Abnormalities on myocardial perfusion images in patients with pacemaker implantation

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Background: We investigated the effect of a permanent pacemaker implantation on myocardial perfusion, because abnormal accumulation on a myocardial perfusion imaging is observed in patients implanted with PPM.

Methods and Results: The subjects were 56 patients treated by permanent pacemaker (PPM) implantation for bradyarrhythmia. Resting myocardial perfusion images were acquired at 1 hour after intravenous injection of 99mTc-SESTAMIBI (MIBI) and at 6 hours thereafter.

Abnormal accumulation was observed in 11 patients on MIBI early SPECT, and 23 patients on MIBI delayed SPECT. The MIBI delayed SPECT severity score correlated significantly with the paced QRS interval with r = 0.546 (p<0.05), and LVEF with r = -0.673 (p<0.01). In 15 patients who displayed abnormalities on MIBI delayed SPECT, diastolic deceleration time (DDT), regarded as an indicator of microcirculation disorder, was measured with a flow wire. There was a significant correlation between DDT and severity score of the MIBI delayed SPECT with r = -0.874 (P<0.001). Also, DDT correlated significantly with the paced QRS interval and LVEF, respectively, with r = -0.572(P<0.05) and r = 0.54(P<0.05).

Conclusions: Prolonged persistence of a wide QRS complex tends to reduce myocardial perfusion and cardiac function, and cannot deny possibility of the myocardial microcirculation disorder for the cause.

Key Words: Myocardial perfusion imaging, technetium-99m sestamibi SPECT imaging, pacing, left bundle branch block

INTRODUCTION

With the usefulness of pacemaker implantation as a therapy for bradyarrhythmias, such as sick sinus syndrome, and atroventricular block, mortality rates reduced, and vital prognosis improved. As for the influence of pacing mode, physiologic pacing is said to be superior in terms of the vital prognosis and is associated with a lower frequency of thromboembolism (1,2). The ventricular pacing sites used have been primarily the apical region of the right ventricle. However, this pacing method has been noted to cause failure of synchronized left ventricular contraction because of delayed intraventricular conduction with resulting deterioration of cardiac function (3). In right ventricular apical pacing, a chronic change might occur in regional myocardial perfusion (4), and the structure (5) and morphology (6) of myo-cardial cells. Also, the condition of electrical excitation of the left ventricle with right ventricular apical pacing is known to have characteristics similar to that of left bundle-branch block (LBBB) (7).

Technetium-99m sestamibi(MIBI), myocardial perfusion imaging agent, are widely used for detecting coronary artery disease in clinical setting. Almost 90% of myocardial MIBI is bound to mitochondria, and, with its marked capacity for myocardial retention, it is retained over a relatively long time (8-11). However, reverse redistribution of MIBI has been observed in a number of patients, and its usefulness has been called into question. Some investigators have reported that reverse redistribution of MIBI was observed in patients with acute myocardial infarction after direct PTCA(12-14), dilated cardio-
myopathy\(^{(15,16)}\) and mitochondrial myopathy\(^{(17)}\). It has also been reported that the clearance of MIBI from the heart can be used to assess ongoing myocardial damage\(^{(18)}\). Also, it is not uncommon for myocardial perfusion image abnormalities to be observed in patients implanted with permanent pacemaker (PPM).

In the present study, we hypothesized that left ventricular synchronization failure associated with right ventricular pacing elicited circulation failure in the microvasculature leading to a decrease in myocardial perfusion, and tested the validity of this hypothesis.

**METHODS**

**Subjects**

A total of 56 patients (25 females, 31 males) implanted with PPM for bradyarrhythmia (15 patients with atrioventricular block, 35 patients with sick sinus syndrome, 6 patients with bradycardic atrial fibrillation) participated in this study. Mean age was 73.5±9.5 years, ventricular pacing (VVI) was used for 19 patients and physiologic pacing (DDD) for 37 patients, and the mean duration of implantation was 5.08±5.88 years.

The pacing QRS interval in 12-lead electrocardiography was measured for all subjects, and patients with a history of myocardial infarction and coronary artery disease were excluded. The test was preceded by obtaining informed consent, in which the radiation dose was fully explained to patients on the basis of ethical regulations of the center, and their understanding and consent were thereby obtained.

**Resting MIBI SPECT imaging**

Single photon emission computed tomography (SPECT) of myocardial perfusion imaging was performed with an E. CAM gamma camera (Toshiba Co., Ltd). Resting myocardial perfusion images were obtained at 1 hour after intravenous injection of 740MBq MIBI (MIBI early SPECT) and 6 hours thereafter (MIBI delayed SPECT).

