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Detection of Coronary Artery Disease by Digital Stress Echocardiography: Comparison of Exercise, Transesophageal Atrial Pacing and Dipyridamole Echocardiography

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Objectives. **This study assessed and compared the diagnostic potential of exercise, transesophageal atrial pacing and dipyridamole stress echocardiography in a clinical setting.**

Background. **Although they have been widely studied, no data exist with regard to comparisons of these procedures in a head-to-head study in different clinical settings.**

Methods. **One hundred four consecutive patients with suspected coronary artery disease undergoing coronary angiography and with no previous myocardial infarction or rest left ventricular wall motion abnormalities underwent digital posttreadmill, transesophageal atrial pacing and dipyridamole echocardiography.**

Results. **Feasibility of digital exercise echocardiography was 84%; 8 of 88 remaining patients had a nondiagnostic exercise echocardiographic test (inadequate exercise or imaging). In 80 patients with feasible and diagnostic digital exercise echocardiography, sensitivity, specificity and accuracy were, respectively, 89%, 91% and 90%. Eighty of the 104 patients underwent transesophageal atrial pacing and dipyridamole echocardiography. Feasibility of the alternative stress procedures was 77% for transesophageal atrial pacing and 96% for dipyridamole. In 60 patients successfully undergoing both alternative stress procedures, sensitivity and specificity were 83% and 76% for atrial pacing and 43% and 92% for dipyridamole echocardiography, respectively. In the group of 24 patients with nondiagnostic exercise echocardiography and consequent indication to alternative stress procedures, accuracy of transesophageal atrial pacing was higher than that of dipyridamole echocardiography (73% vs. 45%, $p = 0.06$).**

Conclusions. **Because of its higher diagnostic potential and additional functional information, exercise is the stress of choice when stress echocardiography is used to detect the presence of coronary artery disease. Alternative stresses can be used in patients with nondiagnostic exercise echocardiography. Transesophageal and dipyridamole echocardiography differ in feasibility and diagnostic reliability (higher sensitivity of transesophageal atrial pacing, higher specificity of dipyridamole). These characteristics must be considered when selecting procedures to be used as alternatives to exercise.**

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Echocardiographic monitoring of left ventricular wall motion during stress-induced ischemia has been widely used for the detection of significant coronary artery disease. Physical exercise is certainly the most physiologic of the various forms of stress suggested to induce ischemia during echocardiography (1–3). When two-dimensional stress echocardiography is planned, alternative stresses need to be used not only in patients for whom exercise is unfeasible, inadequate or contraindicated but also in those with poor quality echocardiographic images during exercise, making interpretation of the stress exam difficult if not impossible.

Transesophageal atrial pacing (4,5) and high dose dipyridamole infusion (6–8) have been proposed as alternative stress procedures to be used in conjunction with echocardiography. Previous studies have demonstrated that both stresses are capable of inducing ischemia (although by different mechanisms) and do not affect echocardiographic image quality. The diagnostic role of these three stress procedures (exercise, transesophageal atrial pacing, dipyridamole) in an actual clinical setting has still not been fully elucidated, because they have not been compared in a single population. We hypothesized that differences in ischemia-inducing mechanism and technical details may affect the diagnostic values obtained by using different stress procedures in the same group of patients, either from an unselected group or a selected group with a nondiagnostic exercise echocardiographic study.

Therefore, we undertook this study to address the following specific problems: 1) to define the role of each of the three stress procedures in a clinical context; 2) to evaluate the diagnostic reliability of the two alternative stresses

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(transesophageal atrial pacing and dipyridamole) in a head-to-head comparison; 3) to assess and compare the diagnostic role of alternative stress procedures in patients for whom exercise echocardiography is neither feasible nor diagnostic.

