Myocardial Perfusion in Patients With Permanent Ventricular Pacing and Normal Coronary Arteries

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OBJECTIVES The purposes of this study were to test the specificity of dipyridamole myocardial perfusion scintigraphy in patients with permanent ventricular pacing (PVP) and to evaluate coronary blood flow and reserve in these patients.

BACKGROUND Permanent ventricular pacing is associated with exercise perfusion defects on myocardial scintigraphy in the absence of coronary artery disease (CAD). On the basis of studies in patients with left bundle branch block, coronary vasodilation with dipyridamole has been proposed as an alternative to exercise testing for detecting CAD in paced patients, but this approach has never been tested.

METHODS Fourteen patients with a PVP and normal coronary arteries underwent stress thallium-201 scintigraphy and cardiac catheterization. In these patients and in eight control subjects, coronary flow velocities were measured in the left anterior descending coronary artery (LAD) and in the dominant coronary artery before and after adenosine administration.

RESULTS In the paced patients, coronary flow velocities in the LAD and in the dominant coronary artery were significantly lower than those in the control subjects. In addition, seven patients showed perfusion defects on dipyridamole thallium-201 single-photon emission computed tomography, with a specificity of 50% for this test. The defect-related artery in these patients had lower coronary flow reserve (2.6 ± 0.5) as compared with those without perfusion defects (3.9 ± 1.0, p < 0.05) or the control group (3.5 ± 0.5, p < 0.05).

CONCLUSIONS Permanent ventricular pacing is associated with alterations in regional myocardial perfusion. Furthermore, abnormalities of microvascular flow, as indicated by reduced coronary flow reserve in the defect-related artery, are at least partially responsible for the uncertain specificity of dipyridamole myocardial perfusion scintigraphy.

Approximately one million patients in the U.S. have a cardiac pacemaker, and as time goes on, the number of implants is increasing, along with the use of pacing systems that are more adaptive to normal physiology (1). These patients are often elderly and may have symptoms, typical or nontypical, of ischemic heart disease, myocardial infarction or left ventricular dysfunction, and thus are often referred for noninvasive evaluation to rule out concomitant coronary artery disease (CAD).

Exercise myocardial perfusion scintigraphy is a widely accepted noninvasive technique for detecting ischemic heart disease; however, as in patients with left bundle branch block (LBBB) (2,3), ventricular paced rhythm during exercise has been associated with a high incidence of perfusion defects in the absence of CAD (4,5). In patients with LBBB, pharmacologic coronary vasodilatation with intravenous dipyridamole (6–8) appears to be associated with a higher specificity than that found with exercise.

On the basis of the aforementioned studies, and given the electrocardiographic resemblance between LBBB and the ventricular depolarization that results from right ventricular apex pacing, the same approach has been proposed for the latter group of patients but has never been tested.

Despite the electrocardiographic similarities, there are significant differences in left ventricular endocardial activation and function between the two situations (9–12). In addition, the perfusion defects are found in different regions, with the majority of them involving the septum in LBBB (2,3,13) and the inferior and apical wall (4,5) in patients with permanent ventricular pacing (PVP).

The different location of the perfusion defects and the lack of data from paced patients raise questions about the underlying mechanism and the validity of the proposed method of assessment.

The purposes of this study were to test the specificity of dipyridamole myocardial perfusion scintigraphy and to further elucidate the effect of PVP on coronary blood flow and reserve.

METHODS

Patients. The study included 19 patients with permanent, dual-chamber, rate-adaptive pacemakers inserted for complete atrioventricular block who consented to undergo stress...
thallium–201 scintigraphy and cardiac catheterization within two months. The patients were recruited into the study from the pacemaker outpatient clinic. All patients had to be in sinus rhythm, with right ventricular capture and ≥95% ventricular paced beats during the preceding week, as shown by a review of the pacemaker’s internal monitor. The following patient groups were excluded: patients with a previous myocardial infarction, significant valvular disease, hypertension or left ventricular hypertrophy, left ventricular ejection fraction <50%, total plasma cholesterol >220 mg/dl or diabetes mellitus. We also excluded obese patients and women with large breasts.

Control group. Eight patients who had coronary angiography for clinical indications and whose coronary arteries were free of stenotic lesions comprised the control group. The same exclusion criteria were also applied to this group. All patients and control subjects gave their written, informed consent to participate in the study. The study protocol was approved by the hospital’s Ethics Committee.

