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Diagnosis of Coronary Artery Disease by Exercise Thallium-201 Tomography in Patients With a Right Ventricular Pacemaker

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Objectives. **We sought to study the accuracy of exercise perfusion scintigraphy in patients with an implanted apical right ventricular pacemaker.**

Background. **The specificity of exercise perfusion scintigraphy is decreased in patients with a left bundle branch block. Patients with a permanent ventricular pacemaker have a similar conduction abnormality that may also potentially result in similar false positive perfusion defects.**

Methods. **One hundred five patients with a right ventricular pacemaker underwent exercise thallium-201 tomography and coronary angiography within 7 days of each other. Patients with a previous myocardial infarction were excluded.**

Results. **Patients were classified into four groups according to the agreement or disagreement between the thallium tomographic and coronary angiographic results. Only 8% of patients with normal results by both techniques were continuously paced during exercise, compared with 78% of patients with normal angiographic results but abnormal scintigraphic results. The mean defect size was 12% in the latter group. Most of the false positive defects were localized to the inferoposterior (71%), apical (50%) and inferoseptal (28%) walls.**

Conclusions. **Patients who are paced in the right ventricular apex and who continue to be paced throughout exercise have a high incidence of false positive thallium-201 single-photon emission computed tomographic defects.**

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Approximately 1 million patients in the United States have an implanted electronic cardiac pacemaker (1). These patients are often elderly and may have a history of angina, myocardial infarction or ventricular dysfunction and thus are often referred for noninvasive evaluation to rule out concomitant coronary artery disease. Exercise myocardial perfusion tomography is a widely accepted noninvasive technique for detecting ischemic heart disease, but the accuracy of this technique is reduced in patients with a left bundle branch block on the rest electrocardiogram (ECG) (2) because this abnormality is often associated with perfusion abnormalities. Most patients with an implanted right ventricular pacemaker have a conduction abnormality that electrocardiographically mimics a left bundle branch block, thereby raising questions as to whether they may also have perfusion abnormalities. Accordingly, the purpose of this study was to evaluate the accuracy of thallium-201 single-photon emission computed tomography to detect coronary artery disease in patients with an implanted right ventricular cardiac pacemaker.

Methods

Study patients. One hundred five consecutive patients with an implanted transvenous pacemaker in the right ventricular apex were included in this study (62 men, 43 women; mean (±SD) age 65 ± 9 years, range 38 to 87). Thirty-nine patients were continuously paced before the exercise test. All patients underwent exercise thallium-201 tomography and coronary angiography within 30 days of each other. Patients with a previous myocardial infarction were excluded from the study.

Exercise testing. All patients performed a symptom-limited exercise treadmill test using the Bruce protocol. The ECG was continuously monitored, and a 12-lead tracing was obtained at rest, at the end of each exercise stage and at 2, 4 and 6 min into recovery. Electrocardiographic ischemia was defined as ≥1 mm horizontal or downsloping ST segment depression or elevation measured 80 ms after the J point in patients who were not continuously paced. The ECG was considered nondiagnostic for ischemia in patients who were continuously paced at a ventricular site during the stress test.

Thallium-201 single-photon emission computed tomography. Thallium-201 tomography was performed according to the standard protocol in our laboratory. Three millicuries of thallium-201 was injected intravenously 1 min before terminating the exercise. Tomographic imaging began 10 min after completion of exercise and was repeated 4 h later. Thirty-two images were acquired for 40 s each over a 180° anterior arc, using a high resolution collimator. Oblique reconstruction was performed using filtered backprojection with reorientation into short, horizontal and vertical long axes. Myocardial segments were qualitatively interpreted in all three standard planes. Thallium-201 activity in each myocardial segment was scored as 3 = normal; 2 = mildly decreased; 1 = severely decreased; 0 = absent. Myocardial perfusion defects were

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Table 1. Clinical Characteristics of Study Cohort

