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^{123}I-MIBG myocardial imaging in hypertensive patients: Abnormality progresses with left ventricular hypertrophy

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Twenty-seven patients with essential hypertension were prospectively studied with ^{123}I-labeled metaiodobenzyl-guanidine (^{123}I-MIBG) to assess the presence and location of impaired sympathetic innervation in hypertrophied myocardium. Thirteen patients had left ventricular hypertrophy on echocardiography, and 14 had normal echocardiograms. The wash-out ratio of ^{123}I-MIBG in these two groups did not differ significantly (35.3 ± 6.1 and 35.4 ± 5.1) but was higher than in control subjects (29.4 ± 6.7). The delayed heart-to-mediastinum count ratio was lower in the patients with hypertrophy than in the patients without hypertrophy (1.93 ± 0.28 and 2.22 ± 0.21; $p < 0.05$) and the control subjects (1.93 ± 0.28 and 2.33 ± 0.25; $p < 0.05$). On SPECT imaging, abnormalities in segmental uptake were frequent at the posterior and postero-lateral wall in both groups, although the hypertrophic group had more significant impairment. Our results lead to the hypothesis that hypertension in more advanced stages may be associated not only with hypertrophic changes but also with more advanced regional impairment of cardiac sympathetic innervation.

Key words: metaiodobenzylguanidine (MIBG), single-photon emission computed tomography (SPECT), hypertension, left ventricular hypertrophy, adrenergic nerve

INTRODUCTION

METAIODOBENZYLGUANIDINE labeled with ^{123}I (^{123}I-MIBG) is a unique pharmacologic agent that can be used to assess the functional condition of sympathetic innervation in the human myocardium.[1–6] Many studies have demonstrated its clinical usefulness in patients with dilated cardiomyopathy,[7–9] valvular heart diseases,[10,11] coronary artery disease,[12–17] hypertrophic cardiomyopathy,[18,19] and dysrhythmias.[20,21] This agent has not, however, been studied in patients with hypertensive heart disease, which is one of the most prevalent types of heart diseases, though the abnormality in the myocardial uptake of ^{123}I-MIBG in patients with left ventricular hypertrophy secondary to valvular aortic stenosis has already been reported.[10] We studied ^{123}I-MIBG images obtained by planar and single-photon emission computed tomography (SPECT) to evaluate whether sympathetic innervation of the myocardium is impaired in hypertrophic left ventricles of hypertensive patients.

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MATERIALS AND METHODS

Patients

We prospectively studied 27 hypertensive patients (12 men and 15 women; age range, 42 to 83 yr; mean age, 61 ± 10 yr), all of whom had a documented history of essential hypertension[22] and were being treated at our outpatient clinic. Thirteen patients had echocardiographic evidence of left ventricular hypertrophy, which was defined as diffuse hypertrophy of the left ventricle with a interventricular septum thickness or posterior wall thickness exceeding 13 mm.[23] The other 14 patients had otherwise normal echocardiograms. Left ventricular mass (LVM) was calculated with the following formula: LVM (in grams) = $1.04[(LVIDd + VSTd + PWTd)^3 - (LVIDd)^3] - 13.6$, where LVIDd denotes the left ventricular internal diameter at end-diastole, VSTd the ventricular septal thickness at end-diastole, and PWTd the posterior wall thickness at end-diastole.[24] No patient had a history of angina pectoris, myocardial infarction, diabetes mellitus,

