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Myocardial clearance of I-123 metaiodobenzylguanidine in dilated cardiomyopathy

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We present the results of sequential imaging studies conducted in two patients with dilated cardiomyopathy whose responses to long-term beta-blocker therapy differed. We evaluated the time course of the myocardial clearance and the heart to upper mediastinal ratios of I-123 metaiodobenzylguanidine (MIBG) scintigraphy. In the first patient, the left ventricular ejection fraction as well as the clinical symptoms were improved by long-term beta-blocker therapy with a concurrent normalization of the myocardial clearance and the heart to upper mediastinal ratio of I-123 MIBG scintigraphy. The myocardial clearance and the upper mediastinal ratio of I-123 MIBG indicated no improvement in the second patient, and the left ventricular function did not change. The myocardial clearance and the heart to upper mediastinal ratio of I-123 MIBG scintigraphy were useful in evaluating the efficacy of long-term beta-blocker therapy in patients with dilated cardiomyopathy.

Key words: I-123 MIBG scintigraphy, dilated cardiomyopathy, beta-blocker

INTRODUCTION

In 1975, Waagstein et al.[1] reported that the chronic administration of a beta-adrenergic receptor blocker may be beneficial in treating patients with congestive cardiomyopathy. Previous studies[2,3] have shown that cardiac norepinephrine is depleted in heart failure. The myocardial clearance (MC) of I-123 metaiodobenzylguanidine (MIBG), an analog of norepinephrine that shares the same mechanisms of uptake, storage and release,[4] is increased in heart failure. In addition, the heart to upper mediastinal ratio (H/M) of I-123 MIBG in patients with dilated cardiomyopathy (DCM) is lower than that of normal control subjects, and is correlated with the left ventricular ejection fraction,[5] but the changes in I-123 MIBG images and in these quantitative parameters after beta-blocker therapy in patients with DCM are still unclear. We therefore documented the myocardial uptake patterns and the quantitative parameters of I-123 MIBG scintigraphy after beta-blocker therapy in two patients with DCM.

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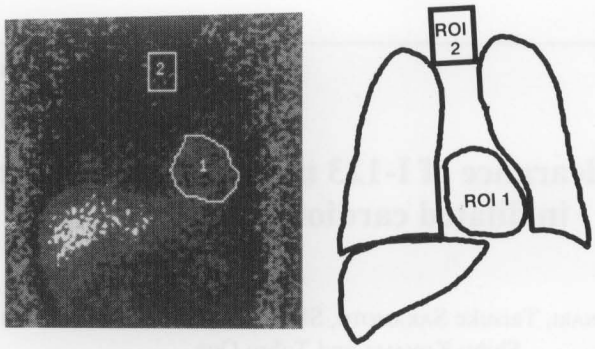
CASE REPORTS

Scintigraphic Methods of Thallium (Tl)-201 and I-123 MIBG

Single photon emission computed tomography (SPECT) was performed with a single head gamma camera (GCA-901A/HG, Toshiba) equipped with a low energy general purpose collimator centered on both the 70 keV photo peak with a 20% window for Tl-201 and the 159 keV photo peak with a 20% window for I-123. The crosstalk correction method was not used. 111 MBq of I-123 MIBG was first injected intravenously and 111 MBq of Tl-201 was injected 15 min later. Thirty-six projections were obtained with a 128 × 128 matrix for 30 seconds each in a 180° arc. The initial and delayed (4 hour) images were recorded simultaneously in the scintigraphic studies. We measured H/M for the I-123 MIBG delayed images and the MC[6,7] to evaluate cardiac sympathetic function, as shown in Fig. 1. Normal values for H/M and MC were obtained from 18 normal Japanese volunteers (9 men and 9 women, mean age; 48 ± 15 years) at our hospital by dual-isotope scintigraphy with Tl-201 and I-123 MIBG. The



$$H/M = \frac{H/A1}{M/A2} \qquad MC = \frac{\left\{\left[H - \frac{(A1 \times M)}{A2}\right]_{early} - \left[H - \frac{(A1 \times M)}{A2}\right]_{delayed}\right\}}{\left[H - \frac{(A1 \times M)}{A2}\right]_{early}}$$

ROI 1
H = Myocardial Counts
A1 = Area of Myocardium

ROI 2
M = Upper Mediastinal Counts
A2 = Area of Upper Mediastinum

Fig. 1 Right panel shows the frontal planar image of I-123 MIBG delayed scan in case 2. ROI number 1 encloses the heart and ROI number 2 encloses the upper mediastinum. The left panel shows the schema of the ROI position. H/M and MC were calculated from two formulas shown.
MIBG: metaiodobenzylguanidine, H/M: heart to upper mediastinal ratio, MC: myocardial clearance, ROI: region of interest.