Stress protocol. All patients underwent a symptom-limited treadmill exercise test according to the standard Bruce protocol. For the purposes of the study, the upper rate of the pacemaker was programmed up to 160 beats/min. Three millicuries of thallium were injected during peak stress, and the patient was encouraged to exercise for 1 min longer. Imaging was performed as soon as possible after the end of exercise and 4 h later.

Patients with exercise perfusion defects also underwent a scintigraphic study under pharmacologic stress with dipyridamole, one month later. All had a 4-min intravenous infusion of 0.56 mg/kg body weight of dipyridamole. Three minutes after the end of dipyridamole infusion, 3 mCi of thallium was administered, and imaging was performed 3 min and 4 h later.

Thallium–201 single-photon emission computed tomography. Thallium–201 single-photon emission computed tomographic (SPECT) imaging was performed with a dual-head SPECT gamma camera (Optima NX, General Electric, Milwaukee, Wisconsin) by use of a step-and-shoot approach every 6° over a 180° clockwise circular orbit, beginning at a 45° right anterior oblique projection and ending at 45° left posterior. Filtered back-projection was performed using a Butterworth filter with a cut-off frequency of 0.4 cycles/pixel to reconstruct transverse tomograms of the left ventricle. These images were further processed to obtain the short-axis and long-axis sections perpendicular to the cardiac axes.

The tomograms were divided into six segments for qualitative interpretation. The short-axis slices were divided into five regions (inferoseptal, anteroseptal, anterior, lateral and inferior). The apex was interpreted from the vertical long-axis view at the mid-ventricular level. Perfusion was scored qualitatively by consensus of two experienced observers who were unaware of the other patient data: 0 = severe perfusion defect; 1 = moderate perfusion defect; 2 = mild or equivocal perfusion defect; and 3 = normal perfusion. Defects in the short-axis slices were confirmed in the other two planes. A reversible defect was defined as a segment with a higher score on the rest images. The vascular territories were assigned as follows: anteroseptal and anterior regions and apex to the left anterior descending coronary artery (LAD); lateral region to the left circumflex coronary artery (LCx); and inferior and inferoseptal regions to the right coronary artery (RCA) or LCx, whichever was the dominant artery.

Coronary angiography. All patients underwent selective coronary angiography. On completion of diagnostic cardiac catheterization, the video record of the procedure was reviewed. Only patients whose coronary arteries were angiographically normal were enrolled in the study.

Coronary flow velocity measurements. Immediately after coronary angiography, a 0.014-in. (0.035-cm), 15-MHz Doppler guide wire (FloWire, Cardiometrics) was advanced through the catheter to the proximal LAD and to the proximal portion of the dominant LCx or RCA. Frequency analysis of the Doppler signals was carried out in real time by fast Fourier transform, using a velocimeter (FloMap, Cardiometrics, Inc, Mountain View, California). Once baseline flow velocity data were obtained, a bolus injection of intracoronary adenosine, 18 μg for the left coronary artery and 12 μg for the RCA were given to obtain data during hyperemia.

In each artery, all measurements were made at a constant heart rate of 100 beats/min for both patients and controls subjects to exclude the influence of variant heart rate. This was accomplished in the patients by programming the basic rate of the permanent pacemaker, and in the control subjects by pacing the right atrial appendage at the same rate through a temporary pacing lead.

Time-averaged peak coronary flow velocity (APV) was measured for each vessel. Coronary flow reserve was determined as the ratio of APV at maximal hyperemia to APV at baseline. Pretreatment and measurements were done as previously described (13).

Statistical analysis. Data are expressed as the mean value ± SD. Two-way repeated measures analysis of variance was used to assess drug (adenosine-induced maximal hyperemia), group and interaction effects. One-way analysis of variance was used for all other comparisons between the three groups. Specificity comparisons between dipyridamole and exercise scintigraphy were performed with McNemar’s
study under pharmacologic stress with dipyridamole. We with exercise perfusion defects underwent a scintigraphic Dipyridamole thallium-201 SPECT. partially reversible. defects, and the remainder of them were completely or segments with a perfusion defect, three (16%) had a fixed defects is shown in Table 1. Perfusion defects were located phy, with a specificity of 36%. The distribution of perfusion showed perfusion defects on exercise myocardial scintigraphy (group I), and seven showed normal myocardial scintigraphy (group II), with a specificity of 50%. This specificity was not statistically significantly different from that found with exercise testing. The distribution of perfusion defects is shown in Table 1. Perfusion defects were located in the inferior (100% [n = 7]) and apical (57% [n = 4]) wall (Table 1).

