Predicting the effects on patients with dilated cardiomyopathy of β-blocker therapy, by using iodine-123 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) myocardial scintigraphy

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We examined whether the iodine-123 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) myocardial scintigraphy was useful for predicting the treatment response to β-blocker in patients with dilated cardiomyopathy (DCM).

Sixteen patients with DCM were studied. BMIPP single photon emission computed tomography (SPECT) was performed before β-blocker therapy. The count ratio of the heart (H) to the upper mediastinum (M) (H/M ratio) was calculated. Several measurements including the BMIPP H/M ratio before the administration of metoprolol were retrospectively compared among the 10 “good responders” (showing improvement by at least one NYHA class or an increase in the ejection fraction of ≥0.10, 6 months after the start of the drug therapy) and the 6 “poor responders.” The bull’s eye map of BMIPP was divided into 17 areas. Each segmental score was analyzed quantitatively by means of a two-point scoring system (good uptake ≥67%, poor uptake <67%). The total score was regarded as the uptake score.

The H/M ratio was significantly higher in the good responders than in the poor responders (2.41 ± 0.24 vs. 1.86 ± 0.17 p < 0.01). There were no significant differences between the two groups in any other variable data at entry.

The uptake score was also a good index for predicting the therapeutic effect. When a relative uptake of 67% or higher was scored as 1, uptake scores of 9 to 17 corresponded to good responses (sensitivity = 100%, specificity = 100%, accuracy = 100%, positive and negative predictive value = 100%).

Although the number of patients studied is small, our results suggest that BMIPP myocardial scintigraphy can predict the response to a β-blocker in patients with DCM.

Key words: dilated cardiomyopathy, β-blocker therapy, iodine-123 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP)

INTRODUCTION

Beta (β)-blocker therapy for dilated cardiomyopathy (DCM) has been used for the past 23 years. Although the efficacy of this therapy has been established, some DCM patients do not respond to it. Few studies have investi-
tigraphy to determine whether myocardial fatty acid uptake evaluated by BMIPP SPECT is useful for predicting the response of DCM patients to β-blocker therapy.

SUBJECTS AND METHODS

Sixteen patients (11 males and 5 females) with DCM were studied. The patients ages ranged from 33 to 77, with a mean of 57 years. In 13 of the 16 patients coronary angiography was performed, and no significant coronary lesions were detected. In the remaining 3 patients, neither the case history nor electrocardiographic findings suggested ischemic heart disease.

1. Administration of metoprolol tartrate as a β-blocker

Administration of metoprolol tartrate was started the day after BMIPP myocardial scintigraphy was performed. The initial dose was 2.5 mg/day or 5 mg/day. The dose was gradually increased at 7-day intervals, and the maintenance dose was 20 mg/day.

2. BMIPP myocardial scintigraphy

BMIPP myocardial scintigraphy was performed 7 to 14 days after acute heart failure was stabilized.

SPECT was performed once 15 minutes after 111 MBq of 123I-BMIPP (Nihon Medi-Physics, Hyogo, Japan) purity exceeded 95% was intravenously injected at rest in the morning after the patient fasted over night. All 16 patients underwent BMIPP SPECT imaging at rest with a rotating gamma camera equipped with a low-energy, general-purpose collimator (Starcam 4000XRT: General Electric, Milwaukee, USA). The SPECT image sequences consisted of 32 projections with a 64 × 64 matrix acquired for 30 seconds over a 180° circular orbit, from left posterior oblique 45° to right anterior oblique 45°. The projection images were processed with a low-pass (Butterworth) filter. Standard backprojection with a ramp filter was performed.

There was no overlap of the left lobe of the liver and the heart in the BMIPP SPECT image and attenuation correction was not applied.

3. H/M ratio and uptake score

We selected one projection image of the anterior planar image derived from 32 projections for the SPECT image and in this planar image the regions of interest (ROIs) were situated on the overall areas of the left ventricular myocardium. Another ROI (3 × 3 pixels in size) was placed over the upper mediastinal area. The heart-to-mediastinum ratio (H/M) was calculated from the 123I-BMIPP uptake as a fraction of the mean counts per pixel in the myocardium divided by those in the mediastinum.

