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Direct Evidence of Impaired Cardiac Sympathetic Innervation in Essential Hypertensive Patients with Left Ventricular Hypertrophy

Taishi Kuwahara, Mareomi Hamada and Kunio Hiwada
The Second Department of Internal Medicine, Ehime University School of Medicine, Ehime, Japan

Increased sympathetic nervous activity has been proposed as one of the causes of left ventricular hypertrophy (LVH) associated with hypertension. However, the precise relationship is not fully understood. **Methods:** To elucidate the relationship between myocardial sympathetic nervous activity and LVH in patients with essential hypertension (EHT), we performed ^{123}I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy in 49 patients with EHT and 17 normotensive control subjects. Sympathetic innervation of the left ventricle was evaluated using SPECT, and the whole heart uptake of the tracer was quantitatively assessed as the heart-to-mediastinum uptake ratio on both the early (15-min) and delayed (5-hr) images. Myocardial washout rate (MWR) of the tracer from 15 min to 5 hr after the isotope administration was also calculated. The left ventricular mass index (LVMI) was determined echocardiographically. **Results:** In 49 hypertensive patients, there was a negative correlation between LVMI and heart-to-mediastinum uptake ratio on both the early and delayed images ($r = -0.55$, $p < 0.0001$; $r = -0.63$, $p < 0.0001$, respectively). In addition, there was a positive correlation between the LVMI and MWR of ^{123}I-MIBG in these hypertensive patients ($r = 0.59$, $p < 0.0001$). As for the regional uptake of the tracer, there was no significant difference between control subjects and hypertensive patients without cardiac hypertrophy, but a significant decrease of the uptake in the inferior and lateral regions was observed in hypertensive patients with cardiac hypertrophy. **Conclusion:** Patients with EHT had decreased accumulation and increased MWR of ^{123}I-MIBG in proportion to the degree of LVH. Hypertensive patients with cardiac hypertrophy had impaired sympathetic innervation in the inferior and lateral regions of the left ventricle.

Key Words: sympathetic nervous system; norepinephrine; left ventricular hypertrophy; iodine radioisotope; hypertension

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Essential hypertension (EHT) is a major risk factor for the progression of cardiovascular damage in such organs as the brain, heart and kidney. Left ventricular hypertrophy (LVH), one of the types of end-organ damage associated with hypertension, is recognized as an independent risk factor for cardiovascular events (*1*), including cardiac sudden death (*2*). It is recognized that not only mechanical factors, but also humoral factors, are related to LVH in hypertension. Increased sympathetic nervous activity has been proposed as one of the influential factors on LVH (*3–5*), based on the observations that catecholamine administration induces LVH (*3*) and that sympatholytic intervention diminishes myocardial hypertrophy (*4*). In addition, alpha-1 adrenergic agonists were found to be potent stimuli for the hypertrophy of fetal cardiac myocytes (*5*). However, some experimental studies reported that chemical or surgical sympathectomy failed to block the development of LVH induced by hypoxia or hypertension (*6,7*). Moreover, Cooper et al. (*8*) postulated that mechanical load itself, rather than catecholamines, was directly responsible for cardiac hypertrophy. Thus, the role of sympathetic nervous activity in the genesis of LVH, especially in humans, has not been fully elucidated.

Iodine-123-labeled metaiodobenzylguanidine (MIBG) is a norepinephrine analog that is taken up by sympathetic nerve

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For correspondence or reprints contact: Mareomi Hamada, MD, The Second Department of Internal Medicine, Ehime University School of Medicine, Shigenobu-cho, Onsen-gun, Ehime, 791-0295, Japan.

terminals and accumulates in intraneural storage vesicles (*9*). It is well known that ^{123}I-MIBG myocardial scintigraphy is a good tool for noninvasively assessing myocardial sympathetic innervation and activity in patients with several heart diseases (*10–12*).

The purpose of this study was to investigate myocardial sympathetic innervation or activity in patients with EHT using ^{123}I-MIBG myocardial scintigraphy and to elucidate the relationship between LVH and myocardial sympathetic nervous activity.