A low-medium energy all-purpose collimator (LMEGP) was used. Energy collection was provided by a 10\% window centered on the 141 keV photopeak and matrix 64 × 64. All images were collected over 360 degrees of arc with the acquisition time of 30 seconds in 1 direction for every 6 degree. Image reconstruction was performed by means of a back projection algorithm with Butterworth filter and Ramp-Hanning filter without scatter and attenuation corrections. MIBI is known to be highly accumulated particularly in the liver and the biliary system, so that patients were allowed to consume water and food to prevent scatter due to excretion via the hepato-biliary system.

The image was interpreted by two independent observers who were unaware of the clinical histories of the patients. In the analysis of SPECT images, the left ventricular short axis images were divided into 16 areas in 3 layers in the long axis direction from the apex to the base of the heart, to which the apical area in the long axis image was added to make the total number of 17 areas. These areas were graded by visual evaluation into 4 steps, which were represented by defect scores of 0 (normal uptake), 1 (slight reduced uptake), 2 (moderate reduced uptake), 3 (severe reduced uptake). Reverse redistribution was defined as a decrease of more than 1 in the segmental score at the delayed images. The grading was settled by consensus between the two observers. When they disagreed on the results, the third observer reviewed the images and made the final judgment. The score of 1 or more was defined as abnormal. An abnormal area was demonstrated by the number of abnormal areas (NAA), and severity by the sum of defect scores (SS). Furthermore, cardiac function was determined by electrocardiographically gated MIBI SPECT using the QGS program, which calculated the left ventricular ejection fraction (LVEF [%]).

**Evaluation of coronary microcirculation by DGW**

In 14 patients who showed abnormalities in the right coronary artery area on MIBI delayed SPECT images, the influence of microcirculation disorder was investigated using a Doppler guide wire (DGW) (Volcano Co., Ltd). Percutaneous coronary angiography (CAG) was performed, and the absence of significant stenosis (75\% or higher) was confirmed by visual examination based on the AHA classification. The waveform of stable coronary blood flow velocity in the proximal part of the right coronary artery was measured with DGW 0.014 inches at 12MHz through a guide catheter for PCI, and the diastolic deceleration time (DDT), an indicator of microcirculation disorder, was calculated. In Figure 3, a line was drawn from the peak of diastolic velocity, and time to the point where it crosses the time axis was thereby worked out.

**Statistical analysis**

All data are presented as means ± standard deviation.
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In the statistical analysis, the paired Pearson test was used for comparisons between groups. Linear regression analysis and correlation coefficients were calculated as required. The unpaired Student’s t-test was used for intergroup comparisons. A probability (P value) of less than 0.05 was considered to be significant.

RESULTS
Detection of abnormality on MIBI early and delayed SPECT images
Abnormal accumulation was detected in 11 patients (19.64%) on MIBI early SPECT images, and in 23 patients (41.07%) on MIBI delayed SPECT images, with a significant difference between early and delayed images (P<0.001). Figure 1 shows the NAA detection rate by the myocardial area (right coronary artery: RCA, left anterior descending artery: LAD, left circumflex artery: LCX). NAA was detected in the RCA in 7 patients (12.5%), LAD in 5 patients (8.9%) and LCX in 2 patients (3.6%) on MIBI early SPECT images, and in the RCA in 18 patients (32.1%), LAD in 9 patients (16.1%) and LCX in 2 patients (3.6%) on MIBI delayed SPECT images. In the comparison between MIBI early and delayed SPECT images, significant differences were detected for the RCA and the LAD (P<0.001), but not for the LCX.

Reverse redistribution of MIBI
In the evaluation of MIBI reverse redistribution, MIBI early and delayed SPECT images were compared, and reverse redistribution was considered to be present in an area where the Δ severity score increased by 1 or more. Reverse redistribution was detected in 22 patients, as the mean severity scores were 3.21±2.92 on MIBI early SPECT images and 6.0±4.15 on MIBI delayed SPECT images, with a significant difference between early and delayed SPECT (P<0.001)(Figure 2).

Comparison between MIBI abnormal and normal groups
In MIBI delayed SPECT, the patients were divided into the abnormal group (23 patients) and the normal group (33 patients).

In the abnormal group, the duration of PPM implantation was 7.13±4.17 years, the paced QRS interval 162±28.40ms, and LVEF 52.78±12.46%. In the normal group, the duration of PPM implantation was 3.66±6.59 years, the paced QRS interval 112±28.53ms, and LVEF 69.27±8.23%, with a significant difference between the two groups (Table 1). As to risk factors for myocardial ischemia, no significant differences were detected between these groups in hypertension, hyperlipemia or diabetes mellitus, but smoking was significantly higher in the abnormal group (P<0.01).

