Cardiac Sympathetic Nervous System in Early Essential Hypertension Assessed by ^{123}I-MIBG

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Sympathetic overactivity has been noted in various clinical stages of essential hypertension. The purpose of this study is to investigate ^{123}I-metaiodobenzylguanidine (MIBG) uptake and washout in patients with borderline and mild hypertension. **Methods:** To assess cardiac sympathetic function in essential hypertension, we performed ^{123}I-MIBG cardiac imaging and echocardiography in 25 normotensive, 25 borderline hypertensive and 24 mildly hypertensive men. Age and body mass index were similar in the three groups. **Results:** Regarding the echocardiographic variables, the left ventricular mass index (LVMI) was significantly higher in the mildly hypertensive group (125.6 ± 28.6 g/m^2) than in the normotensive (99.9 ± 20.7 g/m^2) and the borderline hypertensive (110.0 ± 24.4 g/m^2) groups ($P < 0.001$ and $P < 0.05$, respectively). Regarding the scintigraphic variables, the heart-to-mediastinum (H/M) ratio was significantly lower in the mildly hypertensive group (1.8 ± 0.3) than in the normotensive (2.1 ± 0.3) and the borderline hypertensive (2.1 ± 0.2) groups. In contrast, the washout rate was significantly higher in the mildly hypertensive group (17.6% ± 10.8%) than in the normotensive (7.0% ± 4.9%) and the borderline (11.9% ± 8.9%) hypertensive groups ($P < 0.001$ and $P < 0.02$, respectively). In addition, the borderline hypertensive group had a significantly higher washout rate than the normotensive group ($P < 0.05$). MIBG washout rate had a strong positive correlation with LVMI ($r = 0.77$, $P < 0.0001$). In contrast, the H/M ratio had a weak negative correlation with LVMI ($r = -0.40$, $P < 0.0006$). **Conclusion:** During the course of establishment of essential hypertension, the washout rate becomes higher with the advance of hypertension and with the development of left ventricular hypertrophy. Thus, we suggest a strong relationship between cardiac sympathetic activity and the advance of hypertension at its early stages.

Key Words: ^{123}I-metaiodobenzylguanidine imaging; essential hypertension; left ventricular mass

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Growing attention is being focused on the role of the sympathetic nervous system in the pathogenesis of essential hypertension, since sympathetic overactivity is observed in the early stage of hypertension (*1–3*) and in patients with borderline hypertension (*4,5*). Sympathetic overactivity has also been proposed to be a causal component of the development of cardiovascular disorders, such as ischemic heart disease and ventricular arrhythmias resulting in sudden cardiac death (*6–8*). The cardiac hypertrophy that often accompanies the development of hypertension is a known risk factor for cardiovascular mortality including sudden death (*9*). However, the relation, if any, between hypertrophy and the cardiac sympathetic nerve system remains obscure. According to the Guidelines Subcommittee of the World Health Organization (WHO)/International Society of Hypertension (ISH) Mild Hypertension Liaison Committee (*10*), patients with mild elevation of blood pressure are at increased risk of cardiovascular disease. In their guidelines, the subcommittee emphasized the treatment of borderline hypertensive patients, since 15%–20% are expected to become hypertensive within a few years (*11*). Therefore, assessment of the change in cardiac sympathetic nervous function in the early, developing stage of essential hypertension could help to resolve the role of the sympathetic nervous system in the development of essential hypertension as well as in the progression of hypertension-induced left ventricular hypertrophy.

Although cardiac adrenergic activity has been difficult to assess in vivo, ^{123}I-metaiodobenzylguanidine (MIBG), an analog of guanidine that shares the same neuronal transport and storage mechanisms with norepinephrine, has been used to easily evaluate the sympathetic activity and innervation of the left ventricle (*12*). In particular, MIBG imaging is a most appropriate method to evaluate sympathetic nervous function in the left ventricle. To investigate cardiac sympathetic nervous function during the course of establishment of essential hypertension, we compared the MIBG imaging parameters in mildly hypertensive, borderline hypertensive and normotensive patients.