MATERIALS AND METHODS

Subjects and Study Protocol

A total of 49 hospitalized patients with EHT were selected from 70 consecutive essential hypertensive patients in whom ^{123}I-MIBG myocardial scintigraphy was performed between October 1993 and October 1996. Twenty-one patients who had diabetes mellitus, ischemic heart disease or chronic renal failure (serum creatinine $\geq$ 1.5 mg/dl) were excluded. We classified 49 hypertensive patients into LVH and non-LVH groups on the basis of the left ventricular mass index (LVMI), which was echocardiographically determined. As we reported previously (*13*), LVH was defined as a LVMI $\geq$ 119 g/m^2 in men and 110 g/m^2 in women. The normotensive control (NC) group consisted of 13 patients who had chest pain but angiographically normal coronary arteries and no evidence of spasm and 4 patients who had no cardiac symptoms with normal left ventricular function on echocardiography and no ST-T change during treadmill exercise testing.

Informed consent for the procedure was obtained from each patient.

All patients received a diet containing 7 g NaCl per day, and all medications were discontinued on admission. After a 1-wk stabilization period, 24-hr urinary excretions of catecholamines and plasma levels of catecholamines were determined on 2 consecutive days, and their mean values were used as the daily parameter. Catecholamine concentrations were determined by high-performance liquid chromatography, as reported previously (*14*). Blood pressure was measured with an arm cuff and a mercury sphygmomanometer at 7 a.m., 1 p.m. and 8 p.m. on the day of the ^{123}I-MIBG myocardial scintigraphic examination, and the mean value was used as the baseline blood pressure.

Echocardiographic Measurement

Echocardiographic studies were performed using an SSD-870 echocardiograph with a 3.5-MHz transducer (Aloka Inc., Tokyo, Japan). Left ventricular end-diastolic and end-systolic dimensions, and thicknesses of interventricular septum and left ventricular posterior wall were measured according to the recommendations of the American Society of Echocardiography (*15*). Left ventricular mass was calculated by the formula of Devereux and Reichek (*16*) and was divided by body surface area to obtain LVMI. All recordings were measured by one investigator who did not know the patient's background.

Iodine-123-Metaiodobenzylguanidine Myocardial Scintigraphy

One or two weeks after the withdrawal of the drugs, we performed ^{123}I-MIBG myocardial scintigraphy. On the day of ^{123}I-MIBG scintigraphy, patients were instructed to have no breakfast and to continue fasting until the end of the last imaging session. A 111-MBq dose of ^{123}I-MIBG (Daiichi Radioisotope Laboratory, Tokyo, Japan) with a specific activity of 1665–2035 MBq/mg was administered intravenously, and images of early and delayed SPECT were obtained 15 min and 5 hr after the administration of ^{123}I-MIBG. The SPECT system (GCA 9300; Toshiba, Tokyo, Japan; and Scintipac 2400; Shimadzu, Kyoto, Japan) consisted of a triple-head, digital gamma camera equipped with high-resolution, low-energy, parallel-hole collimators. Energy discrimination was provided by a 15% window centered on the 160-keV photopeak of ^{123}I. Projection images were acquired for 90 sec each at 10° increments over a 360° orbit and were recorded at a digital resolution of 128 × 128. The projection data were smoothed using a Hanning filter, and a series of 3.5-mm-thick transverse slices were reconstructed with filtered backprojection by a ramp filter. Short-axis and long-axis slices perpendicular to the cardiac axes were reorganized, and a bull's-eye polar map was generated from the apical to basal short-axis slices to show the relative tracer distribution in the myocardium (*17*). Attenuation correction was made by uniform correction of the Chang method to multiply the original reconstructed image by the correction matrix (*18*), and scatter correction was not performed.

Quantitative Analysis

For a quantitative analysis of the myocardial ^{123}I-MIBG accumulation, we used the anterior planar projection images acquired in the SPECT studies. A region of interest (ROI) was set on the whole heart, and a square ROI, usually 10 × 10 pixels in size, was set on the mediastinum (Fig. 1A) on both the early and delayed images. The counts per pixel were measured for each ROI, and the heart-to-mediastinum (H/M) ^{123}I-MIBG activity ratio was calculated. The myocardial washout rate (MWR) of ^{123}I-MIBG was determined as the percentage of change in activity from 15 min to 5 hr after the isotope administration.