The degree of BMIPP accumulation was quantified as the uptake score.11,12

The bull’s-eye map of the BMIPP was divided into 17 areas (Fig. 1), and the BMIPP accumulation in the area showing the peak count in each patient was regarded as 100%. The accumulation of 123I-BMIPP in each area was graded on a scale of 0 to 1 by the following scoring system. The cut off level of relative accumulation was determined by ROC analysis. A relative accumulation value the cut off level or higher was given 1 point and that less than the cut off value was given 0 point. The total score for the 17 areas was regarded as the uptake score.

4. Echocardiography

All 16 patients underwent M-mode and two dimensional echocardiography with an ultrasonoscope (SS-H160A, SS-H260A, Toshiba, Tokyo, Japan). From the echocardiographic data, the left ventricular end-diastolic dimension (LVDd) and the left ventricular end-systolic dimension (LVDs) were calculated. The percent fractional shortening (%FS) and ejection fraction (EF) (%) were regarded as indicators of the severity of cardiac dysfunction. The calculation of each of these parameters was based on the standards prepared by the American Society of Echocardiography.

5. Evaluation of treatment response

1) Patients were evaluated according to the New York Heart Association (NYHA) classification of cardiac patients. On echocardiography, FS (%), EF (%), LVDd and LVDs were acquired.

2) These values were measured before and 6 months after the β-blocker administration was started. The follow-up period was 6 months.

3) According to the degree of improvement in NYHA functional class and left ventricular ejection fraction, the patients were classified into two groups: "good responders" had an improvement of at least one functional class or an increase in the ejection fraction of ≥0.10, and the "poor responders" were without such an improvement after β-blocker therapy.6

6. Statistical analysis

A two-factor repeated measures analysis of variance was used for paired data (comparison of echocardiographic data and heart rate, systolic blood pressure, cardio-thoracic ratio (CTR) between before and 6 months after the start of β-blocker therapy). The H/M ratio, FS, EF, LVDd, LVDs, heart rate, systolic blood pressure and CTR value before the β-blocker administration for the two patients

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### Table 1  Patient profile and noninvasive variables data

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P1*  Group 1: Differences between base and after 6 months
P2** Group 2: Differences between base and after 6 months
P3*** Differences between 2 groups before β-blocker administration
5*   Excluded from statistical analyses
groups were compared by means of the unpaired t-test. The cut-off value of the uptake score was determined by ROC analysis. The diagnostic accuracy was determined from the area under the receiver operating curve (ROC) \((A_z)\). The \(A_z\) values were used to analyze the statistical significance of the differences by means of the paired t-test. Fisher’s exact probability test was used to examine differences between medications for the two patient groups. Probability \((p)\) values of \(< 0.05\) were considered significant.

**RESULTS**

Six of the 16 DCM patients showed both symptomatic and objective improvement, whereas 6 patients showed symptomatic deterioration. The remaining 4 patients showed an improvement in functional class without an increase in

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Fig. 2 123I-BMIPP myocardial SPECT planar images. A: Case 2 in Group 1, H/M ratio 2.24, B: Case 6 in Group 2, H/M ratio 1.82.

Fig. 3 Bull’s eye display of 123I-BMIPP myocardial SPECT. A: Case 2 in Group 1; BMIPP accumulation was relatively maintained. B: Case 6 in Group 2; BMIPP accumulation was markedly reduced.

Fig. 4 Comparison of true and false positive rate using different cut-off level of relative uptake by ROC analysis. —△— threshold at 75%, —○— threshold at 67%, —□— threshold at 60%.

the ejection fraction \(\geq 0.10\). Accordingly, 10 of the 16 patients were classified as good responders to the β-blocker therapy (Group 1), and the remaining 6 patients as poor responders (Group 2) (Table 1). Acute heart failure was observed in 7 patients among good responders and all 6 poor responders.

**Cardiac functions**

In Group 1, the FS was increased from 16.1 ± 4.4% to 23.1 ± 5.1% \((p < 0.01)\) and the EF was increased from 33.1 ± 8.5% to 44.8 ± 9.1% \((p < 0.01)\). The LVDD values were improved from 62.4 ± 7.0 mm to 55.1 ± 9.3 mm \((p < 0.01)\), and the LVDs values were reduced from 51.8 ± 8.1 mm to 44.8 ± 9.9 mm \((p < 0.01)\). The CTR was reduced from 58.1 ± 8.9% to 52.4 ± 8.4% \((p < 0.05)\).

