Scintigraphic Assessment of Cardiac Sympathetic Innervation with I-123-Metaiodobenzylguanidine in Cardiomyopathy: Special Reference to Cardiac Arrhythmia

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ABSTRACT. Cardiac sympathetic imagings with I-123-metaiodobenzylguanidine (MIBG) were carried out in 5 cases with dilated cardiomyopathy (DCM), 26 cases with hypertrophic cardiomyopathy (HCM), and 4 cases without cardiac disease as a control to assess cardiac sympathetic innervation qualitatively and quantitatively, and to clarify the relation of MIBG accumulation to arrhythmia. MIBG scintigraphy was performed at 15 min. (early image) and 4 hr. (delayed image) after intravenous injection of MIBG111MBq. The MIBG uptake ratio of mediastinum (H/M) and the cardiac washout rate (WR) from early to delayed images were calculated. On both early and delayed SPECTs, MIBG uptake was assessed by defect scores (DSs). Regarding the cases with HCM, the MIBG uptake ratio, WR, and DS were also compared in cases with and without arrhythmia. In DCM, the MIBG uptake on delayed SPECT was markedly low, the H/M ratio was significantly lower, and the DS was significantly higher than in the control (all $p<0.05$). As for the WR, there was no significant difference between HCM, DCM and the control. In HCM, significantly reduced MIBG uptake was observed in cases with ventricular techycardia (VT) and in cases with atrial fibrillation (Af), as compared with cases without arrhythmia (all $p<0.05$). There results suggest that MIBG scintigraphy might be a useful tool in the assessment of cardiac sympathetic abnormalities in cardiomyopathy, especially in cases with arrhythmia.

Key words: I-123-metaiodobenzylguanidine — cardiac sympathetic innervation — cardiomyopathy

Recently, I-123-metaiodobenzylguanidine (MIBG), an analogue of guanidine, has been developed to assess cardiac sympathetic innervation.[1-4] MIBG has been found to accumulate in sympathetic nerve endings, and to be taken in cathecolamine-containing vesicles in a similar manner to the norepinephrine uptake mechanism.[5-7] MIBG uptake in the myocardium has been found to correlate with myocardial norepinephrine content. Therefore, the cardiac uptake of MIBG can be a useful tool for assessing cardiac sympathetic innervation. In ischemic heart diseases, complications of

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sympathetic abnormalities have been reported.[8,9] Enervated myocardium has been noted in myocardial infarction, and reinnervation has occurred in some cases.[10] In cardiomyopathy, impairment of cardiac MIBG uptake, and increase in washout of MIBG have been reported.[11–13] There may also be an anatomical derangement of cardiac sympathetic innervation contributing to ventricular arrhythmia. In this study, we carried out MIBG scintigraphy in patients with dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM), and assessed this method qualitatively and quantitatively. In addition, among HCM patients, the parameters of MIBG uptake were also compared in cases with and without arrhythmia.

MATERIALS AND METHODS

MIBG scintigraphy was performed in 5 cases with DCM, 26 cases with HCM (Table 1), and 4 cases without cardiac disease (control) at 15 min. (early image) and 4 hr. (delayed image) after intravenous injection of 111 MBq (3 mCi) MIBG. Scintigraphic images were obtained using the GAMMA VIEW-T (Hitachi, Tokyo) equipped with the LEHR collimator, and data processing was performed using the RP-100 (Hitachi, Tokyo). SPECT data were collected from 32 projections, from 45°RAO to 45°LPO, with an acquisition time of 50 sec. for each projection. An anterior planar image was also obtained before

TABLE 1. Patient and control characteristics.

	N	Age (yrs.)	Male	Female
Control	4	44.0±22.0	3	1
DCM	5	57.2±6.3	5	0
HCM	26	53.2±12.7	22	4
Arrhythmia (−)	16	51.4±14.0	14	2
VT (+)	6	53.2±7.4	6	0
Af (+)	4	60.5±14.1	2	2

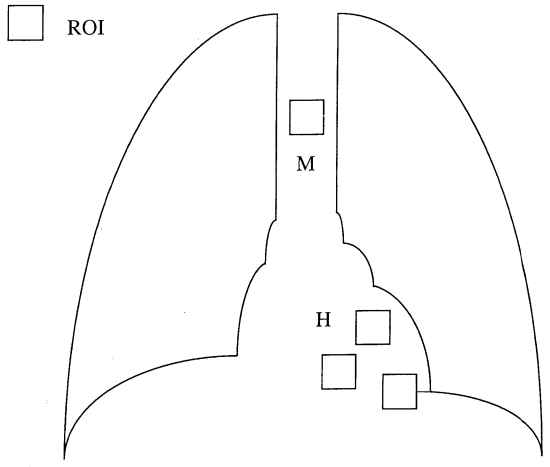

Fig 1. Localization of ROIs (regions of interest) used for assessment of the uptake rate and washout rate. M: mediastinum, M: heart.