To study whether the ^{123}I-MIBG accumulations in organs other than the heart were altered, square ROIs, 10 × 10 pixels in size, were placed over the right upper lung and the right liver lobe, and the lung-to-mediastinum and liver-to-mediastinum ^{123}I-MIBG activity ratios and ^{123}I-MIBG washout rates from these organs were also measured.

Semiquantitative Analysis

For a semiquantitative analysis of the regional ^{123}I-MIBG uptake, the left ventricular myocardium was divided into five segments, anterior, septum, inferior, lateral and apex (*19*), on a bull's-eye polar map. At each segment, the counts per pixel of ^{123}I-MIBG were calculated, and they were expressed as a percentage of the maximum counts per pixel of the five segments (*19*).

Thallium-201 Myocardial Scintigraphy

To exclude myocardial perfusion abnormalities, we performed resting ^{201}Tl myocardial SPECT studies in 42 patients and exercise ^{201}Tl studies in 24 patients within 7 days after ^{123}I-MIBG imaging. Resting ^{201}Tl myocardial images were obtained 10 min after 111 MBq ^{201}Tl were administered intravenously. Stress ^{201}Tl images were acquired immediately after 111 MBq ^{201}Tl were administered at the maximum exercise, and redistribution images were obtained 3 hr after the administration. Thallium-201 SPECT images also were obtained in the same acquisition condition and reconstruction method of ^{123}I-MIBG imaging. Energy discrimination was centered at 70 keV with a 15% window for ^{201}Tl. Regional tracer uptake of ^{201}Tl was assessed visually as normal, reduced or defective by the consensus of two experienced observers without knowledge of the patient's background.

Moreover, ^{201}Tl activity at each segment on the bull's-eye polar map was determined in the same way as in ^{123}I-MIBG imaging. Resting or stress ^{201}Tl images were selected for the analysis.

Systolic Function in Hypertensive Patients

We performed gated radionuclide angiography using 740 MBq ^{99m}Tc-human serum albumin. A single-crystal scintillation camera (Starcam 400AC/T; General Electric Medical Systems, Milwaukee, WI) was used, and processing of the data was accomplished with the Scintipac 2400. Data were recorded at a rate of 40 frames

TABLE 1
Profiles of Hypertensive Patients

	NC	Non-LVH	LVH
n (M/F)	17 (9/8)	19 (11/8)	30 (19/11)
Age (yr)	50 ± 10	48 ± 15	53 ± 13
LVMI (g/m^2)	89 ± 18	88 ± 12	161 ± 39*†
SBP (mmHg)	117 ± 10	134 ± 18‡	153 ± 15*§
DBP (mmHg)	69 ± 5	81 ± 13‡	92 ± 12*¶
Heart rate (bpm)	63 ± 7	68 ± 9	65 ± 7
Duration of hypertension (yr)	—	8 ± 5	11 ± 9

*$p < 0.0001$.
†$p < 0.0001$ vs. non-LVH.
‡$p < 0.01$ vs. NC.
§$p < 0.0005$ vs. non-LVH.
¶$p < 0.01$ vs. non-LVH.
Values are mean ± s.d. DBP = diastolic blood pressure; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; NC = normotensive control; SBP = systolic blood pressure.

per cardiac cycle, and the time-activity curve was obtained. Left ventricular ejection fraction was calculated from the following equation: [(end-diastolic counts − end-systolic counts)/end-diastolic counts] × 100.

Statistical Analysis

Data are expressed as mean values ± s.d. Categorical variables were compared with Fisher's exact test and the chi-square test. The duration of hypertension between the LVH and non-LVH groups was compared with the unpaired Student's t-test. Comparisons among the three groups were performed using one-way analysis of variance with subsequent Scheffe's multiple-range tests. Univariate correlation was analyzed using Pearson's correlation coefficient, and $p < 0.05$ was considered significant.

RESULTS

Baseline Characteristics of the Patients

Profiles of hypertensive patients with or without LVH are shown in Table 1. Thirteen patients of the non-LVH group and 23 of the LVH group had been prescribed one or a combination of the following antihypertensive drugs: beta-blockers, diuretics, calcium channel blockers or angiotensin-converting enzyme inhibitors. There were no significant differences in the distribution and doses of these drugs used for treatment between the non-LVH and LVH groups.

Plasma and Urinary Catecholamine Values in the Three Groups

Plasma levels of norepinephrine in the LVH group were significantly higher than those in the other two groups, as shown in Table 2. However, there were no significant differences in other catecholamine values among three groups.