Methods

The study involved 104 consecutive patients admitted to hospital at the Institute of Cardiovascular Diseases of the University of Bari from November 1991 to January 1993 and who were undergoing coronary angiography for the evaluation of chest pain and suspected coronary artery disease. Patients who had valvular heart disease were preliminarily excluded, as were those with congenital heart disease, cardiomyopathies, previous myocardial infarction or left ventricular wall motion abnormalities in baseline conditions as well as those with echocardiographic images at rest that were technically inadequate to assess left ventricular wall motion. The 104 patients who were included in our study underwent routine exercise echocardiography in the stress echocardiographic laboratory. Eighty-two of the 104 patients (age 58 ± 8 years, 69 men, 13 women) agreed to perform not only exercise echocardiography but also dipyridamole and transesophageal atrial pacing echocardiography. Our local Institutional Review Board approved the study protocol, and all patients gave written informed consent for each stress procedure and participation in the study. Dipyridamole and transesophageal atrial pacing echocardiography were scheduled to be performed in a random sequence at the same time on two consecutive days, 1 to 3 days before coronary angiography. All stress procedures were performed after adequate withdrawal of all cardioactive drugs.

Exercise echocardiography. Echocardiographic examinations were performed using standard equipment (Hewlett-Packard Sonos 1000). Echocardiographic images of the left ventricle were recorded with the patients and in the left lateral decubitus position on 0.75-in. videotape and in digital format using both apical (four-chamber, two-chamber and long-axis views) and precordial tomographic planes (the best of midpapillary short- or long-axis views). After having performed the echocardiographic examination at rest, the patient exercised on the treadmill (DelMar E17 and Cardiovit CS12/M, Exec Software, Schiller) according to the standard Bruce protocol. A 12-lead electrocardiogram (ECG) was continuously monitored, and ECG and cuff blood pressure recordings were obtained at each step. End points of the test were the achievement of maximal heart rate–blood pressure product or the development of ischemia (typical chest pain or ischemia-related symptoms or ST segment depression or elevation ≥1.5 mV). Immediately after the treadmill exercise ended, the echocardiographic recording was repeated in the left lateral decubitus position using the same views as the baseline examination. Images were also stored in quad-screen digital format specifically developed to compare rest and stress images and visualize the time interval occurring between stress interruption and the acquisition of each stress image (Software PreVue III, rel. 4.050, NovaMicrosonics). In all patients the posttreadmill images were recorded in the 1st 2 min after stress interruption, a large majority of them (95%) in the first minute. They were considered technically inadequate if poor quality stress images or problems related to digital acquisition (inappropriate postexercise ECG triggering) did not allow segmental wall motion analysis

Dipyridamole echocardiography. The examination was performed at least 12 h after the consumption of any food or drink containing xanthines that might have an antagonizing effect on the dipyridamole. After a complete echocardiographic examination (apical four-chamber, two-chamber and long-axis and whichever was best of the precordial long- and short-axis views) in baseline conditions, dipyridamole was infused at a dosage of 0.56 mg/kg body weight in 4 min. Immediately after the start of the infusion, ECG, cuff blood pressure and echocardiographic monitoring was started and continued throughout the test. If after 8 min from the start of the infusion no ECG or echocardiographic wall motion abnormalities appeared, then a second dose of 0.28 mg/kg in 2 min was administered. The echocardiographic digital images collected in baseline conditions were visualized throughout the study to be compared with stress wall motion images and were recorded on videotape at 4-min intervals. The test was interrupted if symptoms, ST segment depression or elevation ≥1.5 mV or severe wall motion abnormalities (akinesia or dyskinesia two or more myocardial segments) appeared; otherwise the patient was monitored for 20 min after the end of the drug infusion. At the end of the test, if the signs of ischemia or side effects were present, aminophylline at an intravenous dosage of 240 mg or, if necessary, nitrates were administered either sublingually or intravenously.

Transesophageal atrial pacing echocardiography. Transesophageal atrial stimulation was performed using a special bipolar catheter inserted through the nares into the distal esophagus and connected to a transesophageal atrial stimulator (Arzco, model 7A) emitting 10-ms impulses of an amplitude varying from 8 to 28 mA. Starting at 100 beats/min, the heart rate was increased every 2 min by 10 beats/min until chest pain or severe wall motion abnormalities appeared or until the maximal step of 150 beats/min for 5 min was completed. At the end of each stimulation period, the 12-lead ECG and cuff blood pressure were recorded. Apical tomographic planes (two- and four-chamber and long-axis) and whichever was best of the precordial long- and short-axis images were recorded before and throughout the entire transesophageal atrial pacing procedure. Simultaneous 12-lead ECG was monitored continuously during each stress procedure using a commercially available computerized ECG system (Cardiovit CS12/M, Schiller).