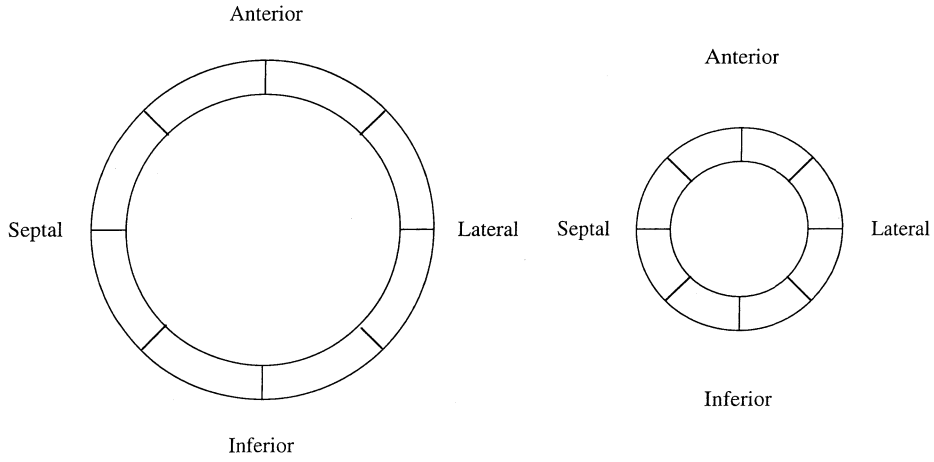

Fig 2. Diagram of the segmentation at the basal (left) and apical (right) regions in the short axis slices used for assessment of the defect score.

SPECT data acquisition. To assess cardiac MIBG uptake, regions of interest (ROIs) were set on the left ventricle (H) and upper mediastinum (M) (Fig 1). Three cardiac ROIs were set, and left ventricular uptake was assessed from the average of three ROI counts. The heart to mediastinum (H/M) ratio was calculated on both early and delayed anterior planar images. Using these images, the MIBG washout rate (WR) of the left ventricle was calculated with a decay correction of I-123. On SPECT, left ventricular short axis images were reconstructed with a slice thickness of 2 pixels (12.2 mm). The defect score (DS) was obtained as follows; on short axis images, cardiac basal and apical slices were selected. Two short axis slices were divided into 16 segments with 8 segments for each slice, as shown in Fig 2. Accumulation of MIBG was defined using a three-point grading system; score 2 for severely decreased uptake, score 1 for mindly decreased uptake, and score 0 for normal uptake for each segment. The summation of scores from 16 segments was defined as DS on early and delayed SPECTs. A high DS value indicates the severily of decreased MIBG uptake, with 32 being the maximum DS, the equivalent of a complete defect. The uptake ratio, WR and DS obtained from early and/or delayed images were compared among the control, DCM and HCM. The 26 HCM cases were classified into three groups; those with ventricular tachycardia (VT), atrial fibrillation (Af) and without arrhythmia. VT was diagnosed when more than three beats of continuous premature ventricular contraction (PVC) were observed in Holter ECG performed for three months before and after MIBG scintigraphy. The uptake ratio, WR and DS were compared among these three HCM groups. Results were expressed as the mean $\pm$ SD. Statistical significance was defined as $p<0.05$. The two-tailed Student's t-test was used to compare the three groups.