TABLE 3
Comparison of Myocardial Accumulation and Washout Rate of Iodine-123-Metaiodobenzylguanidine Among the Three Groups

	NC	Non-LVH	LVH
H/M ratio (early)	2.16 ± 0.25	2.30 ± 0.25	2.07 ± 0.34*
H/M ratio (delayed)	2.41 ± 0.22	2.43 ± 0.35	2.05 ± 0.42†‡
MWR (%)	37 ± 5	39 ± 5	43 ± 6§¶

*$p < 0.05$ vs. non-LVH.
†$p < 0.01$ vs. NC.
‡$p < 0.005$ vs. non-LVH.
§$p < 0.001$ vs. NC.
¶$p < 0.05$ vs. non-LVH.
Values are mean ± s.d. H/M = heart-to-mediastinum uptake; LVH = left ventricular hypertrophy; MWR = myocardial washout rate; NC = normotensive control.

Quantitative Analysis of Iodine-123-Metaiodobenzylguanidine Imaging

Heart-to-mediastinum ratio in the LVH group was lower than that in the non-LVH group on the early images and was also lower than that in the other two groups on the delayed images. On the contrary, MWR was greater in the LVH group than in the other two groups (Table 3). Figure 1 shows the representative pattern of the early and delayed anterior planar images of a normotensive control subject (Fig. 1A, B) and a hypertensive patient with LVH (Fig. 1C, D).

Semiquantitative Analysis of Regional Iodine-123-Metaiodobenzylguanidine and Thallium-201

Table 4 shows the comparison of regional ^{123}I-MIBG uptake among the three groups. On the early images, the regional ^{123}I-MIBG uptake in the inferior region was less in the LVH group than in the other two groups, and that in the lateral region was less in the LVH than in the NC group. The regional ^{123}I-MIBG uptake on the delayed images showed the same pattern as that on the early images. However, there was no significant difference in the regional ^{201}Tl uptake among the three groups. Figure 2 shows ^{123}I-MIBG and ^{201}Tl images of a representative patient with LVH, whose coronary angiography showed completely normal coronary arteries.

Relationship Between Scintigraphic Data and Left Ventricular Mass Index in Hypertensive Patients

As shown in Figure 3, H/M ratios on both the early (upper) and delayed (lower) images in 49 hypertensive patients correlated negatively with LVMI. In addition, there was a positive

TABLE 2
Catecholamine Data

	NC (n = 11)	Non-LVH (n = 15)	LVH (n = 28)
Plasma levels of catecholamines			
Epinephrine (pmol/liter)	131 ± 87.3	126 ± 92.8	142 ± 81.9
Nonrepinephrine (nmol/liter)	0.963 ± 0.29	1.11 ± 0.48	1.64 ± 0.82*
Dopamine (pmol/liter)	117.5 ± 45.7	84.9 ± 19.6	91.4 ± 39.2
Urinary excretion of catecholamines			
Epinephrine (nmol/day)	49.1 ± 21.8	81.9 ± 54.6	87.3 ± 65.5
Nonrepinephrine (nmol/day)	721 ± 443	662 ± 290	981 ± 591
Dopamine (μmol/day)	6.21 ± 4.9	5.70 ± 2.8	7.10 ± 4.7

*$p < 0.05$ vs. NC or non-LVH.
Values are mean ± s.d. LVH = left ventricular hypertrophy; NC = normotensive control.