METHODS

Patients

We selected 74 men over 39 y old (range, 40–69 y) who were referred for cardiac catheterization because of chest pain and/or electrocardiographic abnormalities. Coronary angiography with the acetylcholine provocation test was performed by the standard Judkins technique in all patients who had normal cardiac function and normal coronary arteries without spasm. Four seated blood pressure determinations were made at intervals of at least 1 wk

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using a mercury sphygmomanometer. The subjects were divided, according to the Guidelines Subcommittee of the WHO/ISH Mild Hypertension Liaison Committee (*10*), into three groups: 25 normotensive men (60 ± 7 y), 25 borderline hypertensive men (62 ± 9 y) and 24 mildly hypertensive men (60 ± 8 y), none of whom had diabetes mellitus or any other disease affecting the autonomic nervous system. Within 1 mo after cardiac catheterization, they underwent MIBG imaging. All hypertensive patients were newly diagnosed and had not received any antihypertensive therapy before MIBG imaging, except for diet therapy. Informed consent was obtained from each patient. This study protocol was approved by the hospital's ethics committee.

Echocardiography

Echocardiograms were recorded with the patient in the supine position turned 30° on his left side using an SSD-870 echocardiograph (Aloka Co., Ltd., Tokyo, Japan) with a 3.5-MHz transducer. M-mode echocardiograms were recorded under two-dimensional guidance, and the tracing was recorded at paper speed of 100 mm/s. Measurements were obtained to the nearest millimeter for at least four cardiac cycles during quiet respiration, and the average values were used for analysis. All echocardiograms were recorded in the intercostal and left ventricular area, just below the tip of the mitral leaflets, and with each patient in the same position. Measurements were obtained by the same observer according to the guidelines of the American Society of Echocardiography (ASE) (*13*). The parameters measured or calculated were the left ventricular end-diastolic and end-systolic dimensions, and septal and posterior wall thickness in systole and diastole. In addition, the left ventricular mass (LVM) was calculated as follows (*14*):

$$1.05 \times \pi/3\,[[2(\text{left ventricular end} - \text{diastolic dimension}) + (\text{septal} + \text{posterior wall thickness in diastole})] \times [\text{left ventricular end-diastolic dimension} + (\text{septal} + \text{posterior wall thickness in diastole})]^2/2] - (\text{left ventricular end-diastolic dimension})^3$$

The LVM was divided by the body surface area to obtain the LVM index (LVMI) (g/m^2). The left ventricular ejection fraction (EF) was also calculated according to the ASE criteria by the area length method (*15*).

MIBG Scintigraphy

After an overnight fast, a dose of 111 MBq commercially available MIBG (Daiichi Radioisotopes Labs. Ltd., Tokyo, Japan) was administered intravenously. One 5-min static acquisition in the anterior view was performed at 15 min and 3 h after the injection. Cardiac images were also acquired after each static acquisition, using a triple-head gamma camera (GCA 9300A/HG; Toshiba, Tokyo, Japan). The data were reconstructed by filtered backprojection (Shepp-Logan) on a Toshiba GMS 5500A system. Neither scatter correction nor attenuation correction was performed. Oblique tomographic slices on the short, vertical-long and horizontal-long axes were computed and displayed.

The left ventricular MIBG activity and washout were measured using a square region of interest placed over the left ventricle with the peak count density and over the upper mediastinum. The heart-to-mediastinum ratio (H/M ratio) was calculated to quantify the cardiac MIBG uptake as a fraction of the mean counts per pixel in the heart divided by those in the upper mediastinum (*16*). The myocardial washout rate was defined as the percent change in activity within the left ventricle from the initial to delayed images and was calculated as follows:

$$\text{washout rate (\%)} = (A - B)/A \times 100,$$

where A = average counts/pixel in the left ventricle on the initial image and B = average decay-corrected counts in the same region on the delayed image. Decay correction was performed with the half-life of the radionuclide (^{123}I) assumed to be 13 h.