Digital echocardiographic procedures. During each of the three stress procedures the echocardiographic images were simultaneously recorded on a 0.75-in. videotape and a 5.25-in. floppy disk; images were acquired on-line in quad screen

digital format by using digital echocardiographic equipment and specific stress protocol software (PreVue III Software Version 4.050, NovaMicrosonics) (9). The digital acquisition system allows the selective recording and side-by-side comparison of the systolic phase of cardiac cycles from baseline and stress protocol steps. For the exercise echocardiographic test two separate quad screen images were used to compare views recorded at baseline condition and after stress interruption. For nonexercise procedures one quad screen for each echocardiographic view was constructed so that the images recorded at baseline and at successive protocol steps were simultaneously visualized (at pacing rates of 120, 130 and 150 beats/min or at dipyridamole low dose [0.56 mg/kg], high dose [0.84 mg/kg] and recovery).

Study interpretation. The digital echocardiographic images of the three stress procedures were interpreted by a single experienced observer different from the one performing the test and unaware of patient history, clinical data, results of previously performed procedures and ECG findings of each test. Test positivity was defined as the onset of left ventricular wall motion abnormalities (abnormal motion of the endocardium or myocardial thickening if compared with rest echocardiographic images or both). To perform the analysis, the left ventricular wall was divided into 16 myocardial segments (at basal, mid- and apical levels in the septum, lateral, anterior and inferior walls, and basal and midventricular levels in the anteroseptal and inferolateral walls), and a wall motion score was assigned at each segment, according to the guidelines of the American Society of Echocardiography (10).

Coronary angiography. All the patients underwent complete coronary angiographic study. Multiple projections of the coronary arteries were obtained in all patients by using the Judkins technique. The coronary vessels were visually assessed by one experienced observer, and a lumen narrowing ≥75% of one or more of the major epicardial vessels was considered to be significant coronary artery disease. The decision to perform the angiographic study was not affected by the results of any of the stress procedures.

Statistical analysis. For each of the three procedures sensitivity, specificity and accuracy were assessed. Diagnostic values were expressed by using standard formulas (sensitivity = true positive studies/[true positive studies + false negative studies]; specificity = true negative studies/[true negative studies + false positive studies]; accuracy = true positive and negative studies/total studies). For each variable the value obtained and its 95% confidence interval were calculated. The results of different procedures were compared by using the Fisher exact test.

Results

Coronary angiography. Of the 104 patients who entered the study, 40 showed no significant coronary artery disease, and 64 had significant coronary artery disease (25 single-vessel, 28 two-vessel and 11 three-vessel disease).

Feasibility of exercise, dipyridamole and transesophageal atrial pacing echocardiography. In our series of 104 patients exercise was not performable in four patients because of musculoskeletal diseases; dipyridamole echocardiography and transesophageal atrial pacing echocardiography were not performed in 22 patients because of refused consent to undergo both alternative procedures.

Among the remaining 100 patients who could exercise, the echocardiographic images could not be interpreted in 16 (16%): in 10 (10%) because the quality of the exercise echocardiographic images was considered inadequate for wall motion analysis and in 6 (6%) because of problems related to the digital technology (inappropriate R wave triggering during the immediate postexercise image acquisition). Thus, feasibility of digital exercise echocardiography was 84%. Among the remaining 84 patients, exercise yielded nondiagnostic results in four because of submaximal exercise. Therefore, in 24 of 104 patients, exercise echocardiography, for different reasons, was not useful for diagnostic purposes.

