Noninvasive Pacemaker Stress Echocardiography for Diagnosis of Coronary Artery Disease

A Multicenter Study

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OBJECTIVES

We evaluated the feasibility, safety, and diagnostic accuracy of noninvasive pacemaker stress echocardiography (PASE) test as a potential alternative to exercise or pharmacologic stress in patients with suspected or known coronary artery disease (CAD).

BACKGROUND

Transesophageal atrial pacing echocardiography is an accurate test for detection of CAD, but its practical impact has been blunted by semi-invasiveness. In the expanding population of patients with permanent pacemakers (PMs), a pacing stress test can be administered noninvasively by external programming of the PM.

METHODS

In a prospective, multicenter, international study design, transthoracic stress-pacing echocardiography was performed in 46 consecutive patients with a permanent PM (33 men, 13 women; age 66.6 ± 11.1 years) with suspected or known CAD. All patients underwent noninvasive PM-stress test by external programming (10 beats/min increments up to ischemia or target heart rate). Coronary angiography was performed in all patients independently of test results. Significant CAD was defined as ≥50% visually assessed diameter reduction in at least one major epicardial coronary artery. All coronary angiograms were scored by Duke prognostic weight values.

RESULTS

Fifteen patients were stimulated in atrial, and the remaining 31 in ventricular mode during stress. No significant side effects were observed. Echocardiographic images were interpretable in all patients. The average duration of stress was 8.9 ± 3.5 min. Significant CAD was found in 27 patients. Sensitivity of PASE for identifying patients with significant CAD was 70%, specificity was 90%, and accuracy was 78%. When any abnormal wall motion at rest that remained unchanged at peak stress was regarded as a positive result of PASE, then the sensitivity, specificity, and accuracy levels for identifying patients with significant CAD were 85%, 84%, and 85%, respectively. Four of the eight patients with a false negative did not reach the target heart rate. The Duke values had significant correlation with values of wall motion score index at peak stress (r = 0.67) and with peak heart rate (r = -0.3).

CONCLUSIONS

Noninvasive PASE is a simple, rapid, safe, and diagnostically efficient option for patients with permanent PM and suspected or known CAD. (J Am Coll Cardiol 2002;40:1305–10)

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Noninvasive diagnosis of coronary artery disease (CAD) in patients with permanent pacemakers (PMs) is an extremely difficult task, because the rhythm induced by right ventricular pacing makes the electrocardiogram (ECG) uninterpretable (1,2). Perfusion scintigraphy is also burdened by low specificity in patients with right ventricular PM (3,4), possibly for a real impairment in coronary flow reserve due to alteration of left ventricular mechanical activation and increase in extramural compressive forces (5). The stress echocardiography test can be an effective option in these patients, because wall thickening, differently from wall motion, is not substantially affected by abnormal electrical activation (6). In addition, alterations in coronary flow reserve in the presence of normal epicardial coronary arteries induce perfusion defect more frequently than wall thickening abnormalities during stress (7).

Previous studies suggest that functional imaging with either radionuclide ventriculography associated with intravenous (IV) pacing (8) or two-dimensional (2D) echocardiography associated with transesophageal atrial pacing (9,10) are safe and accurate methods for the detection of CAD. In fact, they have similar diagnostic accuracy to physical and pharmacologic stress—although their practical impact is blunted by lower feasibility, suboptimal patient tolerance (11,12), and relatively long preparation time.

Initial, preliminary experiences suggest that the presence

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of a permanent PM can be exploited to perform a pacing stress test in a totally noninvasive way by programming the PM to increasing frequencies (13–15). The aim of this study was to evaluate the feasibility, safety, and diagnostic accuracy of a noninvasive PM-stress echocardiography (PASE) test as a potential alternative for exercise or pharmacologic stress echocardiography in patients with known or suspected CAD.

METHODS

Study patients. The Institute of Clinical Physiology Institutional Review Board approved the study, and all patients gave informed consent. The study population consisted of 46 patients with a permanent PM (33 men, 13 women; age 66.6 ± 11.1 years) with suspected or known CAD and transthoracic echocardiogram adequate to assess resting regional wall motion (the echocardiogram was considered adequate if ≥13 out of the maximum 16 segments were visualized in at least one projection). Inclusion criteria were: 1) chest pain syndrome, clinically suspected to be ischemic in origin; 2) a patient scheduled to have coronary angiography performed on the basis of the advice of the referring physician, and independently of pacing stress results; and 3) presence of a permanent PM. Exclusion criteria were: 1) dilated cardiomyopathy; 2) severe valvular heart disease; 3) unstable angina or recent myocardial infarction; and 4) technically poor baseline echocardiographic examination. The patients’ characteristics are summarized in Table 1.

Table 1. Patients’ Characteristics (n = 46)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
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<tr>
<td>Age (yrs)</td>
<td>66.6 ± 11.1</td>
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<tr>
<td>Gender (F/M)</td>
<td>13/33 (28.3%/72.7%)</td>
</tr>
<tr>
<td>LVEF</td>
<td>56.2 ± 12.8</td>
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<tr>
<td>Diabetes mellitus</td>
<td>7 (15.2%)</td>
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<tr>
<td>Systemic hypertension</td>
<td>22 (47.8%)</td>
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<tr>
<td>Previous MI</td>
<td>17 (37.0%)</td>
</tr>
<tr>
<td>CABG</td>
<td>8 (17.4%)</td>
</tr>
<tr>
<td>PTCA</td>
<td>5 (10.9%)</td>
</tr>
<tr>
<td>Nitrate treatment</td>
<td>18 (39.1%)</td>
</tr>
<tr>
<td>Beta-blocker treatment</td>
<td>16 (34.8%)</td>
</tr>
<tr>
<td>Calcium-antagonist treatment</td>
<td>10 (21.7%)</td>
</tr>
<tr>
<td>ACE inhibitor treatment</td>
<td>11 (23.9%)</td>
</tr>
<tr>
<td>Diuretic treatment</td>
<td>4 (8.7%)</td>
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</table>

Data are presented as the mean value ± SD (% of patients).
ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft surgery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

PASE protocol. The examination was performed with the patient in the left lateral decubitus position. Two-dimensional (2D) echocardiography images were obtained before echocardiography pacing was begun and every 3 min thereafter throughout the stress test; the last recording was obtained 4 min after pacing stress testing. Pacing was started at the rate of 100 beats/min. Pacing protocol (Fig. 1) was either “standard” (with a 10-beat increment every 3 min) or “accelerated” (with a 10-beat increment every 60 s) until one of these criteria was reached: 1) 85% of maximal heart rate (age-corrected: 220 – age for men, 200 – age for women); 2) PM maximal programmable heart rate (which varied widely, according to the model of PM, up to 170 beats/min during stress); 3) other standard end points. Patients paced in atrial mode sustaining second-degree Wenckebach atrioventricular block during pacing were given IV atropine, 0.4 to 2 mg, as necessary in 0.4-mg increments every 30 s until 1:1 capture was achieved. Diagnostic end points of stress testing were target heart rate; obvious echocardiography positivity; severe chest pain; obvious ECG changes (≥2 mm ST-segment shift). Submaximal nondiagnostic end points were: intolerable symptoms; limiting asymptomatic side effects such as hypertension (systolic arterial pressure >220 mm Hg, diastolic arterial pressure >120 mm Hg); hypotension, relative or absolute (>30 mm Hg drop in blood pressure); supraventricular arrhythmias (supraventricular tachycardia, atrial fibrillation); and ventricular arrhythmias (ventricular tachycardia, frequent and polymorphic premature ventricular beats). A 12-lead ECG was recorded at baseline, at peak heart rate, and immediately after pacing. Left ventricular wall motion abnormalities were evaluated at rest, during peak pacing, and immediately after the pacing was stopped.

For segmental wall motion assessment, we used the 16-segment model according to the recommendation of the American Society of Echocardiography (16) and previously employed in stress echocardiography multicenter trials (17,18). In all studies, segment wall motion was graded as 1 = normal; 2 = hypokinetic; 3 = akinetic; and 4 = dyskinetic. When patients were ventricularly paced, septal function was evaluated based upon systolic thickening—not on septal motion, which may be altered by ventricular
Coronary angiography. Images and videotape recordings were used for analysis. To clinical information and angiographic data. Digitized studies (17,18). The echocardiographers were blinded to the study (including study image interpretation) was recorded. Adverse events were assessed (intolerable symptoms, ventricular or supraventricular tachycardia, hypotension, hypertension, atrial fibrillation).

All studies were performed and interpreted in the 10 peripheral centers recruiting the patients by an experienced cardiologist with documented experience in stress echocardiography and who has passed the quality-control procedures of stress echocardiography reading according to criteria adopted in the Echo Persantine International Cooperative and Echo Dobutamine International Cooperative studies (17,18). The echocardiographers were blinded to clinical information and angiographic data. Digitized images and videotape recordings were used for analysis.

Coronary angiography. Angiographic studies were performed and interpreted by experienced observers who had no knowledge of the PASE test results. All coronary angiogram reports were sent centrally for qualitative evaluation in the coronary laboratory. A vessel was considered to have significant obstruction if its diameter was narrowed ≥50%. From the raw data, a semiquantitative measure of the extent and severity of CAD was also evaluated by means of the Duke scoring system (19). This CAD prognostic index considers the number of the diseased vessels (one-, two-, and three-vessel, as well as left main disease) and also involvement of the left anterior descending coronary artery, particularly when there is involvement of the proximal segment or the stenosis is severe (i.e., ≥95% diameter narrowing). The range of the prognostic weight is a 0 to 100 grade scale (0 = no disease; 100 = severe disease).

Statistical analysis. Continuous measures are expressed as the mean value ± SD. When appropriate, 95% confidence intervals (CI) are given. Continuous variables are analyzed according to the Student t test. Dichotomous variables are compared by chi-square analysis. Calculations of sensitivity, specificity, and accuracy were done according to standard definitions. Standard linear regression analysis was used to analyze relations between peak heart rate and peak wall motion score index versus Duke score. A p value of <0.05 was considered significant.

RESULTS

Forty-six consecutive patients (33 men, 13 women; age 66.6 ± 11.1 years) were studied. In all patients the mean total duration of the test, including technical preparations and interpretation of the echocardiographic images, was 37 ± 6 min, with a median time of 32 min (27 to 46 min). The mean duration of pacing was 8.9 ± 3.5 min, with a median time of 8 min. Sixteen patients were stimulated in VVI mode, 12 in DDD, 15 in AAI, and 3 in VDD mode during stress. The assessment of septal function in the 31 ventricularly paced patients was based upon septal thickening, not on septal motion. In the 15 patients stimulated in AAI mode, IV atropine (0.4 to 0.8 mg) was administered in 2 patients sustaining second-degree Wenckebach atrioventricular block during pacing.

Feasibility of PASE. Pacemaker stress echocardiography was completed in all patients. Echocardiographic images were interpretable in all patients. No major adverse effects were observed. One patient had nausea.

Hemodynamic data. Of 46 patients, 42 (91.3%) achieved at least 85% of their predicted target heart rate or positive test end point, and 4 patients (8.7%) did not reach the target heart rate: 2 patients for fixed upper rate response of the PM and 2 for low Wenckebach point during AAI pacing mode. During the test, heart rate and rate-pressure product increased significantly (p < 0.001), whereas systolic and diastolic blood pressure did not change significantly. The hemodynamic changes are presented in Table 2.

Table 2. Hemodynamic Changes During PASE (n = 46)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base</th>
<th>Peak Stress</th>
<th>p Value</th>
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<tr>
<td>Heart rate (beats/min)</td>
<td>70.5 ± 8.6</td>
<td>127.1 ± 18.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>143.8 ± 17.5</td>
<td>145.1 ± 19.6</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>82.8 ± 8.8</td>
<td>84.6 ± 11.5</td>
<td>NS</td>
</tr>
<tr>
<td>Rate-pressure product (beats/min × mm Hg/100)</td>
<td>102.0 ± 17.0</td>
<td>184.5 ± 36.2</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

NS = nonsignificant; PASE = pacemaker stress echocardiography.

Stress echocardiographic findings. The PASE was positive in 26 patients (56.5%) and negative in 20 others (43.5%). In patients with CAD, wall motion score index increased from 1.32 ± 0.43 at rest to 1.57 ± 0.47 during stress test (p < 0.001). In patients without CAD, wall motion score index did not change significantly (1.05 ± 0.19 vs. 1.11 ± 0.26, p = NS). In 36 of 46 patients the PASE findings accorded with the findings of coronary...
angiography (78% accuracy, 95% CI 64% to 88%). There were 19 patients with true positive and 17 patients with true negative results (70% sensitivity, 95% CI 51% to 84%, and 89% specificity, 95% CI = 68% to 97%) (Fig. 2). Two patients had false positive PASE and 8 had a false negative test. The two false positive results occurred in the septo-apical region in a patient paced in atrial mode, and in the septo-apical, anterior, and lateral wall in a ventricularly paced patient. A submaximal test (inability to reach target heart rate) was found in four of the eight patients with false negative test. In two of them, a low Wenckebach point was seen, but no atropine was given (patient did not give consent to IV drug injection). The peak heart rate was lower in false negative tests when compared to the 17 true negative tests (121.3 ± 14.6 vs. 136.9 ± 17.6 beats/min, p < 0.05). The peak rate-pressure product also tended to be lower in false negative tests when compared to the true negative tests (176.3 ± 42.3 vs. 194.6 ± 32.1, p = NS). The negative predictive value of the test was 68% and the positive predictive value was 90%.

