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Long-Term Effect of Right Ventricular Pacing on Myocardial Perfusion and Function

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Objectives. **The purpose of this study was to investigate the effect of long-term ventricular pacing on myocardial perfusion and function in patients receiving such pacing.**

Background. **The long-term effect of ventricular pacing on myocardial perfusion and function in humans is unclear, although animal studies have suggested that it may be adverse.**

Methods. **Forty-three patients with complete heart block and dual-chamber rate-adaptive (DDDR) pacing were studied. All underwent thallium-201 (Tl-201) exercise myocardial scintigraphy to assess myocardial perfusion and radionuclide ventriculography to determine left ventricular function and regional wall motion. Coronary angiography was also performed in patients with abnormal findings on Tl-201 study.**

Results. **There was no significant difference in mean age, gender, percent ventricular pacing, pacing threshold, ventricular pacing output and metabolic equivalents on exercise testing between patients with or without perfusion defects on exercise Tl-201 scintigraphy. However, the duration of pacing tended to be longer in patients with than in those without perfusion defects (43.9 ± 49.7 vs. 20.1 ± 9.8 months, p = 0.05). Tl-201 perfusion defects were noted in 28 (65%) of 43 of patients (inferior 78% [n = 22], apical 67% [n = 17], septal 21% [n = 6], anterior 7% [n = 2], lateral 3% [n = 1]). Of 16 of 28 patients with abnormal Tl-201 findings who underwent coronary angiography, only 3 (19%) had significant coronary artery disease. Patients with an abnormal perfusion defect had a significantly lower left ventricular ejection fraction (48.5 ± 9.9% vs. 59.6 ± 8.9%, p < 0.001) and a higher percent of wall motion abnormalities (57% vs. 20%, p = 0.026), mainly over apical regions.**

Conclusions. **Long-term right ventricular apical pacing resulted in a high incidence of myocardial perfusion defects that increased with the duration of pacing. These myocardial perfusion abnormalities were associated with apical wall motion abnormalities and impaired global left ventricular function.**

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Although right ventricular (RV) pacing is effective in preventing symptomatic bradyarrhythmias, it has been demonstrated to be associated with a significant negative inotropic effect (1) and long-term impairment of myocardial function (2). Furthermore, long-term ventricular pacing has been shown (5) to cause abnormal histologic changes (3,4) and thinning of the myocardial wall over the activation site in canine hearts. In animal models, ventricular pacing resulted in regional perfusion defects (6) and reduced blood flow and oxygen consumption over the pacing site (7,8). However, whether long-term ventricular pacing in humans may result in myocardial ischemia and subsequently lead to myocardial dysfunction is unclear. The purpose of this study was to determine the effect in patients of long-term ventricular pacing on myocardial perfusion assessed by thallium-201 (Tl-201) exercise myocardial scintigraphy and myocardial function assessed by radionuclide ventriculography.

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Methods

Study patients. Forty-three patients (18 men and 25 women) with complete heart block who received an implanted dual-chamber rate-adaptive (DDDR) pacemaker were studied. Their mean age was 64.7 ± 9.7 years, and the mean duration of pacing was 35.6 ± 41.87 months (range 3 to 216). Five patients had essential hypertension. All patients were asymptomatic and had no clinical evidence of ischemic heart disease.

Study protocol. The ventricular pacing leads were positioned at the RV apex to obtain a satisfactory pacing threshold value (<1 V at a pulse width of 0.5 ms) and sensing value (R wave >5 mV). Bipolar ventricular and atrial pacing were used in all patients. Clinical data and pacing variables are shown in Table 1. The pacemakers were programmed to DDDR mode after implantation, during exercise testing and throughout the study period. All patients underwent 24-h ambulatory electrocardiographic (ECG) (Holter) monitoring, Tl-201 exercise myocardial scintigraphy and radionuclide ventriculography within 1 month of recruitment. Holter recording was used to determine the percent of ventricular pacing beats. Tl-201