In Group 2, one patient (Case 5) died of progressive heart failure 2.5 months after the start of β-blocker therapy. The statistical analysis was performed in 5 patients, being excluded Case 5. The FS was reduced from 14.4 ± 2.0% to 10.8 ± 1.9% \((n = 5, p < 0.05)\). There were no significant changes in the EF \((30.4 ± 4.8\% \text{ vs. } 25.4 ± 2.6\%) \((n = 5, ns)\). There were no significant changes in the LVDD \((66.4 ± 5.3\ mm \text{ vs. } 69.8 ± 6.9\ mm) \((n = 5, ns)\). The LVDs values were increased from 55.6 ± 5.4 mm to 61.8 ± 5.4 mm \((n = 5, p < 0.05)\). The CTR changed little \((55.4 ± 6.3\% \text{ vs. } 55.2 ± 2.6\%) \((n = 5, ns)\).

**H/M ratios**

The H/M ratio in Group 1 was significantly higher than that in Group 2 \((2.41 ± 0.24 \text{ vs. } 1.86 ± 0.17 \ p < 0.01)\) at the start of the study (Table 1, Fig. 2). There were no significant differences between Group 1 and Group 2 at the start in terms of heart rate, systolic blood pressure, CTR, FS, EF,
LVDd or LVDs (Group 1: 10 patients, Group 2: 5 patients excluding Case 5).

**BMIPP uptake scores:**

Bull’s eye display of $^{123}$I-BMIPP relative myocardial uptake in groups 1 and 2 are shown in Fig. 3.

ROC analysis indicated that the optimal cut-off level of relative accumulation was 67%. Groups 1 and 2 could be completely separated by the uptake score with a cut-off level of 67% (Fig. 4).

When a relative uptake of 67% or higher was scored as 1, uptake score of 9 to 17 were good responders (sensitivity = 100%, specificity = 100%, accuracy = 100%, positive and negative predictive value = 100%).

**Blood chemistry**

The serum glucose, triglyceride and total cholesterol concentrations, which may influence fatty acid uptake in the myocardium, were similar in Groups 1 and 2 before β-blocker treatment (glucose 95.1 ± 10.8 mg/dl vs. 107.4 ± 27.7 mg/dl; triglyceride 95.5 ± 52.4 mg/dl vs. 94.6 ± 15.6 mg/dl; total cholesterol 167.9 ± 28.7 mg/dl vs. 199.8 ± 31.6 mg/dl, respectively; p = ns).

No significant difference was observed between the two groups in the incidence of acute heart failure.

**Medications**

Concerning concurrently prescribed agents, diuretics were prescribed to all 16 patients. ACE inhibitors were prescribed to 9 of the 10 patients in Group 1 and to 5 of the 6 patients in Group 2. Nitrile agents were prescribed to 5 of the 10 Group 1 patients and to 2 of the Group 2 patients. Calcium antagonists were prescribed to 4 of the patients in Group 1. None of the patients in Group 2 received Ca antagonists. Nicorandil was administered to 2 Group 1 patients and 1 Group 2 patient. Digitalis was prescribed for 4 Group 1 patient and 2 Group 2 patients. Although the doses of diuretics varied somewhat, the doses of ACE inhibitors, nitrile agents, Ca antagonists and nicorandil were not changed during follow-up.

There were no significant differences between the two patient groups in any of the medications.