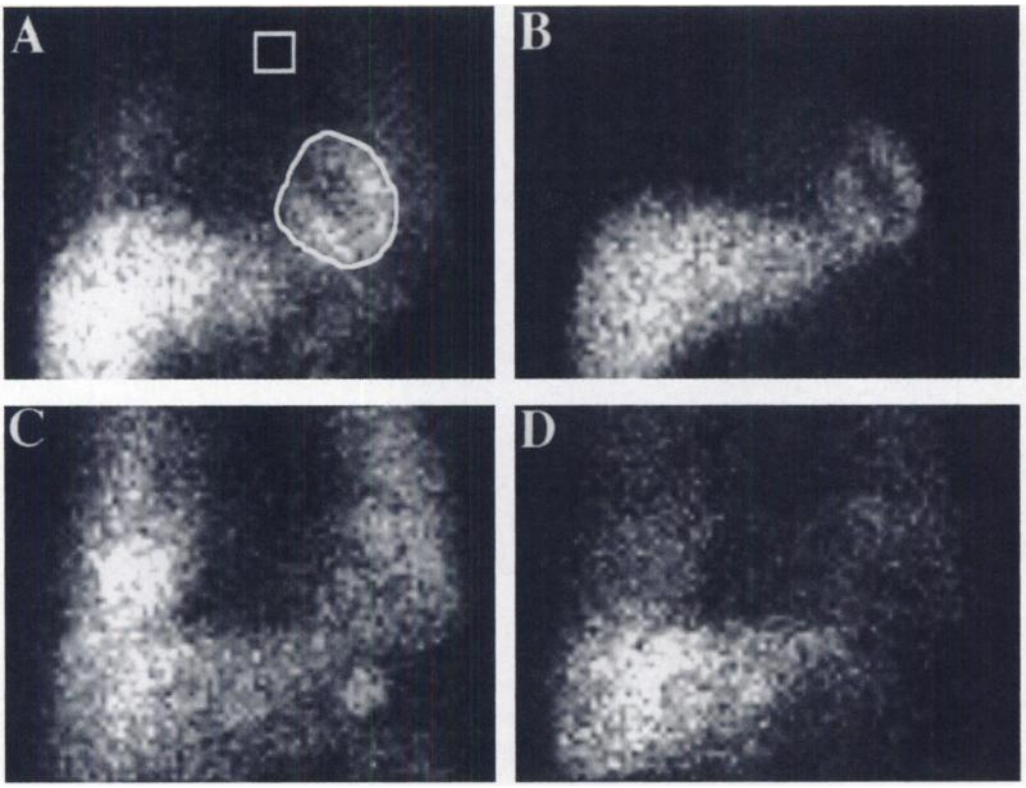

FIGURE 1. Anterior planar images. Rest (A) and delayed (B) images from normotensive control subject. Regions of interest set on whole heart and mediastinum are shown (A). Rest (C) and delayed (D) images of hypertensive patient with left ventricular hypertrophy. Clearance of ^{123}I-MIBG from heart is accelerated, and myocardial accumulation of ^{123}I-MIBG is decreased in patient with left ventricular hypertrophy (D).

correlation between MWR and LVMI in hypertensive patients, as shown in Figure 4.

Relationships Between Scintigraphic Data and Catecholamines

Plasma norepinephrine concentrations inversely correlated with H/M ratio on the delayed images ($r = -0.47$, $p < 0.0005$) and positively correlated with MWR ($r = 0.40$, $p < 0.005$). However, there was no significant correlation between plasma norepinephrine concentrations and the H/M ratio on the early images.

Systolic Function in Hypertensive Patients

Left ventricular ejection fractions of 8 normotensive control subjects, 9 non-LVH and 23 LVH patients were 55% ± 6%, 68% ± 17% and 58% ± 13%, respectively (p is nonsignificant). There were no significant correlations between ejection fraction and ^{123}I-MIBG scintigraphic data.

Liver and Lung Iodine-123-Metaiodobenzylguanidine Uptake

There were no significant differences in liver-to-mediastinum and lung-to-mediastinum ^{123}I-MIBG activity ratios on the early and delayed images or in ^{123}I-MIBG washout rate from these organs among the three groups.

Visual Assessment of Thallium Myocardial Scintigraphy

No patients except three hypertensive patients, one non-LVH and two LVH patients, showed a myocardial perfusion defect on resting or exercise ^{201}Tl myocardial scintigraphy. However, coronary angiography revealed normal coronary arteries in these three patients.