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Abbreviations and Acronyms

AV = atrioventricular
DDDR = dual-chamber rate-adaptive pacemaker
ECG = electrocardiogram, electrocardiographic
LBBB = left bundle branch block
LVEF = left ventricular ejection fraction
RV = right ventricular
Tl-201 = thallium-201

exercise myocardial scintigraphy was used to assess myocardial perfusion and radionuclide ventriculography to determine left ventricular function and regional wall motion. Sixteen patients (57%) with abnormal findings on Tl-201 scan agreed to undergo coronary angiography to define the coronary anatomy. The angiography was performed at a mean interval of 15 days after Tl-201 scintigraphy. The study protocol was approved by the local Ethics Committee. Written informed consent was obtained from all patients.

Holter recording. Bipolar ECG chest leads were fixed to the chest at V_1 and V_6 positions, and all ECGs were recorded for 24 h with use of an Oxford Medilog recorder (Oxford Medical Instruments, UK). The complete ECG pattern of the 1st min of each hour was reviewed and printed at a paper speed of 25 mm/s. RV capture was defined by the presence of a pacing spike followed by a QRS complex with a width ≥12 mm. The percent of QRS complexes with ventricular capture during each observation minute was averaged over the 24-h period.

Tl-201 exercise myocardial scintigraphy. All patients were instructed to fast for 4 h and to avoid theophylline compounds and caffeine-containing beverages for 12 h before the test. In all patients the pacemaker was programmed to DDDR mode during exercise. Myocardial imaging using 2 mCi of Tl-201 chloride was begun after symptom-limited exercise performed on a treadmill according to the modified Bruce protocol. Tl-201 was injected intravenously 1 min before the end of exercise. Cardiac single-photon emission computed tomography (SPECT) images were obtained at 15 min and 4 h after exercise. An additional 1 mCi of Tl-201 was injected before the rest study at 4 h. If a fixed defect was detected in the 4-h images, imaging was also performed at 24 h. Sagittal, short-axis and long-axis tomograms were constructed from the raw scintigraphic data. These constructed stress, reinjection and 24-h images were then analyzed qualitatively. The distribution of Tl-201 uptake was analyzed qualitatively in the three tomographic views: the septal, apical and lateral regions in the horizontal long-axis view (up to 7 slices/view); the anterior, apical and inferior regions in the vertical long-axis view (up to 7 slices/view); and the anterior, septal, inferior and lateral regions in the short-axis view (up to 15 slices/view). The stress, reinjection and 24-h images were standardized to maximal myocardial activity in the stress and 24-h images. The resulting paired images were displayed and graded by two experienced, independent observers using a 4-point scale: 0 = markedly reduced or absent activity, 1 = definitely reduced activity, 2 = mildly or equivocally reduced activity and 3 = normal activity. The grade assigned to a given region was the lowest regional score from all tomographic slices and views.

Radionuclide ventriculography. Multiple gated equilibrium blood pool imaging was performed at rest to determine left ventricular function and to assess regional wall motion. Patients' red blood cells were labeled with 20 to 30 mCi of technetium-99m by using the modified in vivo technique (9). Measurements were made in the left anterior oblique projection and a 64 × 64 matrix of 32 frames/cycle with 150,000 to 200,000 counts/frame. Left ventricular ejection fraction (LVEF) was obtained by means of a semiautomated, operator-assisted method that finds the border of the left ventricle throughout the cardiac cycle and computes the LVEF from the formula: (End-diastolic counts − End-systolic counts) ÷ End-diastolic counts. Serial frames were then displayed for cineangiographic wall motion assessment. Regional wall motion was read without knowledge of other data and represents a consensus interpretation of two experienced observers. Regional wall motion was determined for six approximately equal left ventricular wall segments in the left anterior oblique projection for each acquisition: two inferoapical, two posterolateral and two septal segments. Wall motion was scored for each segment as normal, hypokinetic, akinetic or dyskinetic.