	Normal SPECT/ Normal CA (group A [n = 24])	Abnormal SPECT/ Abnormal CA (group B [n = 64])	Abnormal SPECT/ Normal CA (group C [n = 14])	Normal SPECT/ Abnormal CA (group D [n = 3])	p Value
Age (yr)	61 ± 11	68 ± 7	63 ± 14	71 ± 4	0.12
Gender (M/F)	15/9	38/26	8/6	1/2	0.810
Hypertension	9	12	4	2	> 0.05
Diabetes	3	7	4	1	> 0.25
Prior CABG	10	9	3	0	< 0.05
LVEF (%)	64 ± 5	56 ± 7	62 ± 5	57 ± 7	
Symptoms					
None	10	12	6	1	> 0.05
Angina	7	42	5	2	0.010
Dyspnea	7	10	3	0	> 0.25
Medications					
Calcium antagonists	6	17	3	1	> 0.975
Beta-blockers	6	19	4	1	0.975
Digoxin	6	7	4	0	> 0.10

Data presented are mean value ± SD or number of patients. CA = coronary angiography; CABG = coronary artery bypass grafting; LVEF = left ventricular ejection fraction; SPECT = single-photon emission computed tomography.

quantified using methods previously described from our laboratory (3). In brief, polar maps of the tracer distribution were generated and statistically compared with those of a normal data bank that included data from 50 normal subjects who underwent exercise thallium tomography in our laboratory. Pixels with tracer count-activity <2.5 SD of the corresponding mean values in the normal data bank were considered abnormal. Using this software, the perfusion defect size is automatically calculated by the computer (3).

Coronary angiography. Coronary angiography was performed using standard techniques, and the angiograms were interpreted visually by experienced angiographers not involved in the study. Significant coronary stenosis was defined as >50% lumen diameter stenosis in any one of the major coronary branches. Contrast left ventriculography was performed in all patients after coronary angiography. Left ventricular ejection fraction was calculated with the aid of a microprocessor, using standard techniques.

Statistical analysis. Data are presented as mean value ± SD. The chi-square test was used to compare categoric data. Analysis of variance was used to compare continuous data among the four patient groups, and the Bonferroni-adjusted test was used to assess the significance of differences among groups. A p value <0.05 was considered statistically significant.

Results

Patient demographics. The clinical characteristics of the study cohort are summarized in Table 1. Patients were classified into four groups according to agreement or disagreement of the results of thallium tomography and coronary angiography. As shown, patients were grouped into those with a normal thallium tomogram and a normal coronary angiogram (group A); an abnormal thallium tomogram and an abnormal coronary angiogram (group B); an abnormal thallium tomogram and a normal angiogram (group C); and a normal thallium tomogram and an abnormal angiogram (group D). Angina or angina-equivalent symptoms occurred in 58%, 66%, 57% and 81% of patients in groups A, B, C and D, respectively. Forty-seven patients from the total cohort of 105 were continuously paced during exercise.

Exercise treadmill testing. Table 2 summarizes the results of the treadmill test in the four groups of patients. There were no differences in the total exercise time or the percent target heart rate achieved during exercise among the four groups. Nine (37%) of 24 patients with a normal thallium tomogram and a normal coronary angiogram reached their target heart rate, compared with 2 (14%) of 14 patients with an abnormal thallium tomogram and a normal angiogram ($p < 0.001$).

Ventricular pacing versus perfusion scintigraphy. Only 2 (8%) of 24 patients with both a normal coronary angiogram and a normal scintigraphic study were continuously paced before, during and after the treadmill test, compared with 11 (78%) of 14 patients with a normal angiogram and an abnormal thallium tomogram ($p < 0.001$). Of the remaining three patients, one was intermittently paced during the treadmill test. Patients with perfusion defects and a normal coronary angiogram had a mean perfusion defect size of 12% (range 5% to 46%). The defects were reversible and of mild severity in all patients, except for two patients with mixed defects. Perfusion defects were localized to the inferior/inferoposterior region in 71%, in the apical region in 50% and in the lateral/posterolateral wall in 28% of patients. Figure 1 shows an example of a patient with a normal coronary angiogram and a reversible thallium perfusion defect in the inferoapical distribution.