Comparison of paced QRS interval and LVEF between MIBI early and delayed SPECT images
On MIBI early SPECT, the severity score did not correlate significantly with the paced QRS interval, while correlating significantly with LVEF with r = -0.714 (P<0.01). On MIBI delayed SPECT, the severity score correlated significantly with the paced QRS interval with r = 0.546 (P<0.05), and with LVEF with r = -0.673 (P<0.01). MIBI delayed SPECT thus correlated with the paced QRS interval (Figure 3).

Comparison with microcirculation
In 15 patients who showed abnormalities on MIBI delayed SPECT, DDT, considered to be an indicator of microcirculation disorder, was measured with a flow wire. DDT correlated significantly with the severity score with r = -0.833 (P<0.01) on MIBI early SPECT, and r = -0.874 (P<0.001) on MIBI delayed SPECT (P<0.001). DDT also correlated significantly with the paced QRS interval and LVEF with r = -0.572 (P<0.05) and r = 0.542 (P<0.05), respectively (Figure 4).

Case report
78 years old, female (Figure 5). Major complaint was loss of consciousness. Clinical history was complete atrioventricular block had been demonstrated by holter electrocardiogram 6 years previously, and a DDD pacemaker was implanted. Current histories have hypertension and diabetes mellitus.

Slightly decreased accumulation was detected in the apical area at rest on MIBI early SPECT, and a wide range of decrease in accumulation was observed from the apical area to the inferior wall on MIBI delayed SPECT images at 6 hours thereafter, which indicated acceleration of washout. CAG was performed for detailed examination, but were not able to detect lesions with significant stenosis (75% or more). DDT, an indicator of microcirculation disorder obtained with a flow wire, was 400 msec in the RCA area, 1,400 msec in the LAD area, and 1,600 msec in the LCX area. The DDT value for the inferior wall area, which showed a decrease in accumulation on MIBI delayed SPECT, was lower than in the
other areas, and this finding of a reverse redistribution of MIBI was considered to suggest a microcirculation disorder.

**DISCUSSION**

In the present study, the usefulness of MIBI delayed SPECT images in the evaluation of myocardial ischemia after PPM therapy was discovered, and its significance was discussed.

Accumulation abnormalities on MIBI delayed SPECT were observed in 41% of patients implanted with pacemakers, and were most frequent in the RCA area, followed by the LAD area. Also, reverse redistribution was observed at a high frequency in the RCA and LAD areas. This phenomenon suggests a decrease in cellular blood flow and a functional abnormality, but is related to electrical stimulation by right ventricular apical pacing and diffuse fibrosis (19). Ohkawa et al. (20) reported that chronic atrioventricular block (AVB) in the majority of elderly patients is based on fibrosis, degeneration and fatty change of unknown cause in the conduction system. It is not unreasonable to speculate that coronary perfusion abnormalities and idiopathic fibrosis are causes of cardiac events following pacemaker implantation, though these possibilities are controversial.

**Paced QRS interval and abnormal MIBI SPECT images**

In the treatment of bradycardia with an artificial pacemaker, right ventricular apical pacing using endocardial lead has commonly been established, but physiologic pacing involving atrioventricular (AV) synchronization is now actively used. However, there is no consensus as to the effect of pacing mode on the morbidity rate for cardiovascular diseases. The prognosis of heart failure patients is known to be unfavorable with a LBBB type conduction disorder when presenting with a wide QRS complex. Shukla et al. (21) evaluated the QRS interval on a scale of 80msec to 220msec and higher in 1,026 patients with chronic heart failure, and their analysis of prognosis showed the mortality rate to be higher for patients with wider QRS complexes. When these patients were divided into two groups based on the paced QRS interval, one with 160msec or higher and the other under 160msec, difference between the groups was detected in the rate of hospitalization due to heart failure, and the wider paced QRS complex. According to Sweeney et al. (22), in patients with normal baseline QRS intervals, if the cumulative ventricular pacing rate in DDDR mode exceeded 40%, the rate of hospitalization due to heart failure increased 2.6 fold as compared with that in patients with cumulative ventricular pacing rates under 40%, even if atrioventricular synchronism was maintained. Comparison of between the abnormal group and the normal group on MIBI delayed SPECT images, significant differences were observed in the duration of implantation, paced QRS interval, LVEF and smoking on normal MIBI images. Moreover, SS on MIBI delayed SPECT images correlated with the paced QRS interval and LVEF. While excitation is transmitted with bilateral symmetry from the apex to the base in patients with normal QRS intervals, excitation is delayed in the lateral wall as compared with the septum in patients with LBBB, to produce a time lag in contraction. In this way, as ventricular pacing induces atrioventricular synchronization failure, a long-term atrioventricular transmission disorder itself apparently impairs hemodynamics and causes abnormalities in myocardial cells.