Coronary angiography. Standard coronary angiography was performed by the Judkins technique with use of femoral artery puncture. Each coronary artery was opacified and recorded in multiple views. Angiograms were reviewed by two experienced cardiologists who were unaware of the Tl-201 results. Coronary stenosis was quantitated visually and significant coronary artery disease was defined by >50% lumen diameter stenosis of a major epicardial coronary segment.

Statistical analysis. Values were expressed as mean value ± SD. Comparison between groups was performed by two-tailed unpaired Mann-Whitney test for continuous variables and Fisher exact test for dichotomous outcome. A p value < 0.05 was considered significant.

Results

Patient characteristics and Holter recording (Table 1). There was no significant difference in the mean age, gender distribution, long-term ventricular pacing threshold and pacemaker ventricular output between patients with or without a perfusion defect on Tl-201 exercise study. The duration of pacing tended to be longer in patients with than without perfusion defects (43.9 ± 49.7 vs. 20.1 ± 9.8 months, p = 0.053). All patients were receiving ventricular pacing throughout most (>90%) of the recording. Holter recordings showed no difference in percent of ventricular pacing between patients with or without perfusion defects on Tl-201 exercise study. There was also no correlation between the percent of paced beats and number of wall motion abnormalities (r = 0.286, p = 0.896).

Tl-201 exercise myocardial scintigraphy. Twenty-eight patients (65%) showed perfusion defects on Tl-201 exercise

Table 1. Patient Characteristics, Pacing Variables and Ambulatory Electrocardiographic and Exercise Test Results

	All Patients (n = 43)	With Perfusion Defect (n = 28 [65%])	Without Perfusion Defect (n = 15 [35%])	p Value*
M/F	18/25	12/16	6/9	0.982
Age (yr)	64.7 ± 9.7	65.9 ± 8.6	62.5 ± 11.4	0.269
Pacing variables				
Pacing threshold (V)†	1.3 ± 0.4	1.2 ± 0.3	1.4 ± 0.6	0.371
Pacemaker ventricular output (V)†	2.8 ± 1.2	2.6 ± 1.4	3.0 ± 1.2	0.325
Duration of pacing (mo)	35.6 ± 41.8	43.9 ± 49.7	20.1 ± 9.6	0.053
Ambulatory ECG				
Percent ventricular pacing	92.8 ± 23.1%	92.9 ± 24.9%	92.8 ± 21.3%	0.181
Exercise testing variables				
Metabolic equivalents (METs) achieved	6.2 ± 2.2	6.5 ± 2.4	5.6 ± 1.7	0.149
Percent target heart rate achieved	90 ± 20%	90 ± 19%	88 ± 20%	0.152

*Comparison between patients with or without perfusion defect. †At pacing pulse width of 0.5 ms. Data presented are number of patients or mean value ± SD. ECG = electrocardiogram; F = female; M = male.

myocardial scintigraphy. There was no significant difference in the mean percent of target heart rate and mean metabolic equivalents achieved during exercise testing between patients with or without a perfusion defect on Tl-201 study (Table 1). The distribution of the perfusion defects is shown in Table 2. Perfusion defects occurred most commonly in an inferior or apical segment with half occurring over both segments (inferior 78% [n = 22], apical 67% [n = 17], septum 21% [n = 6], anterior 7% [n = 2], lateral 3% [n = 1]). Of 48 segments with a perfusion defect, 12 segments (25%) had a fixed defect.

Radionuclide ventriculography. The mean LVEF was 52.4 ± 10.8%. Regional wall abnormalities were present in 63% (27 of 43) of patients. Patients with an abnormal perfusion defect on Tl-201 scintigraphy had a significantly lower LVEF (48.5 ± 9.9% vs. 59.6 ± 8.9%, $p < 0.001$) (Fig. 1) and higher percent of wall motion abnormalities (79% vs. 33%, $p = 0.007$), mainly over the apical region (Fig. 2).

Coronary angiography. Of the 16 patients (57%) with abnormal findings on Tl-201 scintigraphy who underwent coronary angiography, only 3 (19%) had significant coronary artery disease (Table 2). The remaining 12 patients refused angiography.

Discussion

Apart from the therapeutic role of heart rate control, the long-term effect of RV pacing in humans remains unknown. RV apical pacing in itself is nonphysiologic; it is associated with asynchronous electrical activation in which conduction of the electrical wave front initially occurs through slowly conducting myocardial muscle cells rather than through the Purkinje system. In early studies (10–12), ventricular pacing alone led to impaired cardiac systolic and diastolic performance, an effect that may be related to lack of atrioventricular (AV) synchrony. However studies comparing atrial with AV synchronous pacing (2,13–16) also showed a deterioration in myocardial function in the AV synchronous pacing mode. These findings suggest that ventricular pacing alone may lead to impaired cardiac function, although the mechanism is unclear.

Functional myocardial abnormalities in left bundle branch block (LBBB). It is well recognized that perfusion defects occur on exercise myocardial scintigraphy despite the absence of coronary artery obstruction or vasomotion abnormalities. The perfusion defects identified by exercise myocardial scintigraphy may also represent the presence of functional myocardial ischemia. This is particularly true in patients with LBBB (17–20). In the presence of LBBB, exercise myocardial scintigraphy is associated with up to 46% of septal perfusion defects (21). Clinical and experimental studies (22–24) demonstrated that regional blood flow within the septum was reduced in LBBB. This functional ischemia is believed to be due to asynchronous septal contraction associated with abnormal ventricular activation in LBBB. Furthermore, alteration in electrical activation sequence in LBBB may induce asymmetry of left ventricular wall thickness (5), lead to septal wall motion abnormalities and result in global left ventricular dysfunction (20,25).

Effect of abnormal ventricular activation pattern due to RV apical pacing. RV apical pacing frequently produces an LBBB pattern with alteration in myocardium depolarization and contraction. Thus, functional myocardial abnormalities similar to those in LBBB may be present during RV pacing. In animal studies, right atrial pacing resulted in homogeneous perfusion and tissue flow in the left ventricle. However, during RV pacing, myocardial perfusion and blood flow were reduced within the septum (23). Recent experimental studies also have shown that ventricular pacing resulted in regional perfusion defects (6) and reduced blood flow and oxygen consumption over the pacing site (7,8). In animal models (5), chronic asynchronous ventricular activation due to pacing induced reduction of myocardial wall thickness in the segment where the pacing electrode was located. Furthermore, after long-term

Table 2. Distribution of Perfusion Defects in Patients With Abnormal Findings on Thallium-201 Exercise Myocardial Scintigraphy and Coronary Angiography

Pt No./Gender	Age (yr)	Tl-201 Exercise Scintigraphy					Coronary Artery Narrowing		
		Ant	Ap	Inf	Sept	Lat	LAD	LCx	RCA
1/F	66	—	RD	FD	RD	—	0	0	0
2/M	48	—	—	RD	—	—	0	0	0
3/F	72	—	—	RD	RD	—	0	0	0
4/M	42	—	RD	RD	—	—	0	0	0
5/F	79	—	RD	RD	—	—	0	0	0
6/M	61	—	RD	RD	—	—	0	0	0
7/M	53	—	FD	FD	—	—	0	0	0
8/M	69	RD	RD	—	—	—	60%	75%	75%
9/F	83	—	RD	FD	FD	RD	60%	100%	90%
10/M	66	—	—	RD	—	—	60%	50%	50%
11/F	74	—	—	—	RD	—	0	0	0
12/F	66	—	RD	—	—	—	0	0	0
13/F	65	—	FD	RD	RD	—	0	0	0
14/M	65	—	—	RD	—	—	0	0	0
15/F	66	—	RD	—	—	—	0	0	0
16/M	58	RD	—	—	RD	—	0	0	0
17/F	69	—	RD	RD	—	—	ND	ND	ND
18/F	64	—	FD	FD	—	—	ND	ND	ND
19/F	67	—	—	RD	—	—	ND	ND	ND
20/M	77	—	—	FD	—	—	ND	ND	ND
21/M	60	—	FD	RD	—	—	ND	ND	ND
22/F	70	—	RD	RD	—	—	ND	ND	ND
23/F	63	—	FD	FD	—	—	ND	ND	ND
24/M	68	—	—	RD	—	—	ND	ND	ND
25/F	72	—	RD	RD	—	—	ND	ND	ND
26/F	69	—	RD	—	—	—	ND	ND	ND
27/F	71	—	—	RD	—	—	ND	ND	ND
28/M	63	—	—	RD	—	—	ND	ND	ND