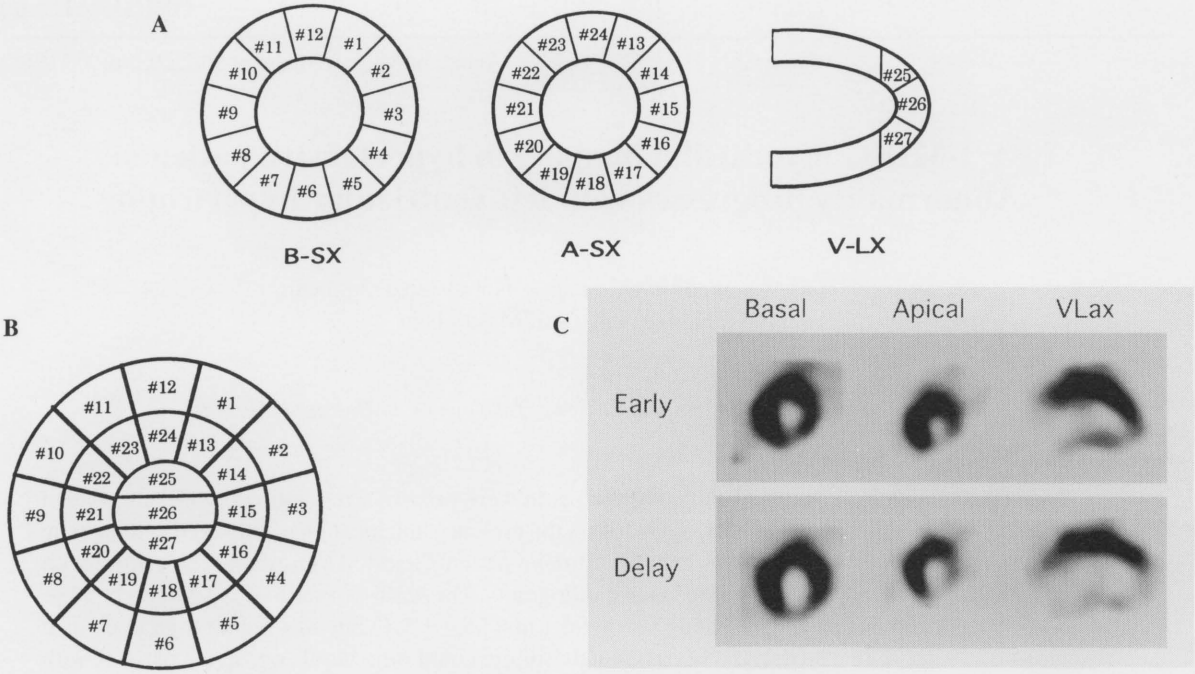

Fig. 1 Schematic diagram of single-photon emission tomographic images. (A) Twenty-seven segments of two short-axis images at the mid-basal (B-SX) and mid-apical (A-SX) levels and one vertical long-axis image at the mid-left-ventricle (V-LX). (B) Schematic representation of the 27 segments, appearing as a polar map image from base to apex. Here, segments, #3 is basal lateral, #6 is basal posterior, #9 is basal septum, #12 is basal anterior, #15 is mid-lateral, #18 is mid-posterior, #21 is mid-septum, #24 is mid-anterior, and #25–#27 are apex. (C) ^{123}I-MIBG SPECT images of a 58-year-old man with left ventricular hypertrophy.

or any evidence of secondary hypertension. All patients underwent treadmill exercise stress electrocardiogram. Exercise stress thallium-201 scintigraphy were added if necessary, and concomitant coronary artery disease was ruled out in all patients. All antihypertensive medication, consisting mainly of calcium channel blockers or angiotensin converting enzyme inhibitors, was continued during this study. No patient received reserpine, tricyclic antidepressants or other drugs that could interfere with the myocardial uptake of ^{123}I-MIBG. We also studied six healthy volunteers (three men and three women; mean age, 56 ± 5 [range 52 to 62] yr) with a normal echocardiogram and with no evidence of organic heart disease or hypertension as the control group.

SPECT study

The early planar and SPECT images were obtained with patients in the supine position 15 minutes after ^{123}I-MIBG (111 MBq) was injected intravenously at rest. Four hours later, both the late planar and SPECT images were obtained with the SPECT system (Shimadzu SNC 510 R-20 and Scintipack 7000), equipped with a low-energy, parallel-hole, general-purpose collimator. Planar images were obtained 15 minutes and 4 hours after tracer administration in the anterior view over a 5-minute interval. SPECT imaging was then performed. Thirty-two projections with 30 seconds per view were obtained over 180 degrees, starting at a 45-degree right anterior oblique projection and ending in a 45-degree left posterior oblique projection. The energy level and window width used for collection of data were 159 keV ± 20% for ^{123}I. The data were recorded in 64 × 64 matrices. After a preprocedure with a Butterworth filter, reconstruction was performed with a Shepp-Logan's filter. Neither scatter correction nor absorption correction was applied. Short-axis, horizontal and vertical long-axis slices were then reorganized. Regions of interest (ROI) in the whole heart and the mediastinum were set manually on the early and delayed planar images and were used to calculate the mean heart-to-mediastinum count ratio (H/M ratio).[8,25] The ratio of tracer wash-out from the myocardium was determined over 4 hr without correction for the physical decay of ^{123}I. The wash-out ratio was calculated with the following formula: wash-out ratio = $[(Ci - Cd)/Ci] \times 100$, where Ci and Cd are the mean count of the whole heart on the initial and delayed planar images, respectively.

Image analysis

Segmental analysis of the four-hour delayed images of ^{123}I-MIBG SPECT was performed visually by three independent observers, and disparity was resolved by consensus. Twenty-seven segments were determined on two

Table 1 Clinical characteristics and scintigraphic variables

	LVH	Non-LVH	Control
n	13	14	6
Age	63 ± 10	58 ± 14	55 ± 4
Sex (Male : Female)	6M : 7F	6M : 8F	3M : 3F
SBP (mmHg)	135 ± 9†	139 ± 13†	123 ± 15
DBP (mmHg)	86 ± 4†	85 ± 6	81 ± 7
MBP (mmHg)	103 ± 5†	103 ± 8	95 ± 9
UCG			
LVIDd (mm)	42.0 ± 7.3	43.6 ± 3.5	40.6 ± 2.9
VSTd (mm)	14.0 ± 2.0**††	10.1 ± 0.9	9.9 ± 0.6
PWTd (mm)	14.6 ± 2.0**††	10.0 ± 0.9	10.6 ± 1.4
LA (mm)	38.5 ± 4.6**††	32.4 ± 4.4†	27.2 ± 3.3
LVM	263 ± 65**††	190 ± 50	154 ± 18
%FS	36 ± 5	37 ± 4	35 ± 4
^{123}I-MIBG			
WOR (%)	35.3 ± 6.1	35.4 ± 5.1	29.4 ± 6.7
H/M	2.09 ± 0.21	2.19 ± 0.26	2.12 ± 0.11
4 hr H/M	1.93 ± 0.28*†	2.22 ± 0.21	2.33 ± 0.25
Abnormal segments	15.5 ± 5.6*†	10.1 ± 6.4	5.2 ± 4.5
Abnormal score	47.2 ± 14.4†	34.3 ± 18.1	22.2 ± 9.5

* $p < 0.05$, compared with Non-LVH by unpaired t test.

** $p < 0.01$, compared with Non-LVH by unpaired t test.

† $p < 0.05$, compared with control by unpaired t test.

†† $p < 0.01$, compared with control by unpaired t test.

Abbreviations: LVH: left ventricular hypertrophy; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; LVIDd: left ventricular internal diameter at end-diastole; VSTd: ventricular septal thickness at end-diastole; PWTd: posterior free wall thickness at end-diastole; LA: left atrium; LVM: left ventricular mass; FS: fractional shortening; WOR: wash-out ratio; H/M: heart to mediastinum mean count ratio.

short-axis images at the mid-basal and mid-apical levels and one vertical long-axis image at the mid-left-ventricle as shown in Figure 1. Each scintigraphic segment was scored as 0 for normal; 1 for slightly reduced uptake; 2 for moderately reduced uptake; 3 for severely reduced uptake; and 4 for no uptake. Segments which scored more than 2 were defined as abnormal. The abnormality score was calculated as the sum of the scintigraphic scores for the 27 segments of the left ventricle.

Statistical analysis

Data were expressed as the means ± S.D. Group differences were compared by unpaired t-tests. P values less than 0.05 were considered to indicate statistical significance.

RESULTS

The clinical characteristics and scintigraphic variables of the hypertensive patients and the control subjects are shown in Table 1. The blood pressure measured at rest on the day of ^{123}I-MIBG imaging was not significantly different among the three groups. Calcium-channel blockers were being prescribed for 11 patients (85%) in the hypertrophy group and 12 patients (86%) in the non-hypertrophy group, and angiotensin converting enzyme inhibitors for 6 patients (46%) and 4 patients (29%), beta-adrenergic antagonists for 4 patients (31%) and 3 patients (21%), and diuretics for 4 patients (31%) and 3 patients (21%), respectively. There were no statistical differences between the two groups in these medications.

The wall thickness and left ventricular mass were significantly greater in the hypertrophy group than in the non-hypertrophy group (VSTd 14.0 ± 2.0 mm vs. 10.1 ± 0.9 mm, $p < 0.01$; PWT 14.6 ± 2.0 vs. 10.0 ± 0.9, $p < 0.01$; LVM 263 ± 65 and 190 ± 50, $p < 0.01$). These variables were also significantly greater in the hypertrophy group than in the control subjects (VSTd 14.0 ± 2.0 mm vs. 9.9 ± 0.6 mm, $p < 0.01$; PWTd 14.6 ± 2.0 vs. 10.6 ± 1.4, $p < 0.01$; LVM 263 ± 65 vs. 154 ± 18, $p < 0.01$). Left