Of the 11 segments with a perfusion defect, two (18%) had a fixed defect, and the remainder of them were completely or partially reversible. There were no significant differences in age between the three groups (group I: 66 ± 6 years; group II: 63 ± 7 years; control group: 62 ± 10 years).  

Exercise thallium-201 SPECT. All patients were paced continuously throughout the study. The heart rate achieved during exercise was 138 ± 10 beats/min. Nine patients showed perfusion defects on exercise myocardial scintigraphy, with a specificity of 36%. The distribution of perfusion defects is shown in Table 1. Perfusion defects were located more commonly in the inferior (78% [n = 7]), inferoseptal (67% [n = 6]) and apical (55% [n = 5]) wall. Of the 19 segments with a perfusion defect, three (16%) had a fixed defect, and the remainder of them were completely or partially reversible.  

Dipyridamole thallium-201 SPECT. The nine patients with exercise perfusion defects underwent a scintigraphic study under pharmacologic stress with dipyridamole. We assumed that the other five would be negative. All patients were paced continuously throughout the study. The maximal heart rate during the pharmacologic stress was 83 ± 11 beats/min, significantly lower than that achieved during exercise stress (138 ± 10 beats/min, p < 0.05).

Seven patients showed perfusion defects on dipyridamole myocardial scintigraphy (group I), and seven showed normal perfusion (group II), with a specificity of 50%. This specificity was not statistically significantly different from that found with exercise testing. The distribution of perfusion defects is shown in Table 1. Perfusion defects were located in the inferior (100% [n = 7]) and apical (57% [n = 4]) wall (Table 1).

In paced patients, APV was 18.7 ± 5.5 cm/s at baseline and 51 ± 12.9 cm/s at maximal hyperemia. In the control subjects, the corresponding values were 25.1 ± 5.2 and 71.7 ± 16.1 cm/s. There was a significant group effect (p = 0.004), both at baseline and during maximal hyper-

### Table 1. Patient Data, Scintigraphic Findings and Coronary Flow Reserve at 100 Beats/Min in Patients With Permanent Ventricular Pacing

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Age (years)/Gender</th>
<th>Exercise TI-201 SPECT</th>
<th>Dipyridamole TI-201 SPECT</th>
<th>DCA CFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73/M</td>
<td>R-inferior, apical, inferoseptal</td>
<td>R-inferior, apical</td>
<td>1.8</td>
</tr>
<tr>
<td>2</td>
<td>71/M</td>
<td>R-inferior, apical</td>
<td>R-inferior, apical</td>
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</tr>
<tr>
<td>3</td>
<td>64/F</td>
<td>R-inferior, Fx-inferoseptal</td>
<td>Fx-inferior</td>
<td>2.2</td>
</tr>
<tr>
<td>4</td>
<td>70/M</td>
<td>Fx-inferior, inferoseptal</td>
<td>Fx-inferior</td>
<td>3.3</td>
</tr>
<tr>
<td>5</td>
<td>68/M</td>
<td>R-inferior, inferoseptal</td>
<td>R-inferior</td>
<td>3.2</td>
</tr>
<tr>
<td>6</td>
<td>61/F</td>
<td>R-inferior, apical, inferoseptal</td>
<td>R-inferior, apical</td>
<td>2.5</td>
</tr>
<tr>
<td>7</td>
<td>57/M</td>
<td>R-inferior, apical, inferoseptal</td>
<td>R-inferior, apical</td>
<td>2.7</td>
</tr>
<tr>
<td>8</td>
<td>55/F</td>
<td>Rx-anterior</td>
<td>Negative</td>
<td>4.9</td>
</tr>
<tr>
<td>9</td>
<td>67/M</td>
<td>R-apical</td>
<td>Negative</td>
<td>4.0</td>
</tr>
<tr>
<td>10</td>
<td>64/M</td>
<td>Negative</td>
<td>—</td>
<td>2.5</td>
</tr>
<tr>
<td>11</td>
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<td>Negative</td>
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<td>4.9</td>
</tr>
<tr>
<td>12</td>
<td>67/M</td>
<td>Negative</td>
<td>—</td>
<td>4.0</td>
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<tr>
<td>13</td>
<td>65/M</td>
<td>Negative</td>
<td>—</td>
<td>2.7</td>
</tr>
<tr>
<td>14</td>
<td>71/M</td>
<td>Negative</td>
<td>—</td>
<td>4.4</td>
</tr>
</tbody>
</table>

CFR = coronary flow reserve; DCA = dominant coronary artery; F = female; Fx = fixed; R = reversible; Rr = reverse redistribution; SPECT = single-photon emission computed tomography; TI-201 = thallium-201.