Ant = anterior; Ap = apical; FD = fixed defect; Inf = inferior; LAD = left anterior descending coronary artery; Lat = lateral; LCx = left circumflex artery; ND = not done; Pt = patient; RCA = right coronary artery; RD = reversible defect; Sept = septal; Tl = thallium; — = not present; other abbreviations as in Table 1.

RV apical pacing, investigators (3,4,26) have observed myocardial histologic abnormalities that were prevented by using septal ventricular pacing to maintain a normal ventricular activation sequence. Recent animal studies (10) also demonstrated that preserving normal ventricular activation with atrial or proximal RV septal pacing can improve cardiac performance over that obtained with RV apical pacing, despite the presence of AV synchrony.

Tl-201 scintigraphy studies (27,28) in patients without coronary artery disease receiving RV pacing showed perfusion defects over inferoposterior and apical regions. In these studies, these perfusion defects during pacing were also correlated with the presence of T wave inversion over inferolateral leads. This observation suggested that the postpacing T waves abnormalities may represent myocardial ischemia over the site of

Figure 1. Left ventricular ejection fraction on radionuclide ventriculography in patients with or without thallium perfusion defects.

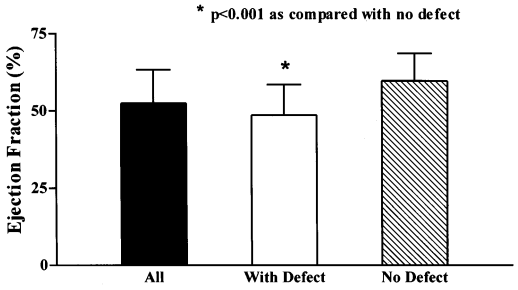
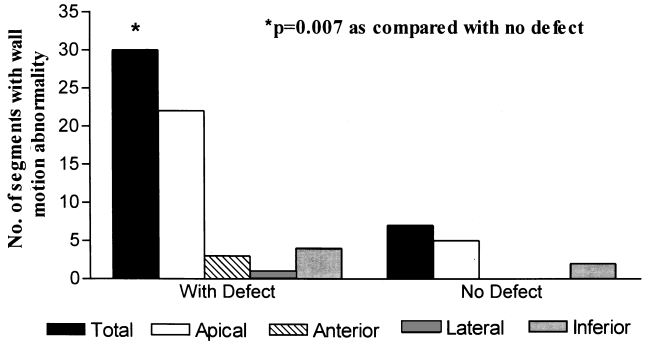


Figure 2. Distribution of wall motion abnormalities on radionuclide ventriculography in patients with or without thallium perfusion defects.



pacing, although the impact of these changes on left ventricular function was not described. However, other studies (2,13) showed that an abnormal ventricular activation sequence during RV apical pacing resulted in impaired left ventricular function as compared with function achieved with atrial or proximal RV septal pacing.

Possible mechanisms of myocardial dysfunction associated with RV apical pacing. As discussed, both animal and human studies suggest that an abnormal ventricular activation pattern due to LBBB or RV apical pacing is associated with alteration of regional myocardial perfusion, structural changes and impaired cardiac performance. Thus, we hypothesize that an abnormal ventricular activation sequence due to RV apical pacing may affect myocardial perfusion, causing functional ischemia and resulting in progressive myocardial dysfunction in the long term.