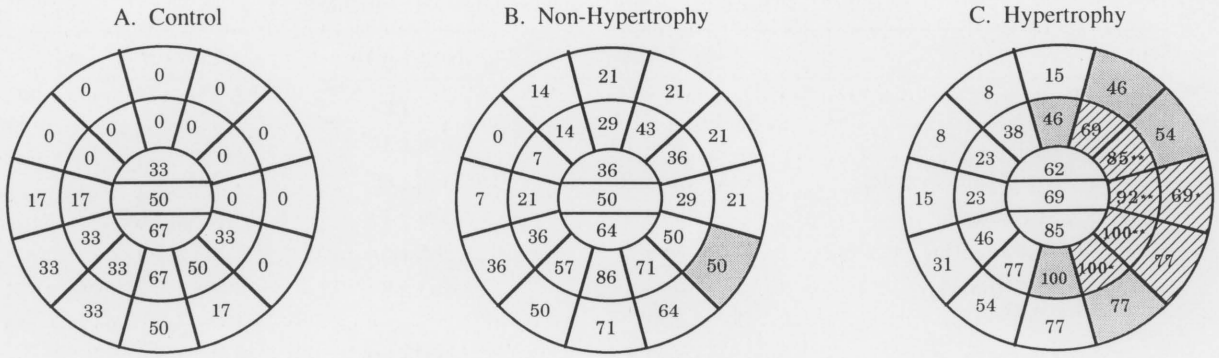

Fig. 2 Segmental analysis of the delayed ^{123}I-MIBG SPECT images.

The number in each column represents the frequency of the abnormality (%). (A) Normal control group. (B) Hypertensive group without left ventricular hypertrophy (LVH). (C) Hypertensive group with LVH. *Shaded area:* $p < 0.05$, compared with the control group. *Hatched area:* $p < 0.01$, compared with the control group. * $p < 0.05$, compared with the non-hypertrophy group with hypertension. ** $p < 0.01$, compared with the non-hypertrophy group with hypertension

atrial dimension in the hypertrophy group was larger than both that in the non-hypertrophy group (38.5 ± 4.6 vs. 32.4 ± 4.4, $p < 0.01$) and that in the control group (38.5 ± 4.6 vs. 27.2 ± 3.3, $p < 0.01$). The ratio of ^{123}I-MIBG washout in the two hypertensive groups were similar (35.3 ± 6.1 vs. 35.4 ± 5.1), and higher than that in the control group (29.4 ± 6.7), although the differences from the control were not statistically significant. The early heart to mediastinum (H/M) ratio did not differ among the three groups (2.09 ± 0.21 vs. 2.19 ± 0.26, vs. 2.12 ± 0.11), but the delayed H/M ratio was significantly lower in the hypertrophy group than in the non-hypertrophy group (1.93 ± 0.28 vs. 2.22 ± 0.21, $p < 0.05$) and the control group (1.93 ± 0.28 vs. 2.33 ± 0.25, $p < 0.05$). The hypertrophy group had significantly more abnormal segments than the non-hypertrophy group (15.5 ± 5.6 vs. 10.1 ± 6.4, $p < 0.05$) and the control group (15.5 ± 5.6 vs. 5.2 ± 4.5, $p < 0.05$). The scintigraphic abnormality score in the hypertrophy group was higher than that in the non-hypertrophy group, but the difference was not significant (47.2 ± 14.4 vs. 34.3 ± 18.1, NS). The score in the hypertrophy group was significantly higher than that in the control group (47.2 ± 14.4 vs. 22.2 ± 9.5, $p < 0.05$).

The delayed SPECT images also underwent segmental analysis by visual scoring (Fig. 2). In the non-hypertrophy group, the abnormal uptake of ^{123}I-MIBG was often seen in the infero-posterior region, and the frequency of abnormal uptake was significantly higher than the control in segment No. 4. In the hypertrophy group abnormalities were more frequent and extensive. The frequency of ^{123}I-MIBG segmental abnormalities was higher in the hypertrophy group than in the non-hypertrophy group in segments No. 3 (69% in the hypertrophy group vs. 21% in the non-hypertrophy group, $p < 0.05$), No. 14 (85% vs. 36%, $p < 0.01$), No. 15 (92% vs. 29%, $p < 0.01$), No. 16 (100% vs. 50%, $p < 0.01$) and No. 17 (100% vs. 71%, $p < 0.05$).

DISCUSSION

Left ventricular hypertrophy is the major cardiac alteration associated with hypertension and accounts for a risk that is independent of the high blood pressure.[24] Recent studies[26–29] have demonstrated a significant relation between left ventricular hypertrophy and increased cardiovascular risk.