Quantitative analysis of the MIBG uptake in the left ventricle was also performed using a computerized two-dimensional polar map of the three-dimensional myocardial radionuclide activity. For semiquantitative analysis, the relative MIBG uptake of the left ventricle was calculated in all short-axis slices using a modified three-dimensional region-of-interest algorithm and setting the maximal MIBG count at 100%. If the maximal MIBG uptake was situated in the inferior wall, we examined whether the site was in the liver. If so, the data were excluded or a two-dimensional polar map was made again. The regional mean MIBG count/pixel on the delayed image was calculated as follows: regional mean MIBG count/pixel = (maximum count/pixel on the polar map) × (regional % MIBG uptake)

Quantitative analysis of the regional washout rate of MIBG was also performed. Washout rates from the heart were calculated using initial and delayed images. The washout rate in a region was obtained from the following formula:

$$\text{washout rate (\%)} = (A - B)/A \times 100,$$

where A = average counts in the region on the initial image and B = average decay-corrected counts in the same region on the delayed image. Decay correction was performed with the half-life of the radionuclide (^{123}I) assumed to be 13 h. On a polar map representation, the territory in the distribution of each of the three major coronary arteries was defined as the anterior, the lateral and the inferior regions (*17,18*).

Statistical Analysis

Data are expressed as mean ± SD. Chi-square test or the Fisher exact test was used to determine the significance of differences in the observed occurrence rates. Analysis of variance with multicomparison test was used for between-group comparisons. A linear regression analysis was carried out to examine the relationships between H/M ratio, washout rate and the echocardiographic variables (LVM, LVMI, EF and wall thickness). Probability values of less than 0.05 were considered significant.

RESULTS

Echocardiographic Variables

The clinical characteristics and echocardiographic variables in each patient group are shown in Table 1. There were no significant differences among the groups in age and body mass index, or in the septal wall thickness or EF. The posterior wall thickness, left ventricular diastolic diameter and LVM were significantly greater in the mild hypertensive group than in the normotensive group. The LVMI was significantly greater in the mild hypertensive group than in the normotensive and the borderline hypertensive groups.

TABLE 1
Distribution of Clinical Variables

	Normotensive subjects	Borderline hypertension	Mild hypertension
Study group			
(n)	25	25	24
Age (y) (range)	60 ± 7	62 ± 9	60 ± 8
Smoking	6	5	6
Hypercholesteremia	4	6	5
FH	8	8	6
Hyperuricemia	4	4	3
Body mass index (kg/m^2)	22.4 ± 3.2	23.2 ± 2.4	22.6 ± 4.1
Ecocardiographic variables			
Septal wall thickness (mm)	9.7 ± 1.4	10.0 ± 1.4	10.5 ± 1.7
PW thickness (mm)	10.1 ± 1.2†	9.8 ± 1.3‡	11.1 ± 1.8
LV diastolic diameter (mm)	48.6 ± 4.6†	49.2 ± 3.8	52.5 ± 3.9
LVM (g)	166.4 ± 38.2‡	171.3 ± 43.0	206.2 ± 46.5
LVMI (g/m^2)	99.9 ± 20.7‖	110.0 ± 24.4†	125.6 ± 28.6
EF (%)	68.4 ± 4.2	70.4 ± 3.3	68.9 ± 4.5
Scintigraphic variables			
H/M ratio (initial image)	2.0 ± 0.3	2.1 ± 0.2	1.9 ± 0.3‡
H/M ratio (delayed image)*	2.1 ± 0.3	2.1 ± 0.2	1.8 ± 0.3
Washout rate (%)*	7.0 ± 4.9	11.9 ± 8.9	17.6 ± 10.8
Regional mean MIBG count/pixel on delayed image			
Anterior region	24.6 ± 7.0‖	27.0 ± 5.3‖	16.5 ± 5.8
Lateral region	26.0 ± 7.0‖	27.9 ± 6.1‖	16.9 ± 5.8
Inferior region	23.0 ± 5.9‖	24.9 ± 6.1‖	15.5 ± 5.1
Regional washout (%)			
Anterior region	6.4 ± 5.0‡	10.6 ± 8.9	15.2 ± 12.1
Lateral region	9.4 ± 5.9‖	13.8 ± 8.9†	20.4 ± 12.0
Inferior region	9.8 ± 5.9‖	12.6 ± 8.9§	17.1 ± 10.4
Maximum count/pixel	33.3 ± 8.9‖	36.1 ± 7.8‖	22.7 ± 7.6

Values are expressed as mean ± SD.