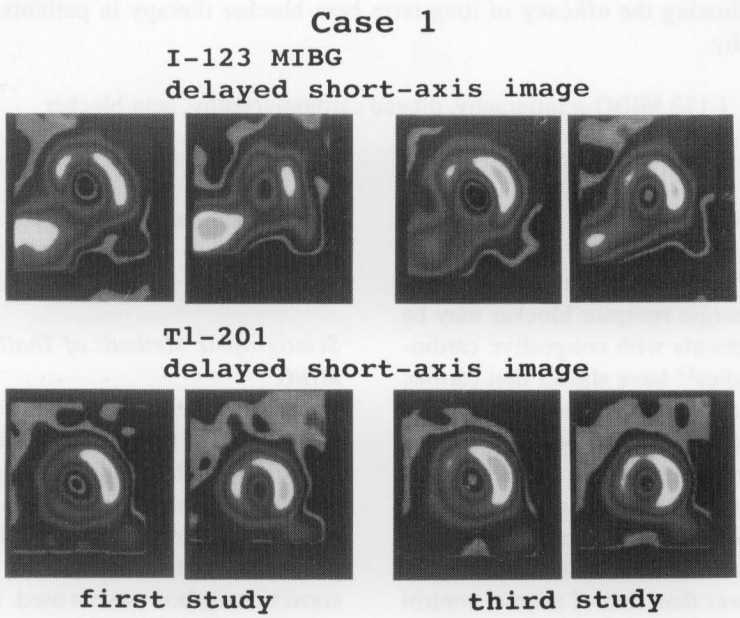


Fig. 2 Upper four panels show I-123 MIBG delayed short-axis SPECT images of the first and third studies in case 1. The areas of reduced uptake of I-123 MIBG were revealed in the anterior, septal and inferior wall in the first study. In the third study, those areas show little change but the liver accumulation is decreased. The lower four panels show Tl-201 delayed short-axis SPECT images of the first and third studies in case 1. The areas of reduced uptake of Tl-201 are about the same compared with those of I-123 MIBG images and serial changes are not revealed.
SPECT: single photon emission computed tomography.

mean value for H/M was 3.4 ± 0.5 and that for MC, 32.5 ± 6.5%. The volunteers had normal physical status, the electrocardiograms and echocardiograms. A difference in quantitative scintigraphic parameters of more than 10% from previous values was interpreted as clinically significant in the present study.

Table 1 Serial changes of scintigraphic parameters in case 1

Scintigraphic study	H/M	MC (%)	LVEF (%)		
			rest	50 W	75 W
Initial	2.6	42.2	41	41	36
Second (1.5 M)	2.5	54.0	46	53	47
Third (15 M)	3.0	27.1	51	57	58

H/M: heart to upper mediastinal ratio; MC: myocardial clearance; LVEF: left ventricular ejection fraction; M: months; W: watt.

Table 2 Serial changes of scintigraphic parameters in case 2

Scintigraphic study	H/M	MC (%)	LVEF (%)		
			rest	50 W	75 W
Initial	2.2	35.8	46	(–)	(–)
Second (1.5 M)	2.1	42.7	(–)	(–)	(–)
Third (14 M)	2.2	48.6	46	47	(–)

H/M: heart to upper mediastinal ratio; MC: myocardial clearance; LVEF: left ventricular ejection fraction; M: months; W: watt.