**DISCUSSION**

**Prediction of response to β-blocker therapy in DCM**

Although the efficacy of β-blocker therapy for DCM patients has been established, some patients do not respond to this therapy,2-6 and the patient factors which contribute to the response status are not yet clear.7 It was reported that patients with mild fibroinogenesis of the cardiac muscle detected on myocardial biopsy responded to β-blocker therapy but those with severe fibroinogenesis did not.6 It is difficult to perform myocardial biopsy in all DCM patients before the start of β-blocker therapy. Some patients showing increased heart rate before administra-

tion responded to β-blocker therapy,1,14,15 but other investigators have indicated that heart rate before administration was not related to treatment response.5,6 It has been reported that patients with a increased systolic blood pressure, increased left ventricular end-diastolic pressure or prolonged isovolumetric relaxation period respond to β-blocker therapy,16 but cardiac catheterization is invasive. Still other studies have reported that systolic blood pressure before administration was not related to treatment response.6 Improvement was obtained in patients with increased systolic blood pressure soon after β-blocker administration.17

Treatment response has not yet been predicted based on thallium or $^{123}$I-BMIPP myocardial scintigraphy findings. There are two reports about the prediction of the effects of β-blocker therapy on DCM patients by means of I-123 metaiodobenzylguanidine (MIBG) imaging. Suwa et al. reported that MIBG imaging can predict the effect of β-blocker therapy before the start of treatment.18 Fukuoka et al. reported that MIBG imaging can’t predict the effect of β-blocker therapy before the start of treatment but can predict the improvement at 1 month.19

The usefulness of BMIPP myocardial scintigraphy for predicting the response to β-blocker therapy in patients with DCM had not yet been investigated; we demonstrated that this method is useful for predicting treatment response (especially for predicting nonresponders) to β-blocker therapy. In patients in whom BMIPP accumulation is relatively maintained, β-blocker therapy would be expected to be more effective. The H/M ratio was significantly higher in the good responders than in the poor responders (2.41 ± 0.24 vs. 1.86 ± 0.17 p < 0.01) at the baseline. We found that the BMIPP uptake score might be a clinically useful method to predict the response of DCM patients to β-blocker therapy. When using a cutoff value of 67% for %uptake, BMIPP SPECT imaging is good for predicting the response to β-blocker therapy.

In the present DCM patient series, there were no significant differences between the good responders and poor responders in heart rate, systolic blood pressure, CTR, FS or EF before treatment. These findings are consistent with those reported by Yamada et al.8 and Eichhorn et al.16

The results of this initial study of a relatively small patient group suggest that BMIPP myocardial scintigraphy can predict the response of patients with DCM to β-blocker therapy. Since BMIPP myocardial scintigraphy reflects myocardial mitochondrial function and adenosine 5'-triphosphate (ATP) levels,9,10 the findings of the BMIPP myocardial scintigraphy before β-blocker administration may reflect the volume of the cardiac muscle that can respond to treatment.

**Reduced myocardial uptake of $^{123}$I-BMIPP in DCM**

BMIPP is a preparation used for imaging myocardial fatty
acid metabolism. Because 123I-BMIPP is a side chain fatty acid, and accumulates in the cardiac muscle for a prolonged period, this agent is the radiopharmaceutical appropriate for SPECT imaging and clear SPECT images can be obtained with it. It has been shown in animal experiments that myocardial uptake of 123I-BMIPP is reduced to the same extent as the myocardial mitochondrial function is impaired. These studies reflect the acute myocardial damage, but no animal experimental study of chronic myocardial damage has been reported. It has also been shown that the myocardial uptake of 123I-BMIPP is reduced in patients with DCM. Abnormalities in myocardial energy metabolism have been reported in patients with DCM. Mitochondrial dysfunction, reduced ATP production, disorders of the cell membrane and fatty acid-binding protein disorder have been reported. Abnormalities in fatty acid metabolism were also found in some cases.

Mody et al. reported that in DCM the disturbed myocardial metabolism included glucose metabolism.

Limitation of this study
A limitation of this study is that comparison with thallium scintigraphy as a blood flow tracer was not made. A comparison of BMIPP and thallium scintigraphy is considered to be necessary, because it is important to learn whether BMIPP scintigraphy add information to thallium scintigraphy as a tracer study. In addition to this preliminary retrospective study, another prospective trial approaching the above problems will be needed to confirm our results.

CONCLUSION
In conclusion, BMIPP myocardial scintigraphy is noninvasive, and provides clear images. Our present findings indicate that BMIPP SPECT can be used to predict the response of DCM patients to β-blocker therapy. If nonresponders can be predicted prior to treatment, it may be a guideline for the early selection of other treatments including heart transplantation.

REFERENCES
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