

Regional cardiac sympathetic reinnervation in transplanted human hearts detected by ^{123}I -MIBG SPECT imaging

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The purpose of this study was to assess the regional cardiac sympathetic reinnervation late (≥ 1 year) after heart transplantation (HTX) by means of ^{123}I -MIBG (MIBG) scintigraphy. Eight patients with a pretransplantation diagnosis of idiopathic dilated cardiomyopathy underwent MIBG scintigraphy more than one year after HTX. The presence or absence of regional MIBG uptake was evaluated in each SPECT image, and global MIBG uptake was semi-quantitatively assessed by the heart to mediastinum ratio (H/M). Five of 8 patients had visible MIBG uptake in both planar and SPECT images (PU group), whereas 3 of 8 patients had no uptake, 2 of them after a period of 2 years, and one of them as long as 5 years after HTX, respectively (NU group). Positive regional MIBG uptake involved the basal anterior region in all 5 patients, the basal septal region in 4 patients, the basal lateral region in 3 patients and the basal posterior region in 1 patient. The H/M value was 1.24 ± 0.10 in the PU group and 1.09 ± 0.03 in the NU group. In conclusion, MIBG SPECT can detect regional sympathetic reinnervation, indicating that basal septal and lateral regions next to the basal anterior are more likely to be reinnervated, but reinnervation is much less likely to occur in the mid-ventricular and apical regions.

Key words: transplantation, ^{123}I -metaiodobenzylguanidine (MIBG) SPECT, reinnervation, denervation

INTRODUCTION

^{123}I -metaiodobenzylguanidine (MIBG) has been reported to be a useful tool to evaluate the cardiac sympathetic nervous function.^{1–5} Congestive heart failure (CHF) in particular, involves a higher MIBG washout rate and lower MIBG delayed uptake, and those parameters reflect the severity of the disease.⁶ MIBG initial uptake is relatively retained among patients with CHF.⁶ This phenomenon may be explained by accelerated adrenergic nerve activity in CHF.⁷

In transplanted human hearts, however, the sympathetic neurons are completely separated from their nerve terminals, therefore causing the depletion of norepinephrine and resulting in complete cardiac denervation.⁸ MIBG initial uptake, which is related to the uptake-1 mechanism should be completely absent in a transplanted heart early (< 1 year) after HTX. Evidence of sympathetic reinnervation has recently been derived from the invasive measurement of transcatheter norepinephrine spillover,⁹ spectral analysis of heart rate variability,^{10,11} ^{123}I -MIBG scintigraphy,^{12,13} or C-11 hydroxyephedrine (HED) positron emission tomography (PET).¹⁴ MIBG and HED PET studies have suggested that reinnervation occurs in transplanted hearts more than one year after orthotopic heart transplantation (HTX).^{12,14} Most recent MIBG studies have proved the evidence generated from anterior planar images or semi-quantitative analysis of the heart to mediastinum ratio, but regional cardiac reinnervation has not been

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presented with MIBG single-photon emission computed tomography (SPECT). It was therefore the purpose of this present study to assess regional cardiac sympathetic reinnervation late (≥ 1 year) after HTX by means of MIBG SPECT imaging analysis.

MATERIALS AND METHODS

Eight Japanese patients aged 13 to 49 years old (33 ± 10 years old; 7 men, 1 woman) with NYHA IV dilated cardiomyopathy underwent HTX in the USA between 1993 and 1997. Donor age was between 15 and 31 years old (22 ± 6 years old). Clinical data for all enrolled patients are listed in Table 1. All patients records were documented by the Heart Institute of Japan after HTX, and they received immunosuppressive therapy consisting of cyclosporine, prednisone and azathioprine. Routine surveillance endomyocardial biopsies were performed after HTX to rule out graft rejection. All patients underwent echocardiography (UCG) to assess cardiac function, and coronary angiography (CAG) and intravascular ultrasound (IVUS) to rule out coronary stenotic and narrowing lesions.

MIBG scintigraphy was performed more than one year (35 ± 17 months; 12 to 66 months) after HTX in all patients, and in 4 of these patients within one year (4.4 ± 2.5 months) after HTX. After thyroid blockade with oral administration of 150 mg potassium iodide, planar scintigraphic images in the anterior and lateral views and SPECT, 15 minutes (initial) and 4 hours (delayed) after intravenous injection of 111 MBq of ^{123}I -MIBG were performed on each patient. The presence or absence of regional MIBG uptake was judged by two independent experienced nuclear physicians using each SPECT image. Global MIBG uptake was assessed semi-quantitatively by the heart to mediastinum ratio (H/M) generated as follows. Two regions of interest were drawn manually on the planar anterior image. The first (ROI 1) delineated the myocardium and the second (ROI 2) delineated the mediastinal region (Fig. 1). The chest X-ray image was set on the myocardial ROI. H/M in both initial and delayed images were calculated by the following formula.¹

$$H/M = \frac{H \times A2}{B \times A1}$$

Where H is the myocardium count (ROI 1), B is the mediastinum count (ROI 2), and $A1$ and $A2$ are the numbers of pixels over the area of ROI 1 and ROI 2. SPECT imaging was acquired with a single-head gamma camera (DS7, Sophy medical) with low energy and high-resolution collimator, 180° rotation (32 views per 40 seconds, beginning at 30° right anterior oblique projection), and a 64×64 matrix. The data were reconstructed by filtered back projection.

