron emission tomography and radionuclide ventriculography and less commonly used stressors such as arbutamine, pacing, ergonovine, cold pressor or hyperventilation will not be discussed.

Indications for exercise stress testing

In the majority of patients capable of performing adequate exercise, exercise electrocardiography should be the test of choice because of the widespread availability and experience, costs, reproducibility of symptoms, assessment of haemodynamics and patient acceptance. Addition of an imaging modality is necessary in patients with a high incidence of false-positive tests because of hyperventilation syndromes, mitral valve prolapse and repolarization abnormalities related to left ventricular hypertrophy, conduction disturbances (left bundle branch block, pre-excitation, ventricular paced rhythm) or digitalis therapy. Stress imaging is also helpful when identification of the site of myocardial ischemia or the direct measurement of specific ancillary information (for example, left ventricular ejection fraction) is necessary for patient management. Whether it is cost-effective to routinely use an imaging modality in women is controversial.

Indications for pharmacological stress testing

In patients unable to perform adequate exercise, because of deconditioning or neurologic, respiratory, peripheral vascular or orthopedic limitations, pharmacological stress testing with a vasodilator (adenosine, dipyridamole) or dobutamine is indicated, because of a decrease in sensitivity associated with submaximal exercise stress. Pharmacological stress is also indicated in patients with left bundle branch block, because of a decrease in specificity associated with exercise

stress. The stressor of choice is dependent on costs, patient characteristics, the imaging modality and local expertise.

Dobutamine is preferred in patients with:
- allergy to vasodilators
- obstructive airway disease (active wheezing or a recent exacerbation)
- atrioventricular node disease
- arterial hypotension
- caffeine-containing beverages used <12 hours before testing
- dipyridamole or theophylline-containing compounds used <24 hours before testing
- echocardiographic imaging

Vasodilators are preferred in patients with:
- allergy to dobutamine
- known susceptibility to ventricular arrhythmias
- relatively uncontrolled atrial fibrillation
- relatively uncontrolled hypertension
- mild hypokalemia
- symptomatic or large aortic aneurysm (?)
- left bundle branch block (?)
- perfusion imaging (?)

Echocardiographic or perfusion scintigraphic imaging is always necessary in combination with pharmacological stress testing because the sensitivity of drug-induced electrocardiographic changes is relatively low. As with the stressor of choice, the imaging modality of choice is dependent on costs, patient characteristics, the stressor and local expertise.

Perfusion scintigraphy is more useful in:
- patients with a poor echocardiographic window (obese, airway disease)
- patients requiring vasodilator stress
- detection of (anatomically defined) mild CAD

Echocardiography is more useful in:
- patients in whom safety is a concern
- assessment of the functional significance of a stenosis
- patients with a suspicion of significant valvular, myocardial or pericardial disease
- studies being performed to assess the adequacy of therapy (?)
- patients with LVH (?)
- patients with heart transplantation (?)
- women (?)

Conclusions and future directions

As described, each imaging modality has its specific benefits. For this moment one could argue that perfusion imaging may be somewhat more sensitive to detect milder forms of CAD, at the cost of a lower specificity. For prognostic purposes, more related to severe forms of CAD, echocardiography and perfusion imaging seem to have comparable strength. However, the choice for one of the imaging modalities should not only be based on their diagnostic or prognostic accuracies but also on patient characteristics, costs (or better cost-effectiveness), and local experience. Furthermore, many technical improvements are expected to find their way into the clinic in the near future. The use of new technetium-99m labeled tracers, multihead gamma cameras, and photon attenuation/scatter or depth resolution compensation all have the potential to enhance perfusion image quality and decrease the number of artifacts. Likewise, edge detection based on backscatter analysis and acoustic quantification with color coding for the assessment of the time course of endocardial motion, tissue Doppler imaging, and the use of contrast agents will hopefully enhance the ability to characterize and quantify echocardiographically detected wall motion and thickening. Contrast echocardiography as well as ECG-gated single-photon emission computed tomographic imaging may eventually allow evaluation of myocardial function and perfusion with the use of only one imaging modality. All these developments will certainly require the reassessment of the relative role of the two imaging modalities in the future!

References

1. Mason JR, Palac RT, Freeman ML, Virupannavar S, Loeb HS, Kaplan E, Gunnar RM. Thallium scintigraphy during dobutamine infusion: nonexercise-dependent screening test for coronary disease. *Am Heart J* 1984; 107: 481-485
2. Pennel DJ, Underwood RS, Swanton RH, Walker JM, Ell PJ. Dobutamine thallium myocardial perfusion tomography. *J Am Coll Cardiol* 1991; 18: 1471-1479
3. Günalp B, Dokumaci B, Uyan C, Vardareli E, Isik E, Bayhan H, Özgüven M, Öztürk E. 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
4. Forster T, McNeill AJ, Salustri A,et al. 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: 1591-6.
5. 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
6. Pennel DJ, Underwood RS, Ell PJ. Safety of dobutamine stress for thallium-201 myocardial perfusion tomography in patients with asthma. *Am J Cardiol* 1993; 71: 1346-1350
7. Hays JT, Mahmarian JJ, Cochran AJ, Verani MS. Dobutamine thallium-201 tomography for evaluating patients with suspected coronary artery disease unable to undergo exercise or vasodilator pharmacologic stress testing. *J Am Coll Cardiol* 1993; 21: 1583-1590

8. Warner MF, Pippin JJ, DiSciascio G, Paulsen WHJ, Arrowood JA, Tatum JL, Goudreau E, Vetrovec GW. Assessment of thallium scintigraphy and echocardiography during dobutamine infusion for the detection of coronary artery disease. *Cathet Cardiovasc Diagn* 1993; 29: 122-127
9. 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: 713-8.
10. Herman SD, Labresh KA, Santos-Ocampo CD, Garber CE, Barbour MM, Messinger DE, Cloutier DJ, Ahlberg AW, Heller GV. Comparison of dobutamine and exercise using technetium-99m sestamibi imaging for the evaluation of coronary artery disease. *Am J Cardiol* 1994; 73: 164-169
11. Thorley PJ, Ball J, Sheard KL, Sivananthan UM. Evaluation of $^{99}Tc^{m}$-tetrofosmin as a myocardial perfusion agent in routine clinical use. *J Nucl Med Comm* 1995; 16: 733-740
12. Henzlova MJ, Padilla ML, Freilich A, Gass AL, Courtney MC, Diamond JA, Machac J. Dobutamine thallium 201 perfusion imaging in candidates for lung transplantation. *J Heart Lung Transplant* 1995; 14: 251-256
13. Di Bello V, Bellina CR, Gori E, Molea N, Talarico L, Boni G, Magagnini E, Matteucci F, Giorgi D, Lazzeri E, Bertini A, Romano MF, Bianchi R, Giusti C. 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
14. Kisacik HL, Özdemir K, Altinyay E, Oguzhan A, Kural T, Kir M, Kütük E, Göksel S. 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
15. Iftikhar I, Koutelou JJ, Mahmarian JJ, Verani MS. Simultaneous perfusion tomography and radionuclide angiography during dobutamine stress. *J Nucl Med* 1996; 37: 1306-1310
16. Huang PJ, Ho YL, Wu CC, Chao CL, Chen MF, Chieng PU, Lee YT. Simultaneous dobutamine stress echocardiography and thallium perfusion imaging for the detection of coronary artery disease. *Cardiology* 1997; 88: 556-562
17. Caner B, Karanfil A, Uysal U, Tokgozoglu L, Aksoyek S, Ogur O, Çiftci I, Atalar E, Kes S, Bekdik C. Effect of an additional atropine injection during dobutamine infusion for myocardial SPET. *J Nucl Med Comm* 1997; 18: 567-573
18. Santoro GM, Sciagrà R, Buonamici P, Consoli N, Mazzoni V, Zerauschek F, Bisi G, Fazzini PF. Head-to-head comparison of exercise stress testing, pharmacoligic 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
19. San Román JA, Vilacosta I, Castillo JA, Rollán MJ, Hernández M, Peral V, Garcimartin I, del Mar de la Torre M, Fernández-Avilés F. Selection of the optimal stress test for the diagnosis of coronary artery disease. *Heart* 1998; 80: 370-376
20. 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
21. Ho YL, Wu CC, Lin LC, Huang CH, Chen WJ, Chen MF, Liau CS, Lee YT. Assessment of the coronary artery disease and systolic dysfunction in hypertensive patients with the dobutamine-atropine stress echocardiography: effect of the left ventricular hypertrophy. *Cardiology* 1998; 89: 52-58

22. Mairesse GH, Marwick TH, Arnese M, Vanoverschelde JLJ, Cornel JH, Detry JMR, Melin JA, Fioretti PM. 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
23. Vaduganathan P, Zuo-Xiang H, Raghavan C, Mahmarian JJ, Verani MS. Detection of left anterior descending coronary artery stenosis in patients with left bundle branch block: exercise, adenosine or dobutamine imaging. *J Am Coll Cardiol* 1996; 28: 543-550
24. Caner B, Rezaghi C, Uysal U, Tokgozoglu L, Kabakci G, Elahi N, Kes S, Aras T, Ugur O, Bekdik C. Dobutamine thallium-201 myocardial SPECT in patients with left bundle branch block and normal coronary arteries. *J Nucl Med* 1997; 38: 424-427
25. O'Keefe JH, Barnhart CS, Bateman TM. Comparison of stress echocardiography and stress myocardial perfusion scintigraphy for diagnosing coronary artery disease and assessing its severity. *Am J Cardiol* 1995; 75: 25D-34D
26. European Coronary Surgery Study Group. Long term results of prospective randomized study of coronary artery bypass surgery in stable angina pectoris. *Lancet* 1982; 2: 1173-1180
27. Kaul S, Lilly DR, Gasho JA. Prognostic utility of the exercise thallium-201 test in ambulatory patients with chest pain: comparison with cardiac catheterization. *Circulation* 1988; 77: 745-758
28. Brown KA. Do stress echocardiography and myocardial perfusion imaging have the same ability to identify the low-risk patient with known or suspected coronary artery disease. *Am J Cardiol* 1998; 81: 1050-1053
29. Chuah SC, Pellikka PA, Roger VL, McCully RB, Seward JB. Role of dobutamine stress echocardiography in predicting outcome in 860 patients with known or suspected coronary artery disease. *Circulation* 1998; 97: 1474-1480
30. Poldermans D, Fioretti PM, Boersma E, Bax JJ, Rambaldi R. Long-term prognostic value of dobutamine-atropine stress echocardiography in 1737 patients with known or suspected coronary artery disease: a single center experience. *Circulation* 1998; Suppl I: I-355 (abstract)
31. Ismail G, Lo E, Sada M, Conant RD, Shapiro SM, Ginzton LE. Long-term prognosis of patients with a normal exercise echocardiogram and clinical suspicion of myocardial ischaemia. *Am J Cardiol* 1995; 75: 934-936
32. Sawada SG, Ryan T, Jo Conley M, Corya BC, Feigenbaum H, Armstrong WF. Prognostic value of a normal exercise echocardiogram. *Am Heart J* 1990; 120: 49-55
33. McCulley RB, Roger VL, Mahoney DW, Karon BL, Oh JK, Miller FA, Seward JB, Pellikka PA. Outcome after normal exercise echocardiography and predictors of subsequent cardiac events: Follow-up of 1,325 patients. *J Am Coll Cardiol* 1998; 31: 144-149
34. Severi S, Picano E, Michelassi C, Lattanzi F, Landi P, Distante A, et al. Diagnostic and prognostic value of dipyridamole echocardiography in patients with suspected coronary artery disease: comparison with exercise electrocardiography. *Circulation* 1994; 89: 1160-1173
35. Stratmann HG, Williams GA, Wittry MD, Chaitman BR, Miller DD. Exercise technetium-99m sestamibi tomography for cardiac risk stratification of patients with stable chest pain. *Circulation* 1994; 89: 615-622
36. Stratmann HG, Tamesis BR, Younis LT, et al. Prognostic value of dipyridamole technetium-99m sestamibi myocardial imaging in >300 consecutive patients with stable chest pain. *J Am Coll Cardiol* 1993; 21: 68A (abstract)
37. 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