DISCUSSION

The major finding of this study is that the cardiac sympathetic innervation was impaired in hypertensive patients with LVH, predominantly located in the inferior and lateral regions of the left ventricle. In addition, hypertensive patients had a decreased

TABLE 4
Comparison of Regional Metaiodobenzylguanidine (MIBG) Uptake Among the Three Groups

	MIBG early image			MIBG delayed image			Thallium-201 image		
Location	NC	Non-LVH	LVH	NC	Non-LVH	LVH	NC	Non-LVH	LVH
Anterior	97 ± 4	97 ± 4	97 ± 4	99 ± 3	98 ± 4	97 ± 7	95 ± 4	92 ± 5	94 ± 5
Septum	90 ± 5	90 ± 4	91 ± 6	88 ± 7	90 ± 7	91 ± 8	86 ± 5	85 ± 6	86 ± 7
Inferior	89 ± 4	86 ± 6	81 ± 6*†	85 ± 6	81 ± 12	74 ± 7‡§	88 ± 4	86 ± 6	84 ± 4
Lateral	99 ± 3	98 ± 4	94 ± 7¶	96 ± 5	92 ± 8	86 ± 11‡	99 ± 1	99 ± 1	99 ± 1
Apex	82 ± 5	81 ± 5	78 ± 8	76 ± 7	74 ± 9	75 ± 11	82 ± 6	82 ± 4	83 ± 6

* $p < 0.0005$ versus NC.
† $p < 0.01$ versus non-LVH.
‡ $p < 0.005$ versus NC.
§ $p < 0.05$ versus non-LVH.
¶ $p < 0.05$ versus NC.
Values are mean ± s.d. LVH = left venticular hypertrophy; NC = normotensive control.

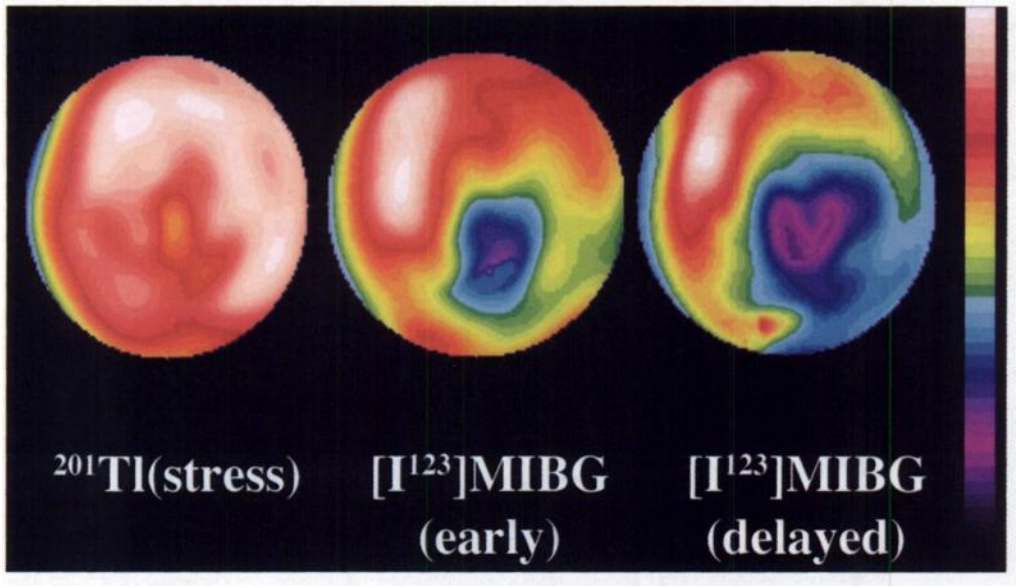

FIGURE 2. A 70-yr-old man with essential hypertension and left ventricular hypertrophy. Stress thallium image shows normal perfusion, but ^{123}I-MIBG images show decreased accumulation of tracer in inferior and lateral regions of left ventricle.

accumulation and an increased MWR of ^{123}I-MIBG in proportion to the degree of LVH.

Myocardial Uptake and Washout of Iodine-123-Metaiodobenzylguanidine

Given that the non-neuronal uptake is not significant in the human heart (*20*), there are some possible explanations for a decreased myocardial accumulation and an increased MWR of ^{123}I-MIBG in the hypertrophied myocardium. First, an accelerated cardiac sympathetic nervous activity in patients with cardiac hypertrophy may be one reason. Recently, Kelm et al. (*21*) have reported that a cardiac norepinephrine release rate is significantly increased in hypertensive patients with cardiac hypertrophy. This hyperstimulated condition of the cardiac sympathetic nervous activity can result in the increased release of ^{123}I-MIBG from the heart, and consequently, myocardial ^{123}I-MIBG accumulation could be decreased. Second, an impaired ^{123}I-MIBG uptake into the sympathetic nerve terminals may be another reason. The uptake of exogenous norepinephrine into the heart is less in the hypertrophied myocardium than in the normal heart (*22*). This evidence can account for the reduction of myocardial ^{123}I-MIBG uptake and the increased washout rate of ^{123}I-MIBG.