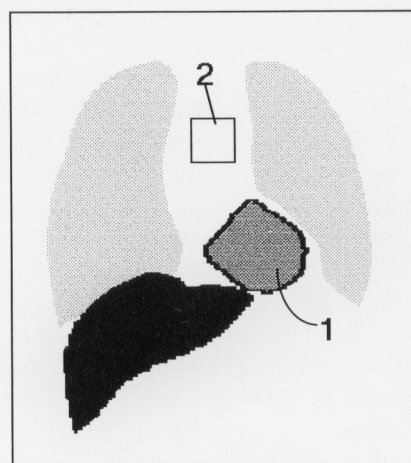
The Institutional Committee on Human Clinical Investigations approved this study protocol. All patients were

Table 1 Clinical characteristics in 8 patients with transplanted hearts

Case No.	Sex	Age (y.o.)	Periods* (months)	Donor age	Rejection grade**
1	M	49	49	21	2
2	F	16	31	31	1A
3	M	24	29	25	1A
4	M	40	28	21	1A
5	M	30	12	19	0
6	M	23	66	15	3B
7	M	20	40	30	3A
8	M	30	24	21	1B

* The periods between heart transplantation and MIBG study.

** International Society for Heart and Lung Transplantation (ISHLT) grade



ROI 1 : Area of myocardium

ROI 2 : Area of mediastinum

Fig. 1 Two regions of interest are drawn manually on the anterior image of MIBG. The first (ROI 1) delineates the myocardium and the second (ROI 2) delineates the mediastinal region. Heart to mediastinum ratio (H/M) is calculated by both the counts of ROI 1 and those of ROI 2.

well informed of these procedures and consented to participate in this study.

All results are expressed as the mean values ± 1 s.d. The unpaired Student's t -test was used to evaluate differences between the variables. Statistical significance was set at a p value of 0.05.

RESULTS

Clinical characteristics

All patients underwent UCG within 3 months (-0.8 ± 1.7 months) before or after MIBG study, and also underwent CAG 8.0 ± 7.4 months after HTX. UCG revealed no patient with depressed left ventricular systolic function under 0.29 in fractional shortening and with regional

myocardial asynergy. Left ventricular end-diastolic diameter, end-systolic diameter and fractional shortening were 45 ± 4.8 (36–53) mm, 29 ± 3.9 (24–30) mm and 0.36 ± 0.06 (0.30–0.46), respectively. CAG showed no significant stenosis in all patients, but IVUS revealed graft narrowing lesions (over 0.5 mm in average intimal wall thickness) in 1 of 8 patients. Serial right ventricular myocardial biopsy monitoring revealed an International Society for Heart and Lung Transplantation (ISHLT) rating of grade 2 at least once during follow-up periods in 3 patients (grades 2, 3A, and 3B).

¹²³I-MIBG scintigraphy

No visible MIBG uptake was demonstrated in any of the 4 patients on which scintigraphy was performed within one year after HTX, but more than one year after HTX, 5 of 8 patients had visible MIBG uptake in initial planar and

SPECT images, whereas 3 of 8 patients had no uptake in either image. We divided all patients into positive uptake group (n = 5: case 1–5) and the no uptake group (n = 3: case 6–8). Regional MIBG uptake analyzed by SPECT images

Table 2 Regional MIBG uptake in 5 cases with cardiac reinnervation

Case	Ant		Sept		Lat		Post		Apex
	B	M	B	M	B	M	B	M	
1	+	+	–	–	+	+	±	–	–
2	+	–	+	–	±	–	–	–	–
3	+	+	+	–	+	+	+	–	–
4	+	–	+	–	+	–	–	–	–
5	+	+	+	–	–	–	–	–	–