Comparative accuracy of exercise thallium-201 tomography in paced versus unpaced patients during exercise. As depicted in Table 3, the sensitivity, specificity, positive and negative

Table 2. Exercise Treadmill Variables in the Four Patient Groups

	Normal SPECT/ Normal CA (group A [n = 24])	Abnormal SPECT/ Abnormal CA (group B [n = 64])	Abnormal SPECT/ Normal CA (group C [n = 14])	Normal SPECT/ Abnormal CA (group D [n = 3])	p Value
Time from angiography (days)	4 ± 5	7 ± 5	10 ± 8	5 ± 1	0.74
Exercise time (s)	378 ± 164	323 ± 176	397 ± 163	328 ± 212	0.07
Target HR (%)	81 ± 18	78 ± 17	70 ± 13	70 ± 8	0.11
Achieved target HR	9	42	2*	2	0.002
Pacing during exercise	2	24	11†	None	0.001

*$p < 0.001$ versus group B. †$p < 0.001$ versus group A. $p < 0.01$ versus group B. Data presented are mean value ± SD or number of patients. CA = coronary angiography; HR = heart rate; SPECT = single-photon emission computed tomography.

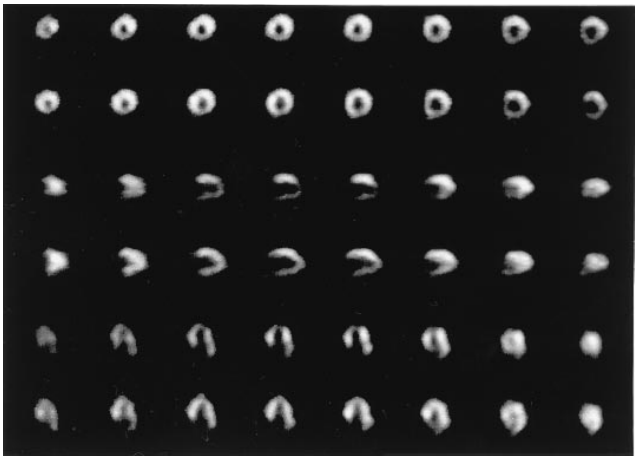
predictive values and overall accuracy of exercise thallium tomography were all significantly reduced in patients who were continuously paced during exercise, compared with the total study cohort or with patients who were not continuously paced during exercise.

Discussion

The present study included 105 patients with an implanted right ventricular pacemaker who were referred to our laboratory to be evaluated for the presence of significant coronary artery disease. Our results indicate that patients who are continuously paced throughout exercise testing have a high incidence of false positive thallium tomographic studies. The observed perfusion defects were usually reversible and of only mild severity and occurred irrespective of the heart rate achieved during exercise. False positive perfusion defects occurred only occasionally in patients who were not paced during peak exercise.

Effect of ventricular pacing on left ventricular function. Recently, He et al. (4) evaluated the impact of right ventricular pacing at two different frequencies (60 and 100 beats/min) on global and regional left ventricular ejection fraction in 14 patients without coronary artery disease. All patients had a significant decrease in the apicoseptal and inferoapical regional ejection fraction during rapid heart rate stimulation.

Figure 1. Example of a patient with a normal coronary angiogram; however, a filling thallium defect is seen in the inferior and apical walls. The defect became almost completely normalized at rest.



Ventricular pacing and conduction abnormalities versus myocardial perfusion. Conduction abnormalities such as a left bundle branch block, Wolff-Parkinson-White syndrome and a paced ventricular rhythm have all been reported to cause perfusion abnormalities in the absence of concomitant coronary artery disease. Tawarahara et al. (5) studied the specificity of exercise thallium tomography for detecting coronary artery disease in patients with various intraventricular conduction disturbances. The specificity was 94% (70 of 74) in normal subjects, 86% (19 of 22) in patients with a right bundle branch block, 50% (5 of 10) in patients with a right bundle branch block associated with a left anterior fascicular block, 44% (4 of 9) in patients with right ventricular pacing and 30% (3 of 10) in patients with a left bundle branch block. The defects were reversible in all patients with right ventricular pacing and involved the apical, inferior and septal walls. These results are in agreement with ours, where most patients who were continuously paced had a reversible perfusion defect in the same distribution as that reported by Tawarahara et al. (5).