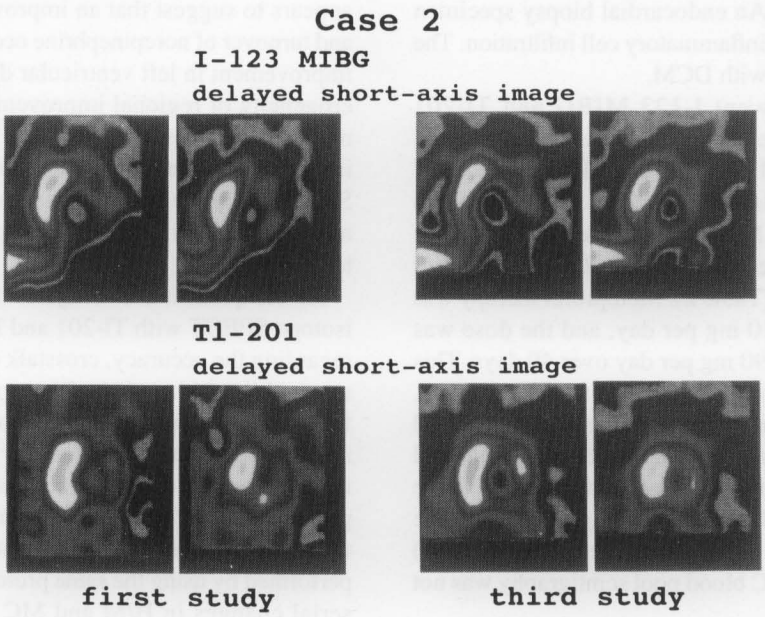


Fig. 3 Upper four panels show I-123 MIBG delayed short-axis SPECT images of the first and third studies in case 2. The areas of reduced uptake of I-123 MIBG were revealed in the anterior, lateral and inferior walls in the first study. The third study showed little change in those areas. The lower four panels show Tl-201 delayed short-axis SPECT images of the first and third studies in case 2. The areas of reduced uptake of Tl-201 are about the same compared with those of I-123 MIBG images and serial changes are not revealed.

Case 1

A 58-year-old Japanese man was admitted to our hospital with a 3-year history of exertional dyspnea. There was no history of hypertension or cardiovascular disease. Three years earlier electrocardiogram had revealed sinus rhythm with a left bundle branch block. The left ventricular diastolic dimension (LVDd) was 59 mm on the echocardiogram. His coronary arteriogram was normal, but left ventriculography revealed a decrease in the left ventricular ejection fraction (LVEF; 36%). Evaluation of a biopsy specimen of the endocardium revealed no inflammatory cell infiltration. The diagnosis was DCM.

I-123 MIBG scintigraphy and Tl-201 myocardial scintigraphy were performed before starting beta-blocker therapy. A reduction in I-123 MIBG uptake was found in the interventricular septum and inferior wall. Similar defects were noted on Tl-201 imaging (Fig. 2). The H/M was decreased (2.6), and the MC was increased (42.2%) (Table 1). The LVEF measured at rest by Tc-99m red blood cell (RBC) blood pool scintigraphy was 41%. Changes in LVEF observed during exercise showed a poor response (Table 1). After these baseline studies, single therapy with metoprolol was started at 5 mg per day, with the dose gradually increased to 60 mg per day over 40 days. The metoprolol dose has since been maintained at 60 mg per day.

A second set of scintigraphic studies was performed 1.5 months after starting metoprolol. The H/M showed a slight decrease (2.5) and the MC a slight increase (54.0%). The LVEF was increased to 46% at rest, and the response to exercise was improved (Table 1).

A third scintigraphic study was performed 15 months after the first scintigrams. The areas of reduced uptake of I-123 MIBG and Tl-201 showed little change from the first study (Fig. 2), but the H/M had increased to the lower limit of the normal range (3.0), and the MC had signifi-

cantly decreased (27.1%). The LVEF had improved to 51% at rest. The response to exercise showed further improvement (Table 1).

Case 2

A 45-year-old Japanese man was admitted to our hospital because of exertional dyspnea which had progressed over 2 years. No history of hypertension or cardiovascular disease was elicited. The LVDd measured 62 mm on the echocardiogram. A coronary arteriogram showed no significant stenosis, and the LVEF was 41% as measured by left ventriculography. An endocardial biopsy specimen showed no evidence of inflammatory cell infiltration. The patient was diagnosed with DCM.

The patient underwent I-123 MIBG and Tl-201 scintigraphic studies before starting beta-blocker. Areas of reduced uptake of I-123 MIBG and Tl-201 were noted in both the inferior and lateral walls (Fig. 3). The H/M was reduced (2.2), and the MC was increased (35.8%). The LVEF at rest measured by Tc-99m RBC blood pool scintigraphy was 46% (Table 2). Metoprolol therapy was initiated at a dose of 10 mg per day, and the dose was gradually increased to 90 mg per day over 40 days. This 90 mg dose of metoprolol has been maintained since then.