Among the 82 patients undergoing dipyridamole echocardiography the test was not performed because of difficulties in finding superficial veins for drug infusion in two patients; in one patient the test was performed, but its images were not evaluable because of inadequate quality as a result of hyperpnea during drug infusion. Therefore, the feasibility of dipyridamole echocardiography was 96% ($p = 0.002$ vs. exercise echocardiography). In 19 of 82 patients transesophageal atrial pacing was not performable either because of intolerance to the transesophageal catheter or electrical stimulation of the esophagus (nine patients), difficulty in obtaining a stable atrial capture (seven patients) or the appearance of second-degree Luciani-Wenckebach–type block at submaximal heart rates (three patients). Feasibility of transesophageal atrial pacing echocardiography was, therefore, 77% (p = NS vs. exercise echocardiography; $p < 0.0001$ vs. dipyridamole echocardiography). All 10 patients with inadequate posttreadmill images were successfully evaluated by transesophageal atrial pacing and dipyridamole echocardiography. A group of 60 patients successfully underwent both transesophageal atrial pacing echocardiography and dipyridamole echocardiography and was therefore used for comparative analysis.

Diagnostic values. *Exercise echocardiography.* In 24 of the 104 patients exercise echocardiography was inconclusive because of the inadequate quality of exercise echocardiographic images or ECG triggering problems or the inadequacy of physical exercise in the presence of a negative stress echocardiographic test. Of the 80 patients with conclusive exercise echocardiography, 47 had coronary artery disease (17 single-vessel, 19 two-vessel, 11 three-vessel disease), and 33 showed no significant coronary artery disease. In the former stress echocardiography was positive in 42 patients (13 with single-vessel, 18 with two-vessel, 11 with three-vessel disease), in the latter in 3. Thus, test sensitivity was 89% (confidence interval [CI] 81% to 98%),

Table 1. Results of Exercise and Alternative Stress Procedures in the 60 Study Patients

	Positive Test (no. of pts)		Negative Test (no. of pts)	
	CAD	No CAD	CAD	No CAD
Ex-2DE (60 pts)	31	3	4	22
TAP-2DE (60 pts)	29	6	6	19
DIP-2DE (60 pts)	15	2	20	23

CAD = coronary artery disease (stenosis ≥75% in at least one major vessel); DIP = dipyridamole; Ex = exercise on treadmill; pts = patients; TAP = transesophageal atrial pacing; 2DE = two-dimensional echocardiography.

specificity 91% (CI 81% to 100%) and accuracy 90% (CI 85% to 95%). The sensitivity of exercise echocardiography in patients with single-, two- and three-vessel coronary artery disease was, respectively, 76%, 95% and 100%.

Head-to-head comparison of exercise echocardiography, transesophageal atrial pacing echocardiography and dipyridamole echocardiography. Results obtained in 60 patients subjected to all three stress procedures are reported in Tables 1, 2 and 3. Peak heart rate as a percentage of age-predicted maximal heart rate and rate-pressure product were, respectively, 86 ± 9% and 25.4 ± 5.2 × 1,000 during exercise echocardiography, 84 ± 5% and 21.9 ± 3.5 × 1,000 during transesophageal atrial pacing echocardiography and 82 ± 7% and 23.1 ± 4.3 × 1,000 during dipyridamole echocardiography. Twenty-five of these 60 patients showed no significant coronary artery disease, and 16, 14 and 5 had single-, two- and three-vessel disease, respectively. In the 25 patients without significant coronary artery disease, exercise echocardiography was negative in 22, transesophageal atrial pacing echocardiography in 19 and dipyridamole echocardiography in 23. The specificity of the three tests was therefore 88%, 76% and 92%, respectively (Tables 1 and 2). In the 35 patients with significant coronary artery disease, exercise echocardiography was positive in 31, transesophageal atrial pacing echocardiography in 29 and dipyridamole echocardiography in 15. The sensitivity of the three tests was therefore 89%, 83% and 43%, respectively. The accuracy of exercise echocardiography, transesophageal atrial pacing echocardiography and dipyridamole echocardiography was 88%, 80% and 63%, respectively (Tables 1 and 2). In these 35 patients typical chest pain and diagnostic ECG changes were respectively present in 12 (34%) and 21 (60%) patients during exercise echocardiography and in 9 (26%) and 13 (37%) during dipyridamole echocardiography. These changes are not well assessed during transesophageal atrial pacing echocardiography. Of the 31 patients with coronary artery disease correctly identified by exercise echocardiography, 13 had single-vessel disease, 13 two-vessel disease, and 5 three-vessel disease. Of the 29 patients with coronary artery disease correctly identified by transesophageal atrial pacing echocardiography, 12 had single-vessel disease, 12 had two-vessel disease, and 5 had three-vessel disease. Of the 15 patients with coronary artery disease correctly identified by dipyridamole echocardiography, 4 had single-vessel disease, 8 had two-vessel disease, and 3 had three-vessel disease. Thus, the sensitivity of exercise, transesophageal atrial pacing and dipyridamole echocardiography was, respectively, 81%, 75% and 25% in patients with single-vessel disease, 93%, 86% and 57% in patients with two-vessel disease and 100%, 100% and 60% in patients with three-vessel disease (Table 3).