*The statistical comparison among the three groups of the H/M ratio on the delayed image and washout rate is described in Figure 1.

†$P < 0.05$; ‡$P < 0.005$; §$P < 0.01$; ‖$P < 0.001$, compared to the mildly hypertensive group.

FH = family history of coronary heart disease; PW = posterior wall; LV = left ventricle; LVM = left ventricular mass; LVMI = left ventricular mass index; EF = ejection fraction; H/M = heart-to-mediastinum.

Scintigraphic Variables

The scintigraphic variables are also listed in Table 1. The initial H/M ratio was significantly higher in the borderline hypertensive group than in the mild hypertensive group. The initial H/M ratio was also higher in the borderline hypertensive group than in the normotensive group, although it did not reach statistical significance ($P < 0.08$). The H/M ratio and maximum MIBG count/pixel on the delayed image were significantly lower in the mild hypertensive group than in the normotensive and the borderline hypertensive groups (Fig. 1A). The regional mean MIBG count/pixel was also significantly lower in the mild hypertensive group than in the normotensive and the borderline hypertensive groups for every region. In contrast, the washout rate was significantly higher in the mild hypertensive group compared to the other groups, and the borderline hypertensive group had a significantly higher washout rate compared to the normotensive group (Fig. 1B).

Correlations Between Scintigraphic and Echocardiographic Variables

The MIBG washout rate had a strong positive correlation with the LVMI ($r = 0.77$, $P < 0.0001$) (Fig. 2) and with the LVM ($r = 0.59$, $P < 0.0001$). The H/M ratio had significant negative correlations with the LVM ($r = -0.45$, $P < 0.0001$) and the LVMI ($r = -0.40$, $P < 0.0006$).

DISCUSSION

Several reported studies (*19–22*) on essential hypertension were conducted using MIBG imaging. All these studies conducted in patients with established hypertension demonstrated that the MIBG uptake was decreased, often accompanied by enhanced washout, in patients with left ventricular dysfunction, suggesting regional or global abnormalities in the cardiac sympathetic nervous system. In our study, the borderline hypertensive patients had a significantly higher MIBG washout rate than the normotensive group and the mildly hypertensive patients had a significantly higher washout rate and lower MIBG uptake than the normotensive and borderline hypertensive patients. In addition, the MIBG washout rate had a strong positive correlation with LVMI. Thus, we demonstrated that the MIBG washout rate is increased from the earlier, developmental phase of hypertension and that the increase in washout rate is associated with left ventricular hypertrophy.

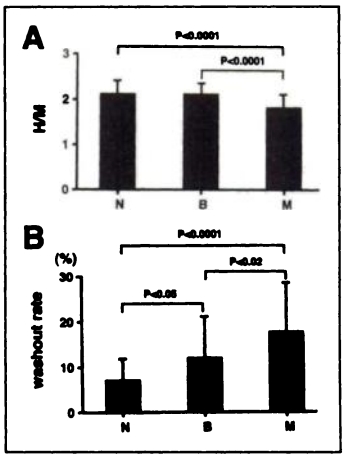

FIGURE 1. Comparison of heart-to-mediastinum (H/M) ratio (A) and washout rate (B) among three groups. H/M ratio is significantly higher in mildly hypertensive group (M) than those in borderline hypertensive (B) and normotensive (N) groups. Washout rate is also significantly higher in group M than in groups B and N. In addition, group B has a significantly higher washout rate than N group. Values are expressed as mean ± SD.