A second set of scintigraphic studies was performed about 1.5 months after starting the beta-blocker. Enalapril was added to the metoprolol regimen in that period. In the second study, the H/M was without significant change (2.1), and the MC was slightly increased (MC = 42.7%) (Table 2). Tc-99m RBC blood pool scintigraphy was not performed.

A third scintigraphic study was performed 14 months after the initial study. The areas of reduced uptake of I-123 MIBG and Tl-201 showed little change from the initial results (Fig. 3). The H/M remained unchanged (2.2), and the MC was further increased (48.2%). The LVEF was 46% and showed no improvement as compared with the initial findings (Table 1). The clinical symptoms of this patient did not improve.

DISCUSSION

The sympathetic nervous system is important in the initial compensatory mechanisms that support the function of the failing heart. Relevant to this point is the finding that patients with heart failure have high circulating levels of norepinephrine.[8,9] In contrast, patients with heart failure show a depletion of cardiac norepinephrine.[2,3] A previous study[10] reported that this was the result of a chronic increase in norepinephrine turnover and of a reduced efficiency of norepinephrine reuptake and storage. Therefore, in the initial I-123 MIBG scintigrams of both of our patients, the H/M, which shows the global left ventricular reuptake and storage of myocardial norepinephrine, was low, and the MC, which shows norepinephrine turnover, was increased.

The long-term administration of a beta-blocker to patients with heart failure often leads to a reduction in the plasma level of norepinephrine together with hemodynamic improvement.[11] The potential mechanisms for the improvement of the left ventricular dysfunction after a beta-blocker in DCM include a protection against catecholamine toxicity,[12] an increase in beta-adrenergic receptors,[13] and a change in the myocardial receptor-G protein-adenylate cyclase complex.[14] H/M and MC in the third scintigraphic study of case 1 were normalized with an improvement in left ventricular dysfunction. This appears to suggest that an improvement in the reuptake and turnover of norepinephrine occurred together with the improvement in left ventricular dysfunction, but no heterogeneity of regional improvement in sympathetic innervation was observed on the I-123 MIBG scintigraphic images acquired after the long-term beta-blocker therapy. Such therapy may change the reuptake and turnover of norepinephrine in global cardiac sympathetic nervous terminals.

As the quantitative analysis of I-123 MIBG in dual-isotope SPECT with Tl-201 and I-123 includes an issue regarding the accuracy, crosstalk correction methods are required.[15,16] Although dual-isotope SPECT was also performed in our study, crosstalk correction methods were not applied, so that the values for H/M and MC obtained in the present study cannot be compared with those in the previous study.[17] Nevertheless, since the serial dual-isotope scintigraphic examinations in the present study were performed by using the same protocol, we believe that the serial changes in H/M and MC were evaluated sufficiently.

It has been reported that, in patients with heart failure, H/M is a more useful predictor of mortality, than the LVEF, cardiothoracic ratio or the echocardiographic index,[18] but the clinical value for MC of I-123 MIBG in patients receiving a beta-blocker for long periods is unknown. Momose et al.[6] and Yamamoto et al.[19] noted that some patients with DCM show a decrease in MC accompanying the improvement in LVEF. Our first patient also presented with a decrease in MC and an improvement in the LVEF, whereas our second patient did not, and his LVEF did not improve. In addition, although the LVEF in case 1 showed slight improvement in the second scintigraphic study after he had received a beta-blocker for 1.5 months, his MC became worse. These results appear to suggest that the long-term changes in the MC of I-123 MIBG in patients with DCM who are receiving a beta blocker reflect an improvement in left ventricular function, but cautious evaluation is needed according to the changes in the MC of I-123 MIBG for short-term beta-blocker therapy.

In conclusion, LVEF with Tc-99m RBC blood pool scintigraphy was useful in assessing the efficacy of long-term beta-blocker therapy in patients with DCM, whereas MC as well as H/M measured by I-123 MIBG scintigraphy

were useful in evaluating improvement in the cardiac sympathetic function and the mechanical function of the heart.

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