Side effects. After transesophageal atrial pacing, in no case was it necessary to administer drugs to obtain remission of the signs of ischemia induced by the test because they regressed a few seconds after stimulation. However, after dipyridamole echocardiography it was invariably necessary to administer aminophylline to stop cephalea or flushing, or both, induced by the drug. In five cases it was also necessary to administer sublingual nitroglycerin and, in two cases, intravenous nitrates to stop angina, ST depression or severe wall motion abnormalities induced by dipyridamole, which tended to persist for several minutes.

Overall comparison between exercise echocardiography and alternative echocardiographic stress procedures. With respect to overall diagnostic values, the sensitivity of exercise echocardiography was comparable to that of transesophageal atrial pacing (89% vs. 83%, p = NS) and higher than

Table 2. Diagnostic Values of Exercise and Alternative Stress Procedures

	Ex-2DE		TAP-2DE		DIP-2DE		
	%	95% CI	%	95% CI	%	95% CI	p Value
Sensitivity	89	78–99	83	70–95	43	26–59	Ex-2DE vs.TAP-2DE = NS Ex-2DE vs.DIP-2DE = 0.0001 TAP-2DE vs. DIP-2DE = 0.0005
Specificity	88	75–100	76	59–93	92	81–100	Ex-2DE vs. TAP-2DE = NS Ex-2DE vs. DIP-2DE = NS TAP-2DE vs. DIP-2DE = 0.12
Accuracy	88	82–95	80	72–88	63	57–74	Ex-2DE vs. TAP-2DE = NS Ex-2DE vs. DIP-2DE = 0.0012 TAP-2DE vs. DIP-2DE = 0.034

CI = confidence interval; other abbreviations as in Table 1.

Table 3. Sensitivity of Exercise and Alternative Stress Procedures in Patients With Single-, Two- and Three-Vessel Disease

	Single-Vessel CAD		Two-Vessel CAD		Three-Vessel CAD	
Sensitivity	No. of Pts	%	No. of Pts	%	No. of Pts	%
Ex-2DE	13/16	81%	13/14	93%	5/5	100%
TAP-2DE	12/16	75%	12/14	86%	5/5	100%
DIP-2DE	4/16*	25%	8/14†	57%	3/5	60%

*p = 0.0061 versus post-treadmill exercise two-dimensional echocardiography (Ex-2DE) and transesophageal atrial pacing two-dimensional echocardiography (TAP-2DE). †p = 0.002 versus post-treadmill exercise two-dimensional echocardiography. Other abbreviations as in Table 1.

that of dipyridamole echocardiography (43%, p = 0.0005). The specificity of exercise echocardiography was slightly higher than that of transesophageal atrial pacing (91% vs. 76%, p = 0.12) and comparable to that of dipyridamole echocardiography (92%, p = NS). The accuracy of exercise echocardiography was slightly higher than that of transesophageal atrial pacing, with a trend for statistical significance (90% vs. 80%, p = 0.08) and higher than that of dipyridamole echocardiography (63%, p = 0.0002).

Transesophageal atrial pacing and dipyridamole echocardiography as alternatives to exercise echocardiography. Transesophageal atrial pacing and dipyridamole echocardiography were successfully performed in 22 of 24 patients with nondiagnostic or nonevaluable exercise echocardiography. In this group of patients, dipyridamole echocardiography was positive in 7 (5 with coronary artery disease, 2 without) and negative in 15 (10 with coronary artery disease, 5 without). In the same series of patients, transesophageal atrial pacing echocardiography was positive in 13 (11 with coronary artery disease, 2 without) and negative in 9 (4 with coronary artery disease, 5 without). In this group, the sensitivity of dipyridamole and transesophageal atrial pacing echocardiography was, respectively, 33% and 73% (p = 0.03), and specificity was 71% and 71%. Therefore, in these 22 patients with inconclusive post-treadmill exercise echocardiography, 10 were correctly identified by dipyridamole echocardiography (accuracy 45%) and 16 by transesophageal atrial pacing echocardiography (accuracy 73%, p = 0.06) (Tables 4 and 5).

Table 4. Results of Exercise and Alternative Stress Procedures in 22 Patients With Nondiagnostic Post-Treadmill Exercise Two-Dimensional Echocardiography

	Positive Test (no. of pts)		Negative Test (no. of pts)	
	CAD	No CAD	CAD	No CAD
TAP-2DE (22 pts)	11	2	4	5
DIP-2DE (22 pts)	5	2	10	5

Abbreviations as in Table 1.

Discussion

The choice of an optimal nonexercise stress procedure in a routine stress echocardiographic clinical setting has recently been raised (11–13), although a direct comparison of such different stress procedures with exercise echocardiography has not been made. Transesophageal atrial pacing and dipyridamole echocardiography are well known procedures routinely used in several stress echocardiographic laboratories to accomplish the diagnostic assessment of patients with suspected coronary artery disease (4–8).

When comparing advantages and disadvantages of different stress procedures it is not sufficient to consider diagnostic values obtained in different studies. In fact, results of diagnostic values obtained in different studies are affected by several factors: patient population size and clinical characteristics (previous myocardial infarction or rest wall motion abnormalities included/excluded, proportion of single/multiple-vessel disease), the degree of lumen stenosis considered to define significant coronary artery disease (75% or 50% stenosis) and visual or quantitative interpretation of coronary angiographic studies, the particular stress modality and protocol used, use of videotape or digital echocardiographic comparison methods for study interpretation and the level of work load reached (13). Thus, different values obtained in different settings are difficult to compare. A correct comparison of different methods can only be performed when they are used in the same group of patients in a head-to-head randomized design.

This study was specifically designed to assess prospectively the comparative diagnostic value of three routinely used echocardiographic stress procedures in the same series

Table 5. Diagnostic Values of Exercise and Alternative Stress Procedures in 22 Patients With Nondiagnostic Post-Treadmill Exercise Two-Dimensional Echocardiography

	TAP-2DE		DIP-2DE		
	%	95% CI	%	95% CI	p Value
Sensitivity	73	51–96	33	9–57	0.03
Specificity	71	38–100	71	38–100	NS
Accuracy	73	58–89	45	27–64	0.06

Abbreviations as in Tables 1 and 2.

of patients and in a clinical context. The diagnostic potential of exercise, transesophageal atrial pacing and dipyridamole echocardiography has been individually evaluated in previous studies (1–8). Moreover, the latter two have also been compared independently with exercise echocardiography (5,7); however, in these comparative studies, transesophageal atrial pacing (5) and dipyridamole (7) echocardiography were compared with supine bicycle exercise echocardiography with no digital cine loop recording or review support. This technical support, as well as the use of a more stressing exercise protocol (such as treadmill), is nowadays considered essential and irreplaceable for optimal exercise echocardiographic performance (9). Finally, only limited data are currently available on a head-to-head comparison of transesophageal atrial pacing and dipyridamole echocardiography as alternatives to exercise echocardiography.

Feasibility, sensitivity and specificity of dipyridamole echocardiography and transesophageal atrial pacing echocardiography. Both atrial pacing and dipyridamole infusion can be performed in patients who, for various reasons, are not able to perform adequate exercise. On the whole, the feasibility of dipyridamole echocardiography was higher than for transesophageal atrial pacing echocardiography because of the number of patients who showed intolerance either to the catheter or to electrical stimulation or because it was impossible to obtain high ventricular rate as a result of a Luciani-Wenckebach atrioventricular block. The feasibility of transesophageal atrial pacing echocardiography, although slightly higher (22 [92%] of 24 patients) in patients with inadequate exercise echocardiography, was not significantly different from the overall group (77%, $p = 0.09$).

In our study the sensitivity of dipyridamole and transesophageal atrial pacing echocardiography was 43% and 83%, and the specificity was 92% and 76%, respectively. Therefore, in our series, transesophageal atrial pacing echocardiography has been shown to be significantly more sensitive than dipyridamole echocardiography. This observation takes into consideration the different ischemia-inducing mechanisms of the two stresses (14,15). Even though it acts exclusively on heart rate and not on blood pressure, atrial pacing consistently induces an increase in myocardial oxygen demand, as shown by the increase in heart rate–blood pressure product (14). However, dipyridamole infusion only minimally changes the myocardial oxygen consumption but acts by inducing blood steal in the coronary areas with fixed stenoses and particular anatomic conditions that favor such mechanisms in different ways (15); this is a somewhat less effective ischemia-inducing mechanism (14). In our series of patients we observed how the proportion of patients with multivessel disease in the group of patients correctly identified as having significant coronary artery disease was higher by dipyridamole than by transesophageal atrial pacing echocardiography (73% and 59%); in patients with single-vessel disease the sensitivity of dipyridamole echocardiography was decidedly lower than that of transesophageal atrial pacing (25% vs. 75%). This suggests that dipyridamole infusion requires a particular anatomic coronary condition to have an ischemia-inducing effect, as reported in recent studies (16). Additional clues to such a view are given by studies considering adenosine infusion (17,18) as a stress-inducing modality. Adenosine is the true agent of dipyridamole's vasodilating effect and, when used in combination with two-dimensional echocardiography, yields low sensitivity values in patients without rest wall motion abnormalities (50% in Marwick et al. [11]; 60% in Zoghbi et al. [17]), similar to ours, and also in patients with rest wall motion abnormalities (40% in Nguyen et al. [18] for the detection of >50% stenoses).

The specificity of dipyridamole echocardiography was higher, although not significantly, than that of transesophageal atrial pacing echocardiography. The reasons for the presence of false positive results during transesophageal atrial pacing echocardiography could lie in 1) the possibility that this stress induces ischemia in subjects with coronary artery disease judged as not significant on the basis of angiographic findings or 2) the fact that an increase in heart rate, without a corresponding increase in contractility induced by atrial stimulation, makes it more difficult to interpret wall motion and at times induces the observer to attribute a pathologic meaning to a normal contractile pattern of certain segments at high heart rates.

Our study has yielded results comparable to those of others. For dipyridamole echocardiography, the value of sensitivity in our study is similar to that found by Margonato et al. (8) and compares well with the sensitivity obtained for adenosine echocardiography by Marwick et al. (11). Mazeika et al. (16) found a sensitivity of 40% and a specificity of 93% for high dose dipyridamole stress echocardiography in an unselected group of patients with suspected coronary artery disease. It has been observed that values of sensitivity obtained in studies including patients with previous myocardial infarction or rest wall motion abnormalities are generally higher than values obtainable in clinical patients (11).

Safety of dipyridamole echocardiography and transesophageal atrial pacing echocardiography. In our experience, no major complications have ever resulted from the use of both tests. In particular, the ischemic alterations induced by atrial pacing regressed spontaneously within a few seconds after the end of the stimulation, and on no occasion was it necessary to administer drugs to terminate the ischemia more rapidly. On the basis of previous experience we can state that atrial pacing is a very safe stress and may be used in more severe patients or as a prognostic stress procedure soon after acute myocardial infarction (19–21). However, in our series of patients dipyridamole infusion almost invariably produced unpleasant side effects requiring the administration of aminophylline, even when there were no ECG or echocardiographic ischemic changes. Moreover, in seven patients with ischemia induced by dipyridamole, aminophylline alone did not bring about a quick return to baseline conditions; this only occurred after several minutes of ad-

ministering nitrates orally or intravenously. Similarly, Mazeika et al. (16) found adverse reactions in 67% of patients.