RESULTS

The clinical features of 4 cases without cardiac disease (control), 5 cases with DCH, and 26 cases with HCM are shown in Table 1. The HCM cases

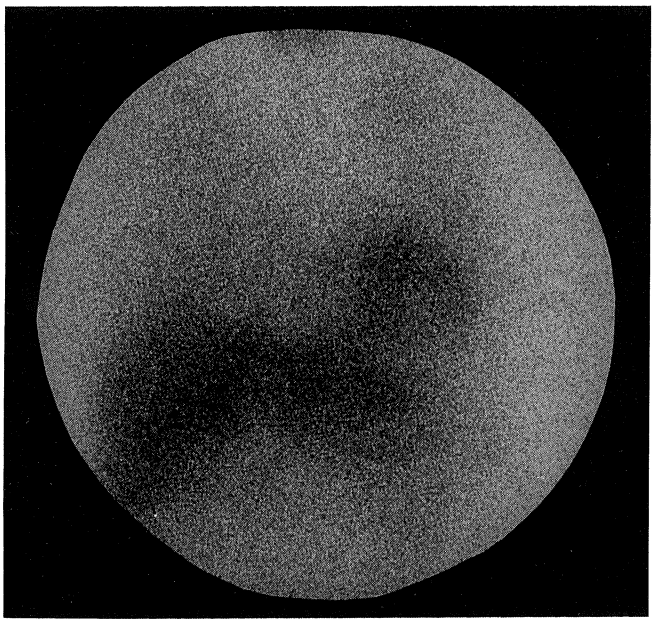

Fig 3. The anterior planar image of MIBG in control case.

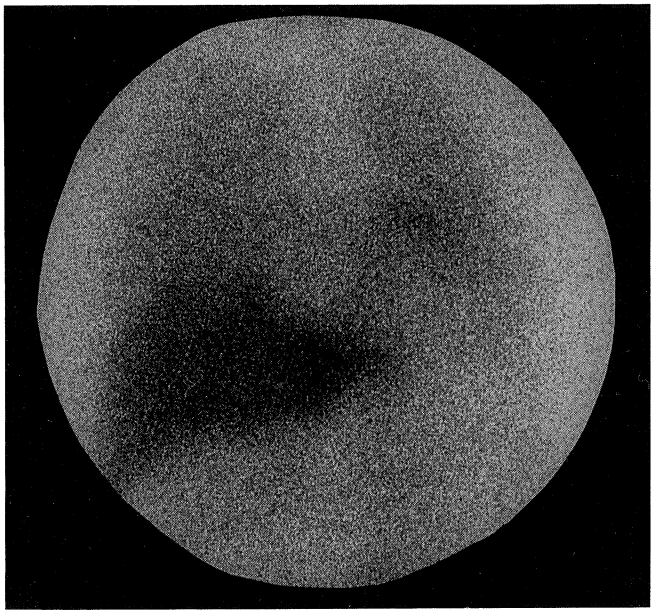

Fig 4. The anterior planar image of MIBG in DCM case.

TABLE 3. Wash-out rate (WR) in whole, anterior, apical, and inferior regions on I-123-MIBG scintigraphies in controls, DCM and HCM patients.

	WR			
	Whole	Anterior	Apical	Inferior
Control	0.17±0.09	0.17±0.10	0.19±0.13	0.18±0.06
DCM	0.31±0.06	0.30±0.09	0.31±0.06	0.34±0.11
HCM	0.28±0.10	0.23±0.26	0.25±0.28	0.21±0.27

(mean±SD)

TABLE 4. Defect score (DS) on I-123-MIBG scintigraphies in controls, DCM and HCM patients (*$p<0.05$ varsus control).

	DS	
	Early	Delayed
Control	6.33±5.51	3.00±3.61
DCM	12.75±13.07	16.80±9.09*
HCM	6.38±7.21	10.79±6.24

(mean±SD)

TABLE 5. Relations between arrhythmia and the H/M uptake ratio, WR and DS in HCM cases (*$p<0.05$ versus arrhythmia (−)).

	H/M		DS	
	Early	Delayed	Early	Delayed
Arrhythmia (−)	2.15±0.42	2.26±0.39	3.80±3.19	8.47±3.76
VT (+)	1.91±0.51	1.92±0.34*	13.33±11.33*	17.00±8.67*
Af (+)	1.85±0.25	1.61±0.52*	5.33±3.06	10.00±2.00

(mean±SD)

	WR			
	Whole	Anterior	Apical	Inferior
Arrhythmia (−)	0.26±0.08	0.27±0.08	0.29±0.11	0.23±0.08
VT (+)	0.28±0.10	0.27±0.09	0.32±0.14	0.28±0.10
Af (+)	0.37±0.10	0.34±0.10	0.36±0.12	0.40±0.09

(mean±SD)

were also classified into cases with and without arrhythmia. Among the 10 cases with arrhythmia, 6 cases showed VT, and 4 cases showed Af.