B = basal region; M = mid-ventricular region

+ = positive uptake; – = negative uptake; ± = equivocal uptake

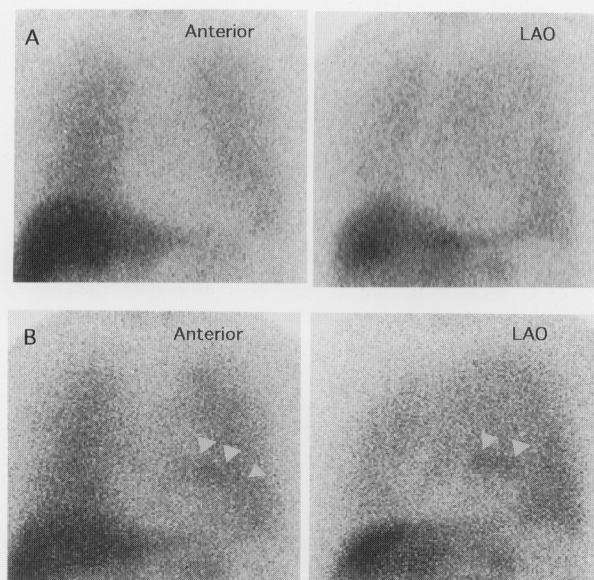


Fig. 2 Anterior and lateral planar ¹²³I-MIBG scintigraphic images are presented in Case 1. A, B represents the images 2 months and 49 months after HTX, respectively. No visible MIBG uptake is observed in both anterior and lateral planar A images, but regional MIBG accumulation is demonstrated in the anterior region in the B images (see arrows).

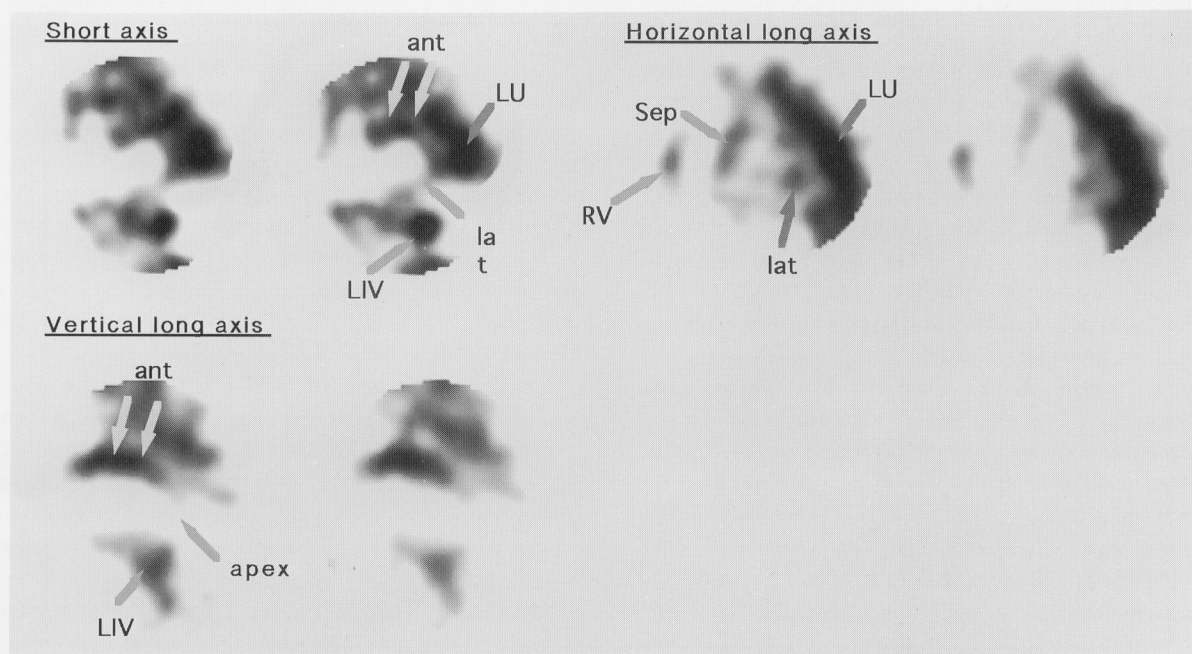


Fig. 3 ¹²³I-MIBG SPECT images are presented 49 months after HTX in case 1. ant = anterior; lat = lateral; RV = right ventricle; LU = lung; LIV = liver. The septal, lateral, and the right ventricle as well as the basal anterior are shown. Equivocal uptake is observed in the posterior region, which is poorly separated from liver uptake. No MIBG uptake is noted in the apical region.

in the positive uptake group is listed in Table 2. Positive regional MIBG uptake involved the basal anterior region in all 5 patients, the basal septal region in 4 patients, the basal lateral region in 3 patients and the basal posterior region in 1 patient. These areas reflected cardiac reinnervation. Equivocal uptake was demonstrated in the basal posterior region in 1 patient and in the basal lateral region in 1 patient. Mid-ventricular and apical regions were much less likely to be reinnervated than the basal region. The above-mentioned MIBG uptake was demonstrated in both initial and delayed images in each patient. Early H/M and delayed H/M were 1.39 ± 0.10 (1.33–1.56), 1.24 ± 0.17 (1.08–1.52) in the positive uptake group and 1.28 ± 0.05 (1.23–1.32), 1.09 ± 0.03 (1.06–1.12) in the no uptake group, respectively. There was no statistical difference between the two groups in H/M. There was no significant difference in age, gender, follow-up period, donor age or fractional shortening between the positive uptake group and the no uptake group. The positive uptake group included rejection grades 0, 1a and 2, whereas the no uptake group included grades 3a, 3b and 1b.