Our present results support this hypothesis. This is the first systematic study to investigate the clinical significance of the changes in myocardium perfusion and function after long-term ventricular pacing. We found that up to 65% of patients undergoing long-term AV synchronous RV apical pacing had perfusion defects noted on Tl-201 exercise myocardium scintigraphy. As in patients with LBBB, only some of the patients with long-term pacing had perfusion defect on exercise scintigraphy. These perfusion abnormalities observed also cannot be totally accounted for by the presence of underlying coronary artery disease, as only 19% of patients with perfusion defects had significant coronary artery disease.

There was no difference in age, gender distribution and exercise variables between patients with or without perfusion defects. Furthermore, we found no difference in the long-term ventricular pacing threshold and output to suggest that the pacing current and voltage may contribute to the perfusion defect. However, patients with perfusion defects tended to have a longer duration of pacing than those without, which may be an alternative cause of these defects. The similar percent of pacing in each patient suggests that the incidence of these myocardial abnormalities may show a time-dependent or dose-response relation to the pacing burden.

Consistent with previous findings (27,28), we observed the perfusion defects mainly over the inferior and apical segments where the pacing electrode was located. In contrast, LBBB is associated with perfusion defects mainly over the septum (18,19). A similar distribution of myocardial thinning has been demonstrated in LBBB and ventricular pacing (5). Recent animal studies (29) indicated that changes in myocardial blood flow caused by ventricular pacing predict changes in local wall mass. It has been suggested that alteration of ventricular activation causes redistribution of mechanical load within the ventricular wall and may lead to reduction of the blood flow and myocardial wall thickness over the site of early activation. Hence, the difference in the distribution of perfusion abnormalities and myocardial thinning between LBBB and RV apical pacing may be explained by their different activation sequences. Whether these perfusion abnormalities are the cause or consequence of myocardial thinning remains to be established. More important, we demonstrated that these perfusion abnormalities were associated with functional myocardial impairment. Patients with abnormal perfusion defects on Tl-201 scintigraphy had a higher percent of regional wall motion abnormalities, mainly over the apical region, and these resulted in a significant reduction in global LVEF as detected by the radionuclide ventriculogram.

Clinical implications. The present study demonstrated that long-term RV apical pacing with an abnormal ventricular activation pattern was associated with regional myocardial perfusion abnormalities and impairment of cardiac performance in a significant proportion of patients with long-term pacing. Preliminary results of others have shown that the use of alternative pacing sites that preserve the normal ventricular activation sequence, such as the His bundle (30) or RV septum (13), may prevent these myocardial abnormalities. In light of our findings, these new pacing methods may have important application in patients with impaired left ventricular function. Further studies are needed to explore these possibilities.

Study limitations. Although our patients had no clinical evidence of ischemic heart disease, they may have had clinically silent coronary artery disease that contributed to the functional myocardial abnormalities. Because our study was not intended to test the sensitivity and specificity of Tl-201 exercise myocardial scintigraphy in the detection of coronary artery disease, we performed coronary angiography only in those patients with Tl-201 perfusion defects who agreed to undergo angiography. We do not know whether the patients with perfusion defects who did not undergo angiography had a similar incidence of coronary disease. Nevertheless, the very low incidence of significant coronary disease detected in the patients who did undergo angiography suggests that pacing itself can lead to Tl-201 perfusion defects in the absence of significant coronary disease.

Conclusions. Our study demonstrated that RV apical pacing, even in the presence of AV synchrony and rate adaptation, was associated with reduced local myocardium perfusion at the site of pacing as detected by Tl-201 scintigraphy. These perfusion abnormalities may have been due to alteration in myocardial activation and contraction in RV apical pacing, and the incidence of impaired perfusion increased with time. In the long term, these perfusion abnormalities may lead to regional wall motion abnormalities, resulting in impaired global left ventricular function as noted on radionuclide ventriculography in this study. Our results provide further insight into the potential mechanism of myocardial dysfunction after long-term ventricular pacing in humans. Our observations raise the possibility that alternative sites of permanent pacing may preserve the normal sequence of ventricular activation and prevent the perfusion abnormalities and myocardial dysfunction noted in this study.

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