The anterior planar image was obtained. Figure 3 shows anterior planar image of MIBG in control case and Fig 4 shows one in DCM case. The cardiac uptake ratio (H/M) and DS in the control, DCM and HCM on both early and delayed images were compared. H/M is shown in Table 2. The cardiac WRs of three regions and the whole heart were not significantly different between three groups (Table 3). The DS in the DCM cases on delayed images was significantly higher than that of the control (Table 4). In the HCM cases, the DS on delayed images tended to be higher than that of the control. However, there was no significant difference in the DS on early images. The cardiac uptake ratio, WR, and DS of the HCM cases with or

without arrhythmia are shown in Table 5. There was no significant difference in the cardiac washout rate. The DS of HCM with VT was significantly higher than that of cases without arrhythmia on both early and delayed images. The cardiac uptake ratio in HCM with VT was significantly lower than that of cases without arrhythmia on delayed images. The same was true of HCM with Af, it was significantly lower than that of cases without arrhythmia on delayed images.

DISCUSSION

In this study, abnormal cardiac MIBG uptake was demonstrated in cases with cardiomyopathy, DCM and HCM. The major MIBG scintigraphy findings were as follows; the H/M ratio was decreased on delayed images in DCM, but not in HCM as a whole. In both DCM and HCM, the cardiac MIBG WR was tended to be increased. Cardiac MIBG uptake was significantly impaired in HCM cases with VT and with Af on SPECT, as compared with those without arrhythmia.

Cardiac MIBG uptake in DCM has been reported to be markedly decreased.[18] In this study, the cases with DCM also showed decreased MIBG uptake. As for the mechanism of this decreased MIBG uptake, it is suspected that abnormal myocardial perfusion due to myocardial fibrotic change or elevated circulating cathecholamin levels due to abnormal left ventricular function might have a pathogenic cause.[19] In our five cases with DCM, the MIBG uptake on delayed images was significantly lower than that of the control. This finding has led us to suspect that the decreased uptake of MIBG in DCM might reflect abnormal myocardial sympathetic nerve terminal function or a perfusion abnormality caused by myocardial fibrosis.

As for HCM, it has been reported that the H/M ratio decreases, and the myocardial WR increases.[19] In this study, the uptake ratio in HCM did not decrease, but the WR significantly increased. This unchanged uptake ratio might be caused by, increased mass of left ventricular myocardium.[19] In addition, the myocardial uptake on delayed images has been reported to be indicative of specific cardiac sympathetic neural activity via the uptake-1 mechanism on delayed images in rat models. It has been suspected that the increased WR in HCM might be dependent on clearance of non-specific activity of initial uptake or increased cardiac sympathetic activity.[13–16] A transplantad heart, namely heart of shmpathetic denervation, has no cardiac uptake.[17] This finding indicates that there is no non-specific uptake in the human heart, and an increased MIBG washout rate might not be based on clearance of the early non-specific uptake component. An increased MIBG washout rate might indicate increased sympathetic nerve activity in HCM. In HCM, significantly decreased cardiac MIBG uptake on SPECT was recognized in cases with VT, as compared with those without arrhythmias. There is evidence of an abnormality of the cardiac sympathetic nerve supply in cases with VT. It has been reported that the genesis of VT seems to be important in the balance between the sympathetic and parasympathetic systems.[23] Arrhythmia in cardiac muscle occurs as a result of three basic mechanisms; enhanced automaticity, triggered automaticity, and re-entry. There is evidence that sympathetic activity enhances automaticity, triggered activity, and the occurrence of re-entry, with

the possibility of arrhythmias.[23] It is well known that arrhythmia is an important factor in the determination of a patient's prognosis.[24,25] In HCM, arrhythmia may reflect the progression of myocardial damage. Cardiac uptake ratio, WR, and DS findings in HCM with or without arrhythmia are summarized in Table 5. No significant differences in the cardiac WR were observed. The H/M ratio was significantly lower than that of cases without arrhythmia on delayed images. In HCM cases with VT, the DS was significantly higher than that of cases without arrhythmia on both early and delayed images. In addition, the N/M ratio was significantly lower than that in cases without arrhythmia on delayed images. This study found evidence of abnormal cardiac sympathetic nerve supply in cases with arrhythmia. VT may have relative deneration which leads to imbalances in the sympathetic supply to the myocardium. However, it remains to be confirmed whether abnormal distribution of MIBG might be of any potential prognostic importance. There results indicate that MIBG scintigraphy is a useful tool for the assessment of cardiac sympathetic abnormalities in cardiomyopathy, especially in cardiac arrhythmia.

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