Case 1 is shown in Figure 2. No visible MIBG uptake is observed in either anterior or lateral planar images 2 months after HTX (A), but regional MIBG accumulation is demonstrated in the anterior portion 49 months after HTX (B). Figure 3 shows SPECT images in the same series of examinations as Figure 2B. Regional reinnervation could be well discriminated segment by segment.

DISCUSSION

Transplanted human hearts have demonstrated no localization of MIBG uptake soon after HTX on either initial or delayed images in the previous study.¹⁵ In this study, sympathetic denervation or reinnervation was detected by the initial image of MIBG scintigraphy late after HTX. Scintigraphic results in the present study showed complete denervation in all 4 patients who were tested early after HTX, but partial cardiac reinnervation in some of the transplanted hearts occurred late after HTX. Regional reinnervation detected by MIBG SPECT frequently involved the basal anterior region, but the inferior-posterior and apical regions were less likely to be reinnervated even among the patients in the positive uptake group. It should be emphasized that the mid-ventricular region of the myocardium showed signs of less reinnervation growth than the basal region. This is the same as the result which was obtained in a previous report with HED PET,^{14,16} suggesting that sympathetic reinnervation appears in the basal region of the myocardium first and then extends further into the distal region, whereas the apex and infero-posterior regions may not be involved even late after HTX. Kaye et al.¹⁷ reported that myocardial norepinephrine concentrations were recovered first in the left and right atrium followed by the basal left ventricular area, and finally in the apical area two years after cardiac

denervation in canine hearts. The reason for this mechanism is unclear, but these experimental data support our present results. One patient with positive uptake even 4 years after HTX, however, had only a 1.33 in H/M ratio, which reflects very little reinnervation compared to the average H/M ratio (2.19 ± 0.20) in our study control group.¹⁸ Bengel et al.¹⁶ previously reported in a HED PET study that a continuous growth of cardiac reinnervation is observed even more than 7 years after HTX. Further MIBG studies may be needed to clarify the maximal level of reinnervation in a particular patient.

Three patients had no MIBG uptake even after much time had elapsed: 24, 40 and 66 months, respectively after HTX. No statistical significance could be obtained in early H/M in the two groups, but up to the early H/M data, every individual value in the positive uptake group was higher than that in the negative uptake group. This may be due to the only small difference between the groups in global cardiac uptake in addition to the small number of patients. There was no significant difference between the positive uptake group and the no uptake group in patient's and donor's clinical findings. Our results indicated that 2 of 3 patients with no uptake showed signs of severe rejection in the biopsy tissue once during the follow-up period. This present study, however, enrolled so few patients that it is unclear whether severe rejection is associated with prolonged denervation late after HTX. De Marco et al.¹² concluded in their study that reinnervation is less likely to occur in patients with a pretransplantation diagnosis of idiopathic cardiomyopathy (DCM) than in those with ischemic heart disease, but have not clarified which factor is related to the likelihood of reinnervation among these patients with prediagnosis of DCM.

In the present study, there were patients with no cardiac reinnervation even 3 or 5 years after HTX. The HED PET study also indicated that complete denervation was seen in one out of 6 patients over 7 years after HTX.¹⁶ Sympathetic reinnervation within 12 to 18 months has been described previously,⁹ but transplanted human hearts with no uptake even 2 years after HTX may not exhibit further growth of reinnervation. Further investigations will be required to find the factor related to the growth of cardiac reinnervation late after HTX.

No clinical outcome which resulted from cardiac reinnervation could be obtained in this study, but a previous experimental study indicated that reinnervation-related neural functional recovery parallels the return of measurable quantities of myocardial norepinephrine and is accompanied by a decrease in supersensitivity to exogenous norepinephrine.¹⁷

MIBG SPECT has limitations when analyzing regional reinnervation after HTX. Relatively higher liver or lung MIBG uptake interferes with the reconstructed cardiac SPECT image,¹⁹ so that it is sometimes difficult to assess trivial regional cardiac accumulation adjacent to the liver and left lung in the inferior, posterior and lateral regions

in the heart.

In conclusion, MIBG SPECT can detect regional re-innervation, indicating that the basal septal and lateral regions next to the basal anterior are more likely to be reinnervated, whereas reinnervation in the mid-ventricular part and apical regions are much less likely to occur. Nevertheless there are transplanted hearts with no uptake even 5 years after HTX, and the underlying mechanisms of this prolonged complete denervation remain to be elucidated.

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