In a cohort of patients with single-vessel disease, sensitivity of the PASE was 38% (95% CI = 14% to 70%), specificity 84% (95% CI = 62% to 94%), and accuracy 70% (95% CI = 51% to 84%). In patients with multivessel disease, sensitivity, specificity, and accuracy were 79% (95% CI = 56% to 91%), 78% (95% CI = 59% to 89%), and 78% (95% CI = 64% to 88%), respectively. The diagnostic accuracy was similar in patients on (n = 16) and off (n = 30) beta-blockers (87%, 95% CI = 63% to 96% vs. 73%, 95% CI = 55% to 86%, p = NS).

When any abnormal wall motion at rest that remained unchanged at peak stress was regarded as a positive result of PASE, the test findings were concordant with the findings of coronary angiography in 39 of 46 patients (85% accuracy, 95% CI = 72% to 92%) (Fig. 2). In 23 patients, results were true positive (85% sensitivity, 95% CI = 67% to 94%), and in 16 patients the results were true negative (84% specificity, 95% CI = 62% to 94%).

The values of the wall motion score index at peak stress showed a good correlation with severity of coronary lesions assessed by Duke prognostic weight values (Fig. 3). The Duke score showed a significant, albeit weak, correlation with peak heart rate during pacing stress (Fig. 4).

**DISCUSSION**

The clinical experience of the last 30 years has supported the efficacy of pacing as a stress test, especially when combined with imaging techniques such as radionuclide ventriculography (8) or 2D echocardiography (9,10,20).

**Pathophysiologic mechanism of pacing-induced ischemia.** The pathophysiologic rationale of pacing stress is obvious, with the stress determined by a controlled increase of heart rate, which is a major determinant of myocardial oxygen demand, and thereby tachycardia may exceed a fixed coronary flow reserve in the presence of hemodynamically significant CAD.

The drop in subendocardial-to-subepicardial flow ratio associated with rapid pacing in the presence of a tight coronary stenosis (21) is critical to the development of regional dysfunction, for regional percent systolic thickening is linearly and tightly related to subendocardial, not to transmural, flow (22). In patients with permanent right ventricular pacing, perfusion defects can often be found in the inferior and apical wall, which are probably the earliest activated sites under right ventricular apical pacing (5).
Advantages of PASE. The presence of a permanent PM can be exploited to perform a pacing stress in a totally noninvasive way by programming the PM to increasing frequencies (13–15). In contrast to exercise echocardiography, during atrial pacing, echocardiographic images are of unchanged quality when compared with resting images. It can also be performed in patients with poor exercise tolerance. In patients with PM, we found that PASE is a feasible, fast, and well-tolerated method. Pacing stress echocardiography has several advantages in comparison to conventional diagnostic techniques: The ability to instantly lower heart rate and to terminate stress result in high test safety. The short duration of PASE and the possibility to perform the test at bedside make it very well tolerated by the patient and user-friendly for the physician. Differently from physical stress, it does not require patient capability to exercise; differently from pharmacological stress, it does not require an IV line and the additional cost (and risk) of drug administration (24). The PASE requires a shorter preparation time than does the pharmacologic test; this is because it does not require the placement of an IV line, unless atropine is needed. It also has a shorter imaging time, because the median time of pacing was 8 min, and even less with the accelerated protocol, which compares favorably with the ~10 min of infusion time for dipyridamole and ~20 min of dobutamine (24). Thus, the PASE has a high potential usefulness for safe and rapid identification of significant coronary artery stenoses in patients with a PM.