38. Olmos LI, Dakik H, Gordon R, Dunn KJ, Verani MS, Quiñones MA, Zoghbi WA. Long-term prognostic value of exercise echocardiography compared with exercise 201Tl, ECG, and clinical variables in patients evaluated for coronary artery disease. *Circulation* 1998; 98: 2679-2686
39. 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

SAMENVATTING

In dit proefschrift werd de methodologie en relatieve diagnostische en prognostische waarde van dobutamine echocardiografie (ECHO) en dobutamine perfusie scintigrafie met technetium-99m (MIBI) besproken bij patiënten met borstklachten mogelijk berustend op ziekte van de kransslagaders.

Test methodologie

Dobutamine is een lichaamsvreemde stof welke na toediening in de bloedbaan leidt tot een stijging van de hartfrequentie, een verbetering van de pompfunctie van het hart en een geringe toename van de bloeddruk. Als gevolg van deze veranderingen heeft de hartspier meer zuurstof nodig. Om aan deze zuurstofvraag te kunnen voldoen zullen de kransslagaders zich verwijden waardoor meer bloed met zuurstof door de hartspier kan stromen. Een zieke kransslagader met een belangrijke vernauwing kan echter de bloedstroom minder laten toenemen dan een gezonde kransslagader. Indien bij een patiënt met kransslagaderziekte technetium-99m wordt ingespoten in de bloedbaan zal dit verminderd worden opgenomen in die hartspierdelen die relatief minder van bloed worden voorzien. Deze verminderde opname uit zich op de nucleaire scan als een perfusiedefect. Indien de bloedvoorziening ook in absolute zin tekortschiet zal het betreffende hartspierdeel door zuurstoftekort verminderd samenknijpen. Dit laatste kan middels echocardiografie gedetecteerd worden daar deze techniek in staat is de zich samenknijpende hartspier in 'real-time' af te beelden.

Zowel dobutamine ECHO als MIBI hebben hun eigen, specifieke voordelen. Echo machines zijn kleiner, verplaatsbaar, in ieder ziekenhuis aanwezig en relatief goedkoop. Middels echocardiografie kan op een nauwkeurige wijze de grootte van de hartholtes en de wanddikte en pompfunctie van de hartspier bepaald worden. Tevens kunnen op eenvoudig wijze andere verklaringen voor borstklachten zoals bepaalde hartklepgebreken of een ontstoken hartzakje zichtbaar gemaakt worden. Een eventueel optredend zuurstoftekort van de hartspier kan bovendien tijdens de test ontdekt worden waardoor de test tijdig kan worden onderbroken (in tegenstelling tot de nucleaire scintigrafie techniek waarbij plaatjes pas na afloop van de test gemaakt kunnen worden). Het vroegtijdig onderkennen van zuurstoftekort is vooral aantrekkelijk bij patiënten waarbij mogelijk ernstig zuurstoftekort wordt verwacht. Afbeelding van zuurstoftekort van de hartspier met nucleaire scintigrafische technieken levert echter soms mooiere plaatjes op. Bovendien zijn de stilstaande nucleaire plaatjes in tegenstelling tot de bewegende echocardiografische beelden veel eenvoudiger te interpreteren en kunnen zij ook geheel automatisch en kwantitatief door een computer geanalyseerd worden.

Diagnostische waarde

- Patiënten met mogelijk kransslagaderziekte

De nauwkeurigheid van een testuitslag wordt bepaald door de sensitiviteit (de kans op een abnormale testuitslag, gegeven aanwezigheid van de ziekte) en specificiteit (de kans op een normale testuitslag, gegeven afwezigheid van de ziekte) van de test. De resultaten van dobutamine ECHO of MIBI zijn echter niet goed te interpreteren indien men de voorafkans op kransslagaderziekte (gebaseerd op geslacht, leeftijd en bepaalde karakteristieken van de borstklacht) niet in ogenschouw neemt. In een studie bij 223 patiënten met mogelijke ziekte van de kransslagaders vonden we dat, volgens de voorafkans op kransslagaderziekte, 15 patiënten zich in de laag risicogroep (kans op ziekte <10%), 53 patiënten zich in de hoog risicogroep (kans op ziekte >80%) en 155 patiënten zich in de intermediaire risicogroep (kans op ziekte 10-80%) bevonden. De sensitiviteit en specificiteit van dobutamine ECHO versus MIBI voor het vaststellen van kransslagaderziekte waren respectievelijk 72% versus 76% en 79% versus 63%. Dobutamine ECHO was significant meer specifiek. Zowel dobutamine ECHO als MIBI verminderden significant het aantal patiënten in de intermediaire risicogroep (de groep patiënten waarbij het onduidelijk is of er sprake is van kransslagaderziekte) van respectievelijk 155 naar 102 en 126 patiënten. Deze vermindering van patiënten in de intermediaire risicogroep was beter voor dobutamine ECHO. Overigens werden met behulp van zowel dobutamine ECHO als MIBI niet alleen in absolute zin meer patiënten voorzien van een diagnostische lage of hoge kans op ziekte maar was bovendien het aantal patiënten zonder daadwerkelijk ziekte in de laag risicogroep en met daadwerkelijk ziekte in de hoog risicogroep (87% voor ECHO en 91% voor MIBI) ook relatief gezien hoger vergeleken met het aantal patiënten met een juiste lage of hoge voorafkans (82%) op kransslagaderziekte.

- Patiënten met een hartinfarct in de voorgeschiedenis

De belangrijkste doelen van de dobutamine stress test bij patiënten met een hartinfarct in de voorgeschiedenis zijn het vaststellen van de ernst van de vernauwing in de kransslagader die het hartinfarct veroorzaakte en de opsporing van patiënten met ziekte van meerdere kransslagaders bij welke ingrijpen middels dotterbehandeling of hartoperatie noodzakelijk kan zijn. In een studie bij 72 patiënten met een hartinfarct in de voorgeschiedenis die tevens een contrastonderzoek van de kransslagaders hadden ondergaan bleek dat de sensitiviteit en specificiteit voor het aantonen van een ernstige vernauwing in de kransslagader die het hartinfarct had veroorzaakt, voor respectievelijk ECHO versus MIBI, 56% versus 44% en 82% versus 82% bedroegen. De sensitiviteit en specificiteit voor het ontdekken van vernauwingen in meerdere kransslagaders op basis van een sterk abnormale testuitslag bedroegen, voor respectievelijk ECHO versus MIBI, 40% versus 36% en 96% versus 96%.

- Patiënten met linker kamerhypertrofie

Hoge bloeddruk is een belangrijke risicofactor voor het ontstaan van kransslagaderziekte. Deze aandoening wordt dan ook veel gezien bij patiënten verwezen voor een dobutamine stress test. Als gevolg van de hoge bloeddruk is vaak hypertrofie (een toename van de spierdikte) van de hartspier ontstaan. In de literatuur is gesuggereerd dat hypertrofie aanleiding kan geven tot perfusiedefecten op de MIBI scan zonder aanwezigheid van kransslagaderziekte. Teneinde de relatieve rol van dobutamine ECHO en MIBI te bepalen onderzochten wij 84 patiënten met hoge bloeddruk (waarvan 59 met hypertrofie van de hartspier) die tevens een contrastonderzoek van de kransslagaders hadden ondergaan. De sensitiviteit en specificiteit voor het ontdekken van kransslagaderziekte bedroegen, voor respectievelijk ECHO versus MIBI, 73% versus 67% en 83% versus 83%. Er kon, zowel voor dobutamine ECHO als MIBI, geen verschil worden aangetoond in diagnostische waarde bij patiënten met en zonder hypertrofie van de hartspier.

- Patiënten met een linker bundeltakblok

Bij patiënten met een linker bundeltakblok verloopt de activatie van de hartspier abnormaal en laten scans gemaakt na een fietsproef vaak perfusiedefecten zien terwijl er geen sprake is van kransslagaderziekte. Deze abnormale uitslagen worden mogelijk veroorzaakt door de sterke stijging van de hartfrequentie tijdens een fietsproef. Bij de dobutamine stress test loopt de hartfrequentie echter minder hoog op en zijn deze perfusiedefecten mogelijk afwezig. Wij vonden bij 20 patiënten met een linker bundeltakblok zonder kransslagaderziekte een specificiteit voor dobutamine MIBI van 80%.

Een dobutamine ECHO studie bij 49 patiënten met een linker bundeltakblok maar zonder kransslagaderziekte liet een specificiteit zien van 97%. Bij 15 patiënten met kransslagaderziekte leek de sensitiviteit bij die patiënten met een hartspier die in rust al slecht samenkneep iets minder (44%) dan bij die patiënten met een hartspier die in rust goed samenkneep (83%). Deze eerste groep patiënten die mogelijk minder gebaat zijn bij een dobutamine ECHO studie konden voor de test al geïdentificeerd worden middels een meer afwijkend hartfilmpje.

Prognostische waarde

- Patiënten met stabiele borstklachten

De prognostische waarde van dobutamine MIBI werd onderzocht bij 392 patiënten met stabiele borstklachten. Deze studie toonde aan dat patiënten met een groter risico op toekomstige ernstige hartproblemen (dood of hartinfarct) of willekeurige hartproblemen (dood, hartinfarct, dotterbehandeling of hartoperatie) kunnen worden ontdekt middels klinische en MIBI scintigrafische parameters. De belangrijkste, onafhankelijke voorspeller van toekomstige

hartproblemen was een abnormale perfusiescan (een scan met aanwijzingen voor zuurstoftekort of een litteken passend bij een doorgemaakt hartinfarct). Een dergelijke scan verhoogde de kans op een ernstige hartprobleem met een factor tien en de kans op een willekeurig hartprobleem met een factor acht. Een geheel normale scan ging gepaard met een zeer laag kans op een ernstige hartprobleem (jaarlijkse kans 0.8%) en een laag kans op een willekeurig hartprobleem (jaarlijkse kans 2.5%). Een scan waarop zuurstoftekort van de hartspier te zien was had aanvullende, onafhankelijke voorspellende waarde. Vergeleken met patiënten zonder zuurstoftekort hadden deze patiënten een driemaal zo grote kans op zowel een ernstig hartprobleem als een willekeurig hartprobleem. Bovendien toonde deze studie een duidelijk verband aan tussen de ernst en uitgebreidheid van de afwijkingen op de scan en de kans op het optreden van hartproblemen.

In een andere studie werd de voorspellende waarde van dobutamine ECHO and MIBI vergeleken bij 220 van de 392 beschreven patiënten. Er werden geen significante verschillen gevonden tussen de twee afbeeldingstechnieken hoewel de kans op een hartprobleem na een dobutamine ECHO studie met aanwijzingen voor zuurstoftekort wat groter leek. Na analyse van verschillende opties van toevoeging van dobutamine ECHO aan MIBI of dobutamine MIBI aan ECHO werd gespeculeerd dat toevoeging van dobutamine MIBI aan een ECHO studie waarbij geen zuurstoftekort van de hartspier gezien werd maar tevens de nagestreefde hartfrequentie niet werd behaald een haalbare en kosten-effectieve methode leek om de voorspellende waarde van de dobutamine stress test te optimaliseren.

In een derde studie bij 200 patiënten met stabiele borstklachten werd aangetoond dat patiënten met een lage of intermediaire voorafkans op kransslagaderziekte en een normale dobutamine ECHO studie een verwaarloosbare kans hadden op hartproblemen binnen 2 jaar. Patiënten met een hoge voorafkans op kransslagaderziekte en een normale dobutamine ECHO studie waarbij de nagestreefde hartfrequentie niet werd behaald hadden echter nog een behoorlijke kans op hartproblemen, met name als tijdens de dobutamine stress test andere tekenen van zuurstoftekort van de hartspier gezien werden zoals borstklachten tijdens de test of veranderingen op het hartfilmpje.

- Patiënten met mogelijk onstabiele borstklachten

Teneinde bij patiënten met mogelijk onstabiele angina pectoris de opnameduur te bekorten en de voorspellende waarde van vroeg verrichte dobutamine ECHO te bepalen werden 102 patiënten met spontane borstklachten en een niet op zuurstoftekort wijzend hartfilmpje bestudeerd. Alle patiënten ondergingen herhaaldelijk hartenzym bepalingen en continue monitoring van het hartfilmpje gedurende tenminste 12 uur. Indien deze onderzoeken normaal waren werd dobutamine ECHO verricht. Patiënten met een dobutamine ECHO studie waarbij geen zuurstoftekort van de hartspier kon worden aangetoond werden vervolgens ontslagen. Gedurende 6 maanden werd vervolg onderzoek gedaan naar het optreden van dood, hartinfarct, onstabiele angina pectoris, dotterbehandeling of hartoperatie. Gedurende de ziekenhuisopname hadden 13 patiënten bewijs voor een hartinfarct (gestegen hartenzymen) of onstabiele angina pectoris (afwijkingen gedurende

de continue monitoring van het hartfilmpje). In de overgebleven 89 patiënten werd dobutamine ECHO verricht na een mediane observatieperiode van 31 uur. Tijdens dobutamine ECHO vonden geen belangrijke complicaties plaats. De dobutamine ECHO beelden waren van te slechte kwaliteit bij 3 patiënten, niet diagnostisch (een studie waarbij geen zuurstoftekort gezien werd maar tevens de nagestreefde hartfrequentie niet werd behaald) bij 6 patiënten, normaal bij 44 patiënten en abnormaal bij 36 patiënten. Een abnormale dobutamine ECHO studie was de enige onafhankelijke voorspeller voor hartproblemen na ontslag.

Conclusies

Zoals beschreven heeft elk van beide afbeeldingstechnieken zijn eigen, specifieke voordelen. Men zou kunnen stellen dat dobutamine MIBI wat meer gevoelig is voor het vaststellen van milde vormen van kransslagaderziekte, ten koste van een iets geringere specificiteit. Voor het voorspellen van toekomstige hartproblemen, meer gerelateerd aan ernstige vormen van kransslagaderziekte, lijken dobutamine ECHO en MIBI weinig voor elkaar onder te doen. De keuze voor één van de twee afbeeldingstechnieken hangt echter ook af van de soort patiënt, de kosten (of beter de kosten-effectiviteit) en de ervaring van de arts met de afbeeldingstechnieken. De definitieve plaatsbepaling van dobutamine ECHO en MIBI zal onder meer afhankelijk zijn van de vele technische verbeteringen die bij beide afbeeldingstechnieken binnen afzienbare tijd hun weg in de kliniek zullen vinden!

DANKWOORD

Een proefschrift is altijd het resultaat van samenwerking met anderen. Zonder de medewerking van de cardiologen, fellows, verpleegkundigen en medewerkers van de afdeling echocardiografie en nucleaire geneeskunde van het Hartcentrum Rotterdam zou dit proefschrift nooit tot stand gekomen zijn. Een aantal mensen die op wat voor manier dan ook een bijdrage hebben geleverd aan de totstandkoming van dit proefschrift wil ik in het bijzonder bedanken.

Allereerst mijn promotor prof.dr. J.R.T.C Roelandt. Beste Jos, het was en is een groot genoegen met jou te mogen samenwerken in het Hartcentrum Rotterdam. Met name jouw aanstekelijke liefde voor de wetenschap, enorme ervaring en altijd positieve kritiek werkten en werken zeer stimulerend. Ondanks jouw drukke werkzaamheden wist jij altijd op korte termijn ruim tijd vrij te maken. Ik hoop dat de tijd bedoeld voor de verdediging van het proefschrift net zo snel (en op dezelfde wijze) voorbij zal gaan als de tijd tijdens onze gesprekken.

Mijn co-promotor dr. P.M. Fioretti. Beste Paolo, jij bracht mij in contact met jouw "hotte doboetamine date". De eerlijkheid gebied te zeggen dat het geen grote kunst was de door jou veroorzaakte stroom van data af te varen, of het moest wel het in balans houden van de boot met Egyptische en Italiaanse fellows zijn. Helaas kon jij de afronding van het proefschrift niet meemaken doordat jij het prachtige Hartcentrum Rotterdam verliet voor een Italiaanse kliniek om daar als (naar verluid) inmiddels grijze professor de ongetwijfeld heerlijke lunches voor te zitten. Ik hoop dat je over het uiteindelijke resultaat net zo tevreden bent als ik over onze samenwerking.

Veel dank ben ik ook verschuldigd aan prof.dr. M.L. Simoons. Beste Maarten, jouw hulp en betrokkenheid bij het opzetten van studieprotocollen en de aanvraag tot verlening van subsidie bij de Nederlandse Hartstichting is door mij zeer gewaardeerd.

Mariarosaria Arnese, Jan Hein Cornel en Alessandro Salustri dank ik voor de hulp bij de beoordeling van de stress echocardiogrammen. Joyce Postma-Tjoa en Ambroos Reijs dank ik voor de hulp bij de analyse van de nucleaire scans.

Van de fellows op kamer BA 302 ben ik (wetende dat ik nu tientallen Belgische, Bulgaarse, Chinese, Duitse, Egyptische, Franse, Hongaarse, Italiaanse en Russische fellows tekort doe) veel dank verschuldigd aan Abdou Elhendy, Jarek Kasprzak en Riccardo Rambaldi. Tevens dank ik de meer permanente bewoners van deze kamer René Frowijn en Wim Vletter voor hun hulp.

De toenmalige collega arts-assistenten Walter Hermans, Hans Luyten, Benno Rensing en Jeroen Vos dank ik voor de extra inspanningen die zij hebben verricht teneinde mij aan mijn onderzoek te laten werken.

Eric Boersma, Jaap Deckers en vooral Ron van Domburg dank ik voor de statistische adviezen en vele meters berekeningen.

Van de diverse secretariaten en de afdeling beheer ben ik vooral Miranda Broeders, Yvonne Kalkman, Willeke Korpershoek, Arita Orgers en Ad van Drunen dankbaar voor de ondersteuning.

Irene van Loon dank ik voor de snelle levering van de vele aangevraagde artikelen.

Marianne Eichholtz dank ik voor het uit handen nemen van alle formele administratieve zaken rondom de promotie.

Tenslotte dank ik de Nederlandse Hartstichting voor de financiële ondersteuning die het mogelijk maakte enkele jaren volledig aan de in dit proefschrift beschreven studies te werken.

CURRICULUM VITAE

Marcel Leonard Geleijnse werd op 3 januari 1965 te Delft geboren. Het eindexamen VWO werd in 1983 behaald aan de Scholengemeenschap "Guillaume Farel" te Ridderkerk. In 1983 werd begonnen met de studie Geneeskunde aan de Erasmus Universiteit Rotterdam. Het doctoraal examen werd behaald in 1990. Van 1992 tot 1993 was hij ondermeer betrokken bij onderzoek naar computer simulatie van linker ventrikel instroom patronen en diastolische disfunctie na het hartinfarct. Het artsexamen werd behaald in 1993. Van 1993 tot 1995 was hij werkzaam als arts-assistent cardiologie van het Academisch Ziekenhuis Rotterdam en werd gestart met de in dit proefschrift beschreven onderzoeken. Van 1995 tot 1997 was hij voltijds aan de afdeling cardiologie verbonden als wetenschappelijk onderzoeker. Sinds september 1997 is hij in opleiding tot cardioloog (opleider, prof. dr J.R.T.C Roelandt) en volgt daartoe momenteel de stage Inwendige Geneeskunde in het Merwedeziekenhuis te Dordrecht (opleider, dr J. van der Meulen).

LIST OF PUBLICATIONS

1. **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

2. Elhendy A, **Geleijnse ML**, Roelandt JRTC, Cornel JH, Van Domburg RT, Fioretti PM. Stress-induced left ventricular dysfunction in silent and symptomatic myocardial ischemia during dobutamine stress test. *Am J Cardiol* 1995; 75: 1112-1115

3. Elhendy A, **Geleijnse ML**, Roelandt JRTC, Van Domburg RT, Cornel JH, TenCate FJ, Postma-Tjoa J, Reijs AEM, El-Said GM, Fioretti PM. Evaluation by quantitative 99m-technetium MIBI SPET and echocardiography of myocardial perfusion and wall motion abnormalities in patients with dobutamine-induced ST-segment elevation. *Am J Cardiol* 1995; 76: 441-448

4. **Geleijnse ML**, Fioretti PM. Selection of myocardial perfusion or function for the diagnosis of CAD. In: Marwick TH (editor). *Cardiac Stress Testing & Imaging*. Churchill Livingstone Inc. 1996: 97-116

5. **Geleijnse ML**, Elhendy A, Van Domburg RT, Cornel JH, Reijs AEM, Fioretti PM. Prognostic significance of normal dobutamine-atropine stress sestamibi scintigraphy in women with chest pain. *Am J Cardiol* 1996; 77: 1057-1061

6. **Geleijnse ML**, Rambaldi R, Fioretti PM. Current status of stress echocardiography in the selection of patients for PTCA and post-PTCA evaluation. *Emodinamica* 1996; 8: 3-7

7. **Geleijnse ML**, Elhendy A, Van Domburg RT, Cornel JH, Reijs AEM, Roelandt JRTC, Krenning EP, Fioretti PM. Prognostic value of dobutamine-atropine stress technetium-99m sestamibi perfusion scintigraphy in patients with chest pain. *J Am Coll Cardiol* 1996; 28: 447-454

8. Elhendy A, **Geleijnse ML**, Roelandt JRTC, Van Domburg RT, TenCate FJ, Cornel JH, Reijs AEM, El-Said GM, Fioretti PM. Dobutamine-induced hypoperfusion without transient wall motion abnormalities: less severe ischemia or less severe stress? *J Am Coll Cardiol* 1996; 27: 323-329

9. Rambaldi R, Dall'Agata A, **Geleijnse ML**, Fioretti ML. Angina instabile raffreddata: stratificazione prognostica predimissione. In Rovelli F, De Vita C, Moreo A (editors). *Cardiologia* Scientific Press 1996: 270-275

10. Elhendy A, Cornel JH, Roelandt JRTC, Van Domburg RT, Nierop PR, **Geleijnse ML**, El-Said GM, Fioretti PM. Relation between contractile response of akinetic segments during

dobutamine stress echocardiography and myocardial ischemia assessed by simultaneous thallium-201 single-photon emission computed tomography. *Am J Cardiol* 1996; 77: 955-959

11. Elhendy A, Van Domburg RT, Roelandt JRTC, **Geleijnse ML**, Cornel JH, El-Said GM, Fioretti PM. Accuracy of dobutamine stress echocardiography for the diagnosis of coronary artery stenosis in patients with myocardial infarction: the impact of extent and severity of left ventricular dysfunction. *Heart* 1996; 76: 123-128

12. Elhendy A, **Geleijnse ML**, Roelandt JRTC, Cornel JH, Van Domburg RT, Reijs AEM, Nierop PR, Fioretti PM. Altered myocardial perfusion during dobutamine stress testing in silent versus symptomatic myocardial ischaemia assessed by quantitative MIBI SPET imaging. *Eur J Nucl Med* 1996; 23: 1354-1360

13. Elhendy A, **Geleijnse ML**, Salustri A, Van Domburg RT, Cornel JH, Arnese M, Roelandt JRTC, Fioretti PM. T wave normalization during dobutamine stress testing in patients with non-Q wave myocardial infarction. A marker of myocardial ischemia? *Eur Heart J* 1996; 17: 526-531

14. Elhendy A, **Geleijnse ML**, Roelandt JRTC, Cornel JH, Van Domburg RT, El-Refaee M, Ibrahim MM, El-Said GM, Fioretti PM. Assessment of patients after coronary artery bypass grafting by dobutamine stress echocardiography. *Am J Cardiol* 1996; 77: 1234-1236

15. Elhendy A, Cornel JH, Roelandt JRTC, Van Domburg RT, **Geleijnse ML**, Hoeymans PAJ, Reijs AEM, TenCate FJ, Fioretti PM. Dobutamine 201-thallium SPECT imaging for the assessment of peri-infarction and remote myocardial ischemia in patients with prior myocardial infarction. *J Nucl Med* 1996; 37: 1951-1956

16. **Geleijnse ML**, Elhendy A, Cornel JH, Rambaldi R, Van Domburg RT, Salustri A, Reijs AEM, Roelandt JRTC, Fioretti PM. 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

17. **Geleijnse ML**, Fioretti PM, Roelandt JRTC. Methodology, feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography. *J Am Coll Cardiol* 1997; 30: 595-606

18. **Geleijnse ML**, Elhendy A, Van Domburg RT, Rambaldi R, Reijs AEM, Roelandt JRTC, Fioretti PM. Prognostic significance of systolic blood pressure changes during dobutamine-atropine stress technetium-99m sestamibi perfusion scintigraphy in patients with chest pain and known or suspected coronary artery disease. *Am J Cardiol* 1997; 79: 1031-1035

19. **Geleijnse ML**, Salustri A, Marwick TH, Fioretti PM. Should the diagnosis of coronary artery disease be based on the evaluation of myocardial function or perfusion? *Eur Heart J* 1997; 18 (Suppl D): D68-D77

20. **Geleijnse ML**, Fioretti PM. Prediction of infarction by stress echocardiography. *J Am Coll Cardiol* 1997; 29: 226-228

21. **Geleijnse ML**, Elhendy A, Fioretti PM. Usefulness of dobutamine perfusion imaging in patients with prior myocardial infarction. In: Maresta A. Ed. *Role of nuclear cardiology in the diagnosis and prognostic stratification of acute myocardial* infarction. Publisher 1997: xxx-xxx

22. Elhendy A, **Geleijnse ML**, Van Domburg RT, Nierop PR, Poldermans D, Bax JJ, TenCate FJ, Nosir YFM, M Mohsen Ibrahim, Roelandt JRTC. Gender differences in the accuracy of dobutamine stress echocardiography for the diagnosis of coronary artery disease. *Am J Cardiol* 1997; 80: 1414-1418

23. Elhendy A, Cornel JH, Trocino G, Nierop PR, Van Domburg RT, Roelandt JRTC, **Geleijnse ML**, Fioretti PM. Impact of severity of coronary artery stenosis and the collateral circulation on the functional outcome of dyssynergic myocardium after revascularization in patients with healed myocardial infarction and chronic left ventricular dysfunction. *Am J Cardiol* 1997; 79: 883-888

24. Elhendy A, **Geleijnse ML**, Roelandt JRTC, Van Domburg RT, TenCate FJ, Nierop PR, Bax JJ, El-Refaee M, Ibrahim MM, El-Said GM, Fioretti PM. Comparison of dobutamine stress echocardiography and 99m-technetium sestamibi SPECT myocardial perfusion scintigraphy for predicting extent of coronary artery disease in patients with healed myocardial infarction. *Am J Cardiol* 1997; 79: 7-12

25. 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

26. Elhendy A, Cornel JH, Roelandt JRTC, Van Domburg RT, **Geleijnse ML**, Nierop PR, Bax JJ, Sciarra A, Fioretti PM. Relationship between ST segment elevation during dobutamine stress test and myocardial viability after a recent myocardial infarction. *Heart* 1997; 77: 115-121

27. Elhendy A, **Geleijnse ML**, Roelandt JRTC, Van Domburg RT, Reijs AEM, Kasprzak JD, Fioretti PM. Dobutamine 99m-technetium sestamibi SPECT myocardial perfusion scintigraphy in the prediction of restenosis after percutaneous transluminal coronary angioplasty in patients unable to perform exercise test. *J Nucl Med Comm* 1997; 18: 122-128

28. **Geleijnse ML**, Elhendy A, Van Domburg RT, Cornel JH, Roelandt JRTC, Fioretti PM. Prognostic implications of a normal dobutamine-atropine stress echocardiogram in patients with chest pain. *J Am Soc Echocardiogr* 1998; 11: 606-611

29. Cornel JH, Bax JJ, Elhendy A, Maat APWM, Kimman GJP, **Geleijnse ML**, Rambaldi R, Boersma E, Fioretti PM. Biphasic response to dobutamine predicts improvement of global left ventricular function after surgical revascularization in patients with stable coronary artery disease. Implications of time course of recovery on diagnostic accuracy. *J Am Coll Cardiol* 1998; 31: 1002-1010

30. Elhendy A, Van Domburg RT, Nierop PR, **Geleijnse ML**, Bax JJ, Kasprzak JD, Liqui-Lung AFL, Ibrahim MM, Roelandt JRTC. Impaired systolic blood pressure response to dobutamine stress testing: a marker of more severe functional abnormalities in patients with myocardial infarction. *J Am Soc Echocardiogr* 1998; 11: 436-441

31. Elhendy A, **Geleijnse ML**, Van Domburg RT, Bax JJ, Nierop PR, Beerens SAM, Valkema R, Krenning EP, Ibrahim MM, Roelandt JRTC. 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

32. Elhendy A, Van Domburg RT, Bax JJ, Nierop PR, **Geleijnse 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

33. Rambaldi R, Hamburger JN, **Geleijnse ML**, Poldermans D, Kimman GJ, Aiazian AA, Fioretti PM, Ten Cate FJ, Roelandt JRTC, Serruys PW. Early recovery of wall motion abnormalities after recanalization of chronic totally occluded coronary arteries: A dobutamine echocardiographic, prospective, single-center experience. *Am Heart J* 1998; 136: 831-836

34. Elhendy A, Van Domburg RT, Poldermans D, Bax JJ, Nierop PR, **Geleijnse ML**, Roelandt JRTC. Safety and feasibility of dobutamine-atropine stress echocardiography for the diagnosis of coronary artery disease in diabetic patients unable to perform an exercise stress test. *Diabetes Care* 1998; 21: 1797-1802

35. Elhendy A, Valkema R, Van Domburg RT, Bax JJ, Nierop PR, Cornel JH, **Geleijnse ML**, Reijs AER, Krenning EP, Roelandt JRTC. Safety of dobutamine-atropine stress myocardial perfusion scintigraphy. *J Nucl Med* 1998; 39: 1662-1666

36. Elhendy A, Van Domburg RT, Bax JJ, Nierop PR, Valkema R, **Geleijnse ML**, Kasprzak JD, Liqui-Lung AFL, Cornel JH, Roelandt JRTC. Dobutamine-atropine stress myocardial perfusion SPECT imaging in the diagnosis of graft stenosis after coronary artery bypass grafting. *J Nucl Cardiol* 1998; 5: 491-497

37. Elhendy A, Van Domburg RT, Bax JJ, Nierop PR, **Geleijnse ML**, Ibrahim MM, Roelandt JRTC. The functional significance of chronotropic incompetence during dobutamine stress test. *Heart* 1999; 81: 398-403

Additional financial support for visiting congresses during the research period and for publication of this thesis was generously provided by:

Astra Pharmaceutica, Bayer Nederland, Bristol-Myers Squibb, Boehringer Ingelheim, Boehringer Mannheim, Byk Nederland, Hoechst Marion Roussel, Eli Lilly, Lorex Synthélabo, Merck Sharp & Dohme, Parke-Davis, Pfizer, Roche, Rhône-Poulenc Rourrer Nederland and Servier.