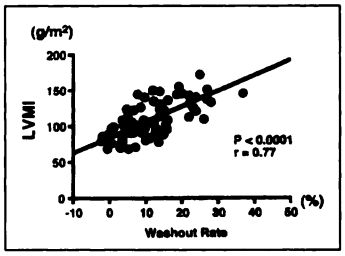

FIGURE 2. Scatterplots showing relationship between ^{123}I-MIBG washout rate and LVMI.

Cardiac Sympathetic Nervous System in Essential Hypertension

Based on earlier studies on hypertension, the hypothesis was advanced that the abnormality of the sympathetic nervous system involved in the pathogenesis of hypertension is derived from the elevated plasma norepinephrine level observed in hypertensive patients (*3*). However, this hypothesis does not address the mechanisms contributing to the elevated plasma norepinephrine level in hypertension. Recent microneurographic studies (*2,4*) have demonstrated that central sympathetic neural outflow is augmented in essential hypertension and that muscle sympathetic nervous activity is elevated in young borderline hypertensives and in mild essential hypertensives, suggesting that central sympathetic overactivity contributes to the development and maintenance of essential hypertension. Activation of the cardiac sympathetic nervous system in essential hypertension was similarly documented using power spectral analysis (*6*) and measurement of tritirated norepinephrine (*1*).

Using MIBG imaging, we demonstrated that the cardiac sympathetic nervous function changed according to the clinical stage of essential hypertension from its early stage. In general, it is considered that an enhanced washout rate reflects enhanced release of norepinephrine from presynaptic sites and that reduced MIBG uptake reflects reduced norepinephrine content at presynaptic sites or reduced neural density. Furthermore, most investigators (*16–24*) believe that MIBG washout reflects cardiac sympathetic activity in the heart affected by various diseases. In our study, borderline hypertensive patients had clinical characteristics similar to those in the normotensive group, except for blood pressure level. In borderline hypertensive patients, therefore, the higher washout rate is considered simply to reflect their greater cardiac sympathetic activity. This is supported by the observation that muscle sympathetic nervous activity is elevated in young borderline hypertensives (*4*). In general, the normal MIBG uptake at 3 h represents a normal MIBG reuptake, normal MIBG uptake by storage vesicles and normal washout. Regarding a possible mechanism for enhanced washout rate combined with normal MIBG uptake at 3 h in the borderline hypertensives, Dubois et al. (*21*) demonstrated that enhanced washout combined with a high initial uptake was observed in the genetically determined hypertension of the spontaneous hypertensive rat. This could be the result of either an increase in adrenergic reuptake sites, an increase in reuptake efficacy or both. Because we could find a higher initial uptake in the borderline hypertensive patients than in the normotensive subjects, the enhanced MIBG washout may simply result from enhanced initial uptake. Therefore, enhanced initial uptake may be characteristic in the very early stage of essential hypertension.

Thus, the borderline hypertensive patients appear to have physiologically high cardiac sympathetic activity. In contrast, it is not simple to assess cardiac sympathetic activity from the MIBG kinetics in the mildly hypertensive patients, because they had cardiac hypertrophy that could affect MIBG washout rate and uptake (*25,26*).

Cardiac Hypertrophy and MIBG Kinetics

Decreased number of cardiac sympathetic nerve endings (denervation), decline in reuptake function, reduction in MIBG uptake by storage vesicles and increased norepinephrine release have been proposed as possible mechanisms contributing to changes in MIBG uptake and washout in patients with left ventricular hypertrophy (*25,26*). However, sympathetic denervation and impairment of reuptake function are unlikely to have occurred in the mildly hypertensive patients, because their hypertrophy (<160 g/m^2) was considered not to be so severe as to produce cardiac sympathetic nerve denervation. There have been no reports on cardiac denervation in uncomplicated mild hypertension. In addition, Meredith et al. (*27*) have reported that patients with heart failure due to hypertension and coronary artery disease show increased neural release of norepinephrine, which results from an increase in sympathetic nerve firing, but they show preserved reuptake of norepinephrine. Therefore, it is not likely that only mild hypertrophy due to hypertension can result in sympathetic denervation and/or a decline of reuptake function. A reduction in the MIBG uptake by storage vesicles was proposed in patients with severe hypertrophy and heart failure (*26*). Therefore, it is also unlikely that this mechanism contributes to reduced MIBG uptake and enhanced washout in the mild hypertension with normal cardiac function examined in this study. Taken together, the findings to date suggest that the most probable mechanism for the enhanced washout rate combined with reduced MIBG uptake in the mildly hypertensive patients is enhanced norepinephrine release overwhelming reuptake capacity due to cardiac sympathetic overactivity. A similar MIBG finding is observed in heart failure, which is well known to be associated with cardiac sympathetic overactivity (*23*). In addition, this contention is supported by several reports demonstrating the activation of efferent sympathetic nerve discharge in patients with mild hypertension (*2,5*). Considering the MIBG washout rate, therefore, it seems likely that the mildly hypertensive patients have higher sympathetic activity than the borderline hypertensive patients.

Cardiac Hypertrophy and Sympathetic Nervous Function

Because hypertension-induced cardiac hypertrophy often occurs in hypertensive patients, it is necessary to consider the relationship between cardiac hypertrophy and the cardiac sympathetic nervous system. It has been demonstrated that cardiac norepinephrine content and turnover do not increase in parallel with the increase in ventricular mass in hypertensive hypertrophy (*28,29*), which indicates that the increased release of norepinephrine from the heart to the plasma in patients with essential hypertension is unlikely to be due to coexistent left ventricular hypertrophy. In addition, it has been reported that abnormality of parasympathetic nervous activity is important in established essential hypertension (*30,31*). We could not evaluate severely hypertensive patients, because we could not exclude the effects of antihypertensive drugs and concomitant organ damage such as left ventricular dysfunction on the sympathetic nervous system. But Mitani et al. (*22*) demonstrated that hypertensive patients with normal cardiac function who had hypertrophy more severe than that in our mildly hypertensive patients had reduced MIBG uptake without enhanced washout compared to hypertensive patients without hypertrophy. In established and advanced essential hypertension, it is clear that the sympathetic activity is not always in parallel with the progression of hypertrophy and the development of severe hypertension (*22,28–30*). In this study, however, a strong positive correlation between MIBG washout and LVMI was observed in the earlier, developmental phase of essential hypertension. It is unlikely that increased washout resulted from cardiac hypertrophy alone in these patients, although severe hypertrophy causes various changes in the cardiac sympathetic nervous system (*25,27*). The strong positive correlation between LVMI and MIBG washout suggests a strong relationship between cardiac sympathetic activity and progression of hypertension-induced cardiac hypertrophy in the early phase of essential hypertension.

Study Limitation

All patients in the study had chest pains (n = 64), most of which were thought to be atypical, and/or abnormal resting electrocardiogram (n = 38), and they may not be exactly normal in their coronary physiology, despite normal cardiac function and normal coronary arteries without spasm. Therefore, MIBG uptake and washout in normotensive subjects may be abnormal compared to those in normal subjects. However, since they did not have any other abnormalities except for electrocardiographic abnormality or chest pain and their MIBG data were similar to those from a previous study with normal volunteers (*31*), we consider normotensive subjects as not abnormal. In addition, high washout rate and/or low MIBG uptake in hypertensives may, in part, result from patient selection. However, because patient characteristics in each group are similar, possible effects of patient selection are negligible when compared among the three groups.

CONCLUSION

Based on the present results, we suggest that cardiac sympathetic activity increases from the early phase of essential hypertension and is strongly associated with the progression of cardiac hypertrophy. One might be able to identify an individual at high risk for developing essential hypertension using MIBG cardiac imaging, since MIBG washout is already increased before essential hypertension is established. In addition, early reduction in cardiac sympathetic overactivity may affect the advance of hypertension as well as the progression of cardiac hypertrophy. However, a prospective trial with rigorous entrance criteria and long-term follow-up is needed to test this hypothesis.

MIBG washout is increased from the early stage of essential hypertension and in accordance with the progression of hypertrophy. Thus, this study suggests a strong relationship between cardiac sympathetic activity and the advance of hypertension at its early stages.

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