Limitations of PASE. The major obvious pathophysiological limitation is that pacing stress determines only an increase in heart rate, while systolic blood pressure remains unchanged. Accordingly, the rate-pressure product increased only moderately, and to a lower extent than during exercise stress test—as demonstrated (11). As previously shown, the normal response to tachycardia induced by atrial pacing was a decrease in ventricular volumes without a change in ejection fraction or cardiac output (25). This hemodynamic profile may account for the suboptimal sensitivity of the PASE echocardiography in patients with single-vessel disease, especially when the target heart rate cannot be achieved.

From an echocardiographic viewpoint, ventricularly paced patients have abnormalities in septal motion (6). One should clearly separate AAI mode from ventricular pacing mode. In the AAI mode, there is a normal septal contraction pattern (26), and there are no special interpretation problems. About two out of three of our patients were studied in the ventricular pacing mode. In about 30% of right ventricular-paced patients, the septal wall motion is normal (26), but in the majority of them an anterior systolic interventricular septal motion (paradoxal motion) is present at baseline. In this case the interpreter must focus on wall thickening rather than endocardial excursion, and on nonseptal regions of the left anterior descending territory to identify left anterior descending stenosis, but this interpretation will always be a challenge, especially at high heart rates.

Another obvious limitation of PASE is that it can only be applied to patients with a permanent PM, which are, however, a large and expanding population in today’s cardiology practice (27). The external programming of the permanent PM is also simple and fast, but it requires technology (external programmer) and expertise not readily available in the echocardiography laboratory—with the need of minimum cooperation and coordination with the pacer-maker laboratory—which is usually, but not always and anywhere, easy to obtain.

Comparison with earlier studies. We found that PASE has a diagnostic accuracy of 85%, similar to that observed in other validation studies of permanent pacing (13–15), transesophageal pacing (9,10), and pharmacologic or exercise stress echocardiography (11,12). However, differently from transesophageal pacing, PASE has a markedly higher feasibility with shorter preparation time.

The PASE proved to be effective not only for primary diagnosis, but also for CAD severity stratification, especially when peak wall motion score index was estimated. This is consistent with previous studies with transesophageal atrial pacing, describing a good correlation between coronary score and peak pacing wall motion score index (28). We were able to achieve target heart rate or positive test end point in 42 patients (91.3%) despite the fact that a significant number of patients received beta-blockers (34.8%) and calcium antagonists (21.7%). The main source of a false negative result was the inability of some type of PM to reach the target heart rate and/or low Wenckebach point. The results of the PASE test in some of these patients is negative, submaximal, and cannot be considered an adequate form of stress testing.

Study limitations. The gold standard used for comparison of noninvasive test results was the angiographically assessed CAD. It is known that angiographic stenosis is not necessarily related to the degree of impairment in regional coronary flow reserve. Furthermore, the visual assessment suffers from relatively high intraobserver and interobserver variability. Although a subjective visual estimate of “percent stenosis” lacks accuracy and repeatability and does not provide accurate insight into the hemodynamic impact of a lesion, the simplicity of the percent stenosis estimate and the force of tradition favor its continued use: in most cardiology centers, the visual assessment of coronary stenosis remains the definitive gold standard.

A second limitation is inherent in the sensitivity-specificity approach that we used; this approach requires a dichotomous response for both test results and CAD when
all, in fact, show a continuous spectrum of severity. Therefore, in the present study we also evaluated an integrated semiquantitative parameter of CAD severity (Duke score) and of pacing echocardiography response (wall motion score index, pacing time). The titration of positive response by PASE was effective in disease-severity stratification.

In our study there was no centralized reading of stress echocardiogram. Each echocardiogram (either at baseline or during stress) was interpreted at the peripheral center, and this reading was directly entered into the data bank. In some centers only a few studies were performed. Results might have been affected by interinstitutional variability in readings of stress echocardiograms (29). However, this system allowed substantial sparing of human and technologic resources. In addition, all centers observed strict quality control for stress echocardiography reading prior to entering the study. Furthermore, both the data collection and the data interpretation in the primary care recruiting centers were more likely to offer a realistic picture of the “effectiveness” of the test—that is, the real performance of the test in the clinical arena, outside the “ideal” conditions of an “efficacy” study (30).

Conclusions. Noninvasive PASE is a simple, rapid, safe, and diagnostically efficient option for patients with permanent PM and suspected or known CAD. Noninvasive PASE might become the method of choice for diagnostic assessment of CAD in patients with a permanent PM. The main source of false negative result is the inability to reach the target heart rate. The main limitation of the test is the clearly suboptimal sensitivity in patients with single-vessel disease.

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REFERENCES