Left ventricular hypertrophy is also associated with an increased risk of sudden death,[30,31] although the mechanism is not completely understood. A relation between sudden death and autonomic system dysfunction has also been demonstrated.[32–35]

^{123}I-MIBG is considered to be a non-metabolizable analog of norepinephrine that can be used to evaluate the functional status of sympathetic innervation in the myocardium.[2,3,5] After intravenous injection, ^{123}I-MIBG present in the synaptic gap is taken up by the sympathetic nerve endings (neuronal uptake) and by the myocardial cells (extraneuronal uptake).[10,36,37] The relative proportions of these two types of cardiac uptake have not yet to be defined, but apparently most of the intraneuronal tracer is sequestered within vesicles and released at a very slow rate. On the other hand, the extraneuronal uptake is washed away faster than the intraneuronal uptake,[38] although the former is thought to be very low in humans.[10,39,40]

A previous study[7] revealed that the myocardial uptake index 4 to 6 hr after intravenous injection is significantly correlated with the myocardial norepinephrine concentration. Four-hour delayed images are considered to be better than 6-hr images for the evaluation of the intraneuronal

uptake of ^{123}I-MIBG by the heart. Heart-to-mediastinum count ratio essentially provides an estimate of neuronal ^{123}I-MIBG activity.[7,8,10,18]

In heart failure with mechanical overload, the uptake of tracer norepinephrine is depressed, reflecting an impaired uptake-1 process,[41–43] which is involved in the transport of norepinephrine across neuronal membranes. Fagret[10] reported that in patients with left ventricular hypertrophy secondary to valvular aortic stenosis, the index of myocardial ^{123}I-MIBG uptake was less than that in control patients at all measurement times, and, in addition, the wash-out of cardiac radioactivity from 1 hr to 4 hr after injection was faster in the patients with left ventricular hypertrophy. Nakajima[44] also reported a high wash-out ratio in various cardiac diseases, such as dilated cardiomyopathy, hypertrophic cardiomyopathy, ischemic heart disease, hypertension and arrhythmias, as well as in hypothyroidism.

Our results demonstrated that the H/M ratio on 4-hr delayed images was significantly lower in the hypertrophy group than in the non-hypertrophy group and the control group. The H/M ratio in the non-hypertrophy group was also lower than that in the control group although the difference was not statistically significant. Our results suggested that myocardial ^{123}I-MIBG washout might be accelerated in hypertensive patients.

Fagret[10] proposed two hypotheses to explain the presence of a small myocardial ^{123}I-MIBG pool with rapid turnover in patients with aortic stenosis: (1) hyperstimulation of the sympathetic nervous system in patients with left ventricular hypertrophy;[45,46] and (2) a cellular energy deficit of the myocardium, resulting in a reduction in the activity of the different norepinephrine transporters,[47] which, in turn, leads to a reduction in norepinephrine storage and an increase in its neuronal release.[5,38]

Our results are consistent with those of Fagret and indicate that the hypertensive heart may also have a small myocardial ^{123}I-MIBG pool with rapid turnover. The reason for this is unknown, but hyperstimulation of the sympathetic nervous system may play an important role. A cellular energy deficit of the myocardium was not likely in our patient population.

Heterogeneity and regional abnormality of myocardial ^{123}I-MIBG uptake has been reported.[25,48] In normal subjects, there is heterogeneity of cardiac sympathetic innervation, with fewer cathecholaminergic nerve terminals in the inferior and septal walls of the left ventricle. Furthermore, the inferior wall uptake of ^{123}I-MIBG decreases with age in individuals without cardiac diseases, especially men.[25] Regional abnormality also occurs in areas of myocardial ischemia and infarction.[12,13,49,50]

In our study the patients with left ventricular hypertrophy were considered to be in the advanced stage of hypertensive heart disease. None of the patients was likely to have coronary artery disease, so myocardial ischemia due to coronary artery disease would not be the reason for the segmental impaired uptake of ^{123}I-MIBG. In the hypertensive non-hypertrophy group, an abnormally reduced uptake of ^{123}I-MIBG was often seen at the inferoposterior region (4 to 7 o'clock), but the abnormalities in the hypertensive hypertrophy group were more frequent and extensive (12 to 6 o'clock), extending to the anterolateral wall. The differences in abnormalities in the lateral and postero-lateral regions between the two hypertensive groups reached statistical significance in some segments.

Our results lead to the hypothesis that hypertension in more advanced stages may be associated with not only hypertrophic changes, but also the more advanced regional impairment of cardiac sympathetic innervation. We conclude that in hypertensive patients cardiac sympathetic innervation may become abnormal and progress globally, as well as regionally, in parallel with hypertrophic changes.

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