### Table 2. Left Anterior Descending and Dominant Coronary Artery Doppler Flow Velocity Measurements in Patients With Permanent Ventricular Pacing, With (Group I) and Without (Group II) Dipyridamole Scintigraphic Perfusion Defects, and in Control Subjects

<table>
<thead>
<tr>
<th>r-APV (cm/s)</th>
<th>h-APV (cm/s)</th>
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<tbody>
<tr>
<td>Group I</td>
<td>Group II</td>
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<tr>
<td>Group I</td>
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<td>Group II</td>
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chi-square test. A p value <0.05 was considered as statistically significant.

### RESULTS

Of the 19 patients initially included in the study, five had CAD. These patients were excluded from the final analysis. The mean age of the remaining 14 patients (10 men and 4 women) was 65 ± 7 years. Three of them had typical angina and eight had nontypical chest pain syndrome. In the control group (6 men), the mean age was 62 ± 10 years (p = NS).
emia. There was also a significant drug effect ($p < 0.001$) and interaction ($p = 0.026$).

Doppler flow velocity measurements for the three groups are given in Table 2. There was a significant group effect ($p = 0.006$), both at baseline and during maximal hyperemia. The APV was significantly lower in group II than in the control group, both at baseline and during maximal hyperemia. There was also a significant drug effect ($p < 0.001$) and interaction verging on significance ($p = 0.051$).

Coronary flow reserve was $2.7 \pm 0.8$ in group I; $3.0 \pm 0.3$ in group II; and $2.9 \pm 0.4$ in the control group. The differences between these values were not statistically significant.

DOMINANT CORONARY ARTERY. Two patients from group I, one patient from group II and one from the control group had left-dominant coronary arteries.

In paced patients, APV was $16.7 \pm 7.0$ cm/s at baseline and $50.5 \pm 15.5$ cm/s at maximal hyperemia. The corresponding control values were $24.8 \pm 2.4$ cm/s and $84.8 \pm 10.4$ cm/s. There was a significant group effect ($p < 0.001$), both at baseline and during maximal hyperemia. There was also a significant drug effect ($p < 0.001$) and interaction verging on significance ($p = 0.051$).

Coronary flow reserve was $2.7 \pm 0.8$ in group I; $3.0 \pm 0.3$ in group II; and $2.9 \pm 0.4$ in the control group. The differences between these values were not statistically significant.

DISCUSSION

To our knowledge, this study is the first to assess the specificity of dipyridamole myocardial perfusion scintigraphy and to evaluate coronary blood flow and reserve in patients with PVP. Our main findings were: 1) exercise and dipyridamole myocardial perfusion scintigraphy have a similar specificity in the detection of CAD; 2) there are alterations in regional myocardial blood flow associated with PVP; and 3) impairment of microvascular flow in the defect-related artery appears to be the underlying mechanism for the intermediate specificity of scintigraphic studies.

Coronary blood flow. This is the first study of coronary blood flow in patients with long-term ventricular pacing ($32 \pm 16$ months). In these patients, we observed a significant reduction of coronary flow velocity at baseline and during maximal hyperemia in both measured coronary arteries, as compared with that in control subjects. Although coronary blood flow velocities do not actually represent volumetric flow, given the similarities between our patients and control subjects in terms of age, systolic ($118 \pm 13$ vs. $122 \pm 16$ mm Hg) and diastolic ($69 \pm 8$ vs. $67 \pm 9$ mm Hg) blood pressure, pretreatment regimens and heart rate (both paced at 100 beats/min), it seems reasonable to assume that flow velocities provide a valid means of comparing blood flow between the two groups. Thus, the differences we observed can most likely be explained in terms of a different regulation of coronary artery blood flow due to local alterations in mechanical work ($11,14$) arising from long-term functional and/or structural abnormalities induced by PVP ($15–19$).
Coronary flow reserve. Coronary flow reserve differences were found only in the dominant coronary artery in patients with scintigraphic perfusion defects (group I). This implies that in these patients, there is impairment of coronary microvascular flow in the inferior wall, because that wall was involved in all of the patients with perfusion defects. This was caused not only to lower coronary blood flow velocities as compared with control subjects during maximal hyperemia, as already discussed, but also to the higher values as compared with group II at baseline. The latter may be explained by differences in the degree of associated structural and functional abnormalities with PVP, because a similar difference was observed in the corresponding flow velocities in the LAD.

The absence of differences in coronary flow reserve in the LAD between the three groups may explained by the low number of patients with apical perfusion defects (n = 4) and the lower contribution of the apex to total LAD flow.

Stress thallium-201 SPECT. Perfusion defects on exercise myocardial scintigraphy, mainly in the inferior, apical and inferoseptal wall, have been observed in 65% to 75% of patients free of CAD who were paced through the right ventricular apex during exercise (4,5). Several hypotheses have been suggested to explain this. First is coronary autoregulation, according to regional alterations of mechanical work; second, small-vessel disease as the result of associated fibrodegenerative changes; third, compression of the septal arteries during tachycardia; and finally, diaphragmatic photon attenuation based on the location of the findings (20,21).

In our study, during the exercise protocol, the heart rate was 138 ± 10 beats/min, and perfusion defects were observed in the same vascular territories and with a similar incidence as found in previous studies (4,5). During the dipyridamole protocol, the heart rate was 83 ± 11 beats/min, and perfusion defects were observed in the same regions, although inferoseptal regions were preserved (Fig. 3).

Ono et al. (21) found that, in dogs, right ventricular pacing itself may reduce regional myocardial blood flow in the septum at a pacing rate of 196 ± 16 beats/min by compression of the septal arteries, although LAD flow did not significantly change.

Combining these findings, the most probable explanation is that reduced septal flow is a rate-dependent phenomenon and that the septal hypoperfusion found by Ono et al. (21) was due to compression of septal branches arising from the posterior descending coronary artery, rather than from the LAD.

We found that the remainder of the defects observed, both during exercise and on dipyridamole scintigraphy, were associated with reduced coronary flow reserve in the defect-related artery, indicating abnormalities in microvascular flow in the same vascular territory. These probably represent true rather than false positive perfusion defects. Thus, the low specificity of both exercise and dipyridamole myocardial perfusion scintigraphy in patients with PVP may explained by associated abnormalities of microvascular flow.

Previous studies. There is one experimental animal study (14) and one human study (22) showing that asynchronous ventricular activation with ventricular pacing at heart rates slightly above the intrinsic rate is associated with reduced coronary blood flow in the early-activated region. Also, reduced regional myocardial work (11,14), oxygen uptake (11) and free fatty acid metabolism (23) have been observed in the early-activated region under ventricular pacing. This is consistent with our findings of reduced coronary flow velocity at baseline in paced patients as compared with control subjects, because the LAD supplies the apex and the dominant coronary artery supplies the inferior wall: these are probably the earliest activated sites under right ventricular apical pacing (11).

Although Amitzur et al. (22) showed that this effect disappears after intracoronary adenosine administration—a finding that conflicts with the persistence of the effect in our study group—they performed their measurements in the early phase of ventricular pacing. Thus, they could only detect early functional changes resulting from pacing in an apparently healthy substrate and did not take into account the functional and histologic changes that long-term ventricular pacing produces (15–19).

Two previous studies (24,25) of the effect of right ventricular apex pacing on coronary flow reserve did not find any differences in the LAD, as in our study group, but neither study included the RCA in the results, nor were the effects of long-term pacing investigated.
Study limitations. A coronary flow reserve of 2.6 is normally not considered to be associated with the presence of myocardial perfusion defects (26). However, because our measurements were made in the proximal part of the main coronary arteries, in the case of localized defects, contributions from other unaffected regions might be expected to inflate the values measured.

The small number of patients in this study is another limitation. This was due to the strict screening criteria we used to exclude other factors that might influence coronary microvascular flow. Despite this, or perhaps because of this, we were able to obtain statistically significant results.

Clinical implications. Although our findings should be confirmed in a larger patient group, it seems that dipyridamole scintigraphy in patients with PVP has nothing to add in ruling out CAD, as compared with exercise scintigraphy, and that given the specificity of 50% we found in these patients, the best approach to exclude concomitant CAD in such cases is coronary angiography.

Also, because PVP from the right ventricular apex is associated with alterations in regional myocardial perfusion and impairment of microvascular flow that may exacerbate the effects of concomitant CAD, there is one more reason to investigate alternative and more physiologic sites of pacing.

Conclusions. The findings of this study show that permanent pacing from the right ventricular apex is associated with alterations in regional myocardial perfusion, and that impairment of microvascular flow is the underlying mechanism for the perfusion defects during either exercise and dipyridamole myocardial scintigraphy. The low specificity of the latter method suggests that it is of limited usefulness in ruling out CAD in paced patients.

References