**The microcirculation**

It is possible to evaluate the coronary microcirculation by the myocardial contrast method involving injection of an echo contrast medium into the disorder artery after reperfusion therapy. Microcirculation disorder in the ischemic area is closely related to the viability of myocardial cells, and the no-reflow phenomenon is considered to be an important finding of impaired anterograde coronary flow (23).

In clinical assessment of coronary flow, the use of DGW provides information about the velocity of coronary blood flow, that is, it allows measurement of several parameters. When DGW is used to assess no-reflow, regurgitation occurs in the early systolic period, and diastolic flow shows a characteristic steep fast waveform in both acceleration and deceleration. Kawamoto et al. (24) reported the mean systolic peak flow rate and DDT in the coronary waveform after reperfusion in acute myocardial infarction correlated closely with improvement of wall movements in the chronic phase, and particularly by using DDT = 600msec as the baseline, it was possible to predict a favorable myocardial viability group with a sensitivity of 86% and specificity of 89%. It shows an association between myocardial viability and coronary microcirculation disorder, and indicates that analysis of the coronary flow waveform is also useful in the evaluation of myocardial viability. In patients with no-reflow, the
myocardial blood pool is considered to be reduced due to coronary microcirculation disorder. Thus, the myocardial blood pool would fill rapidly in the diastolic phase with a resulting rapid elevation of intravascular pressure and rapid decrease in coronary perfusion pressure, and the diastolic flow rate would be sharply reduced (25). Suzuki et al. (26) measured DDT by coronary artery Doppler wire in 33 patients with acute myocardial infarction treated by reperfusion therapy, and compared mismatch with thallium-201(Tl-201) and Iodine-123 BMIPP. In regression analysis, the mismatch score on SPECT images correlated with DDT with \( r = 0.54 \), and it was demonstrated to be significantly higher in the group without an early systolic regurgitation waveform, from which it was considered to be a useful indicator of myocardial salvage in early evaluation.

From research on washout concerning MIBI and mitochondria, MIBI early SPECT image is considered to represent blood flow, and MIBI delayed SPECT images is mitochondrial disorder, respectively (27, 28). In this study, a significant correlation was detected between the severity score on MIBI delayed SPECT and DDT in regression analysis, which suggested that myocardial mitochondrial disorder developed due to the influence of the coronary microcirculation. Regression analysis also revealed a significant correlation between the paced QRS interval and DDT. This was considered to indicate that nonsynchronous electrical excitation of the left ventricle due to right ventricular apical pacing contributed to an adverse effect. The same characteristics as those of LBBB were observed in the path of left ventricular electrical excitation elicited by right ventricular apical pacing. It indicated that abnormality occurred in ventricular synchronization and hemodynamics, with the resulting development of a coronary microcirculation disorder. However, in the present case, the MIBI defect area was intense in the RCA and LAD areas of the left ventricle. From this finding, it could not be ruled out that the cells themselves were strongly affected by electrical stimulation in pacing and had changed. However, Lenegre et al. (19) detected myocardial infarction in 29 cases and diffuse fibrotic lesions in 6 cases among 62 AVB cases. Kneiriem et al. (29) considered this to have been caused by a coronary perfusion abnormality, and, reporting increased fibrosis in both ventricles, inferred that a diffuse fibrotic lesion was caused by post-healing myocarditis. Nonetheless, it is unclear how numerous fibrotic lesions on histological observation are related to acceleration and defects of MIBI washout. More study cases are necessary to elucidate underlying cause.

**CONCLUSIONS**

The results of the present study have clinical significance for elucidating the causes of myocardial damage with PPM implantation therapy. It is possible to reduce the risk by altering the therapeutic strategy by early detection of myocardial abnormalities. Long-term persistence of a wide QRS interval tends to reduce myocardial blood flow and cardiac function, and myocardial microcirculation disorder as a possible cause of this tendency cannot be ruled out.

**REFERENCES**

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Figure 1. Comparison of regional number of abnormal areas (NAA) between MIBI early SPECT and MIBI delayed SPECT.
*: $P<0.001$, ns: not significant.
Figure 2. Comparison of severity score between MIBI early SPECT and MIBI delayed SPECT. Data are expressed as mean ± SD. early: MIBI early SPECT. delay: MIBI delayed SPECT. *: P<0.001

Figure 3. Correlations between severity score of MIBI delayed SPECT and paced QRS width (A), severity score of MIBI delayed SPECT and LVEF (B). SSd: Severity score of MIBI delayed SPECT. LVEF: Left ventricular ejection fraction.
Figure 4 Correlations of Diastolic deceleration time (DDT) with SSe (A), SSd (B), paced QRS width (C), LVEF (D).

SSe: severity score of MIBI early SPECT. SSd: severity score of MIBI delayed SPECT.
LVEF: Left ventricular ejection fraction.

Figure 5 Case of atrioventricular (AV) block with permanent pacemaker, 52-year-old, female