Digital stress echocardiography: Which role for exercise and alternative stresses? In our series of patients digital exercise echocardiography showed good feasibility (84%), sensitivity (89%) and specificity (91%), comparable to the previously reported data. In both the overall and head-to-head comparisons, sensitivity and accuracy were higher than those obtained with dipyridamole and were not significantly different from those of transesophageal atrial pacing echocardiography. Moreover, exercise is a physiologic procedure that gives useful additional functional information on patient exercise capacity and allows the patient to adjust to a new life style. For these reasons, exercise (treadmill) digital echocardiography can be considered the first choice for dealing with the problem of identification of patients with coronary artery disease by stress echocardiography. Alternative stress procedures, such as transesophageal atrial pacing (4,5), dipyridamole (6–8) and the recently introduced dobutamine stress test (22), would have to be limited to that subgroup of patients for whom exercise echocardiography would be of limited value and usefulness.

In our series of 104 patients, 23% had "nondiagnostic exercise echocardiography" (poor exercise image quality, digital triggering problems, inadequate or unfeasible exercise) and therefore had a strong clinical indication for an alternative stress echocardiographic procedure. Transesophageal atrial pacing appeared to be more reliable and therefore more useful than dipyridamole because it correctly diagnosed a greater percent (73% vs. 45%) of patients. To date, studies suggest that dobutamine echocardiography can be a better alternative stress procedure than dipyridamole echocardiography (13), but no data are available for a direct comparison between transesophageal atrial pacing and dobutamine echocardiography in a routine clinical setting. In addition, although all our studies have been performed after cardioactive drug withdrawal, inadequate or omitted withdrawal of such drugs, especially beta-adrenergic blocking agents, can potentially reduce the sensitivity of exercise echocardiography more than alternative stress procedures, an interesting issue that should be specifically addressed in future studies.

Role of digital technology. The evaluation of echocardiographic stress images has been helped enormously by the use of digital technology, particularly for exercise echocardiography. This problem is negligible for stresses, such as transesophageal atrial pacing or dipyridamole, that do not affect echocardiographic image quality. However, even for these stress methods, digital systems can be of great benefit. The storage and adequate combination of simultaneously displayed images related not only to the peak stress phase but also to the intermediate phases allow easy evaluation of onset and extent of wall motion abnormalities during any stage of transesophageal atrial pacing or dipyridamole protocols (an operation that is practically impossible when examining a videotape sequentially), thus obtaining additional information on coronary artery disease severity.

Conclusions. Exercise echocardiography, because of its good sensitivity and specificity and because it uses the most physiologic stress, would be the test of choice in stress echocardiography in a routine clinical setting (23). Transesophageal atrial pacing and dipyridamole echocardiography are two diagnostic tests that are clinically useful and can be used as alternatives to exercise echocardiography in patients for whom the latter stress test would be "nondiagnostic." Transesophageal atrial pacing echocardiography is relatively invasive, and this limits its feasibility; it requires special equipment for transesophageal stimulation but at the same time is very safe to use. Its good sensitivity, with lower specificity, makes it particularly useful when there is a need to confirm the absence of significant coronary artery disease. Dipyridamole echocardiography, on the other hand, is easier to perform, but it has side effects and persistent ischemia-producing effects that require special attention in the recovery phase. Its high specificity, which contrasts with a relatively low sensitivity, makes it particularly useful for confirming a diagnosis and assessing the prognostic severity of coronary artery disease in subjects with more severe disease. In view of their good diagnostic potential and low costs, alternative stress tests used in conjunction with echocardiography should be given greater consideration as methods for routine noninvasive diagnosis of coronary artery disease (23). It seems reasonable to state that each echocardiographic laboratory should routinely use an exercise procedure and, related to its specific expertise, have available an alternative nonexercise stress procedure.

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