The perfusion defects in our patient cohort had an anatomic distribution that was different from that which occurs in patients with a left bundle branch block (2,6), despite the fact that both groups of patients have a similar, albeit not identical, ECG pattern. The prevalence of exercise-related septal defects in patients with a left bundle branch block has been reported to vary from 14% to 100%. Ono et al. (7) induced left bundle

Table 3. Exercise Thallium Single-Photon Emission Computed Tomography in Patients With a Ventricular Pacemaker

	All Patients (n = 105)	Nonpaced Rhythm (n = 77)	Paced Rhythm (n = 28)
Sensitivity	95% (64/67)	98% (51/52)	86% (13/15)
Specificity	63% (24/38)	84% (22/25)	15% (2/13)*
Positive predictive value	82% (64/78)	94% (51/54)	54% (13/26)*
Negative predictive value	88% (24/27)	95% (22/23)	50% (2/4)*
Overall accuracy	79% (88/105)	91% (73/78)	54% (15/28)*

*$p < 0.01$ versus nonpaced rhythm.

branch block by right ventricular pacing in anesthetized dogs. They noted a significant decrease of thickening of the interventricular septum, associated with an increase in intramyocardial pressure during diastole. These findings were associated with reduced thallium uptake and decreased regional blood flow to the septum.

However, other reports showed that perfusion defects in patients with a left bundle branch block are not always confirmed to the interventricular septum. Jazmati et al. (8) studied 93 consecutive patients with a complete left bundle branch block who underwent symptom-limited exercise thallium scintigraphy. Segmental analysis of the planar images revealed that 49% of the patients had reversible defects. Seventy-four percent of the defects were in the apical distribution, 54% were in the inferior wall, and only 28% were in the septum. Three of six patients with septal defects and who underwent coronary angiography had left anterior descending coronary artery stenosis. A recent study from our laboratory demonstrated a high rate of septal perfusion defects but a low rate of defects in other anatomic sites during exercise in patients with a left bundle branch block. Patients undergoing pharmacologic stress had a much lower incidence of septal defects (9).

Despite the ECG similarities between classic left bundle branch block and the ventricular depolarization that results from ventricular pacing, there are also significant differences between them (10): Ventricular pacing produces early electrical activation in regions close to the pacemaker lead site, resulting in early shortening and later lengthening (or bulging). This probably explains why the defects we observed were not confined to the interventricular septum, with the majority of defects involving the inferior left ventricular wall. This unexpected location of the perfusion defect raises a question of whether they could be simply artifacts from photon attenuation. We considered this possibility remote for three main reasons: 1) most defects were reversible and one would not expect an attenuation artifact to be reversible on thallium tomography; 2) the defects occurred nearly exclusively in patients who were paced continuously during exercise and only 3 of 25 patients with normal angiograms who were not paced during exercise had a perfusion defect; and 3) there was no significant difference in the body weights between patients with normal coronary angiograms who had a normal or abnormal thallium study (180 ± 53 vs. 168 ± 37 lb, $p = 0.073$).

Mechanism of perfusion defects during ventricular pacing. It has been speculated that the decreased specificity of thallium tomography in patients with right ventricular pacing could be explained on the basis of regional changes in myocardial perfusion due to asynchronous septal contraction (11). This explanation, however, is insufficient, as transient defects occurred in regions other than the septum. Some authors have suggested that exercise-induced ischemia in patients with right ventricular pacemakers may be due to small-vessel disease associated with fibrodegenerative changes that might cause an intraventricular conduction disturbance, which in turn results in asynchronous contraction and heterogeneous myocardial blood flow distribution (12). This argument is invalid in our study, as patients who had a normal coronary angiogram and were not paced during exercise testing did not usually have perfusion defects. Massaaki et al. (13) studied coronary blood flow velocity, coronary arterial diameter and coronary blood flow reserve in the left anterior descending coronary artery during right ventricular pacing at 100 beats/min using a Doppler flow wire in 15 patients with a normal coronary angiogram. Patients with right ventricular pacing had a significant decrease in coronary blood flow reserve despite a significant increase in coronary arterial diameter, compared with unpaced patients.

Based on our results, we speculate that right ventricular pacing results in a heterogeneous electrical activation of the left ventricle. This heterogeneity results in asynchronous contraction and possibly to uneven blood flow distribution to different regions of the left ventricle. This disparity in timing of myocardial contraction may become exaggerated with increased pacing rate during exercise, causing scintigraphic perfusion defects. This explanation is in keeping with the frequent occurrence of perfusion defects during exercise and the absence of similar defects during pharmacologic stress in patients with a left bundle branch block. By analogy with left bundle branch block, one is tempted to advance that a pharmacologic stress might be more appropriate than exercise stress in patients with a ventricular pacemaker, but this remains to be proven. Geometric changes secondary to asynchrony may also play a role in the perfusion scan pattern through a partial volume effect (14,15).

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