The elevated level of plasma norepinephrine may be another possibility of the reduced cardiac uptake of ^{123}I-MIBG. However, there was only a weak correlation between plasma norepinephrine and the H/M ratio on the delayed images. Moreover, there was no significant difference in lung ^{123}I-MIBG accumulation, which was competitively reduced by norepinephrine (*23,24*), among the three groups. Therefore, we speculate that elevated plasma levels of norepinephrine are not closely related to the decreased cardiac ^{123}I-MIBG accumulation in hypertensive patients with LVH.

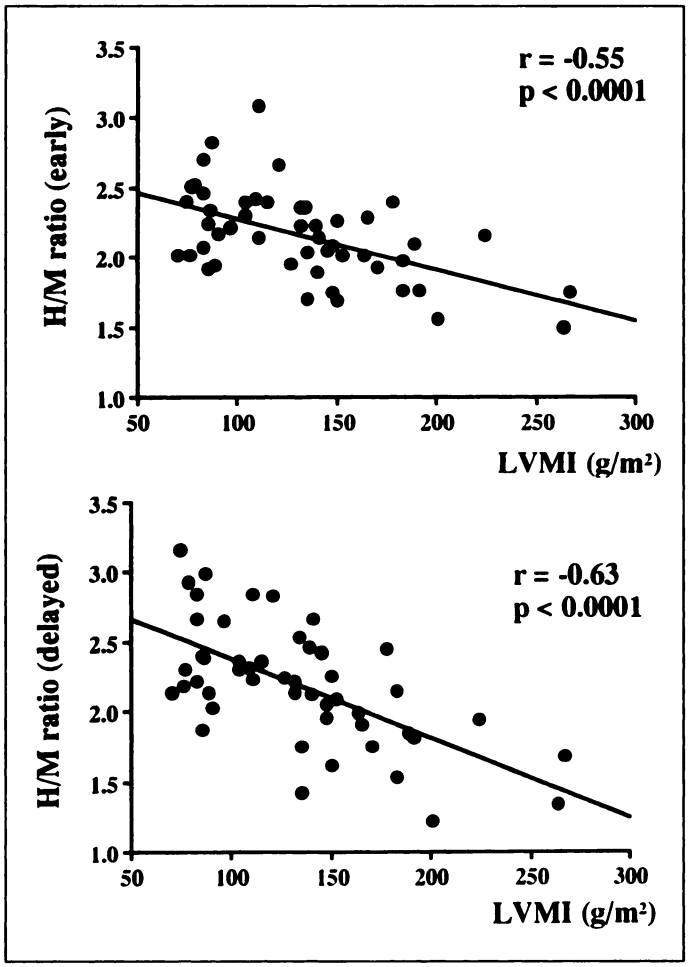

FIGURE 3. Relationship between LVMI and H/M ratio on early (upper) and delayed (lower) images in 49 hypertensive patients.

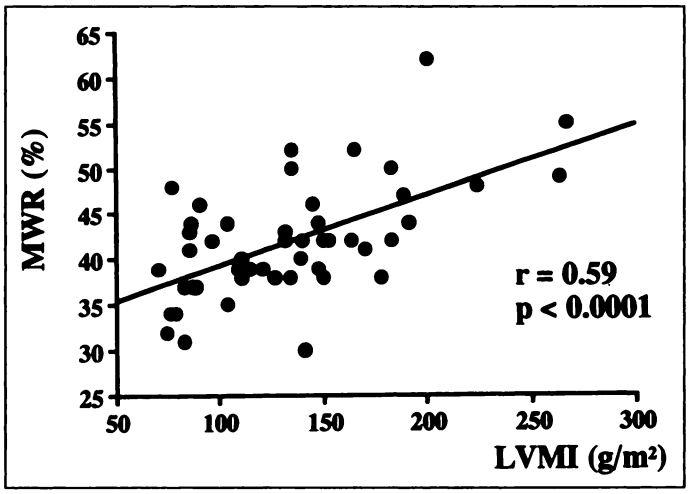

FIGURE 4. Relationship between LVMI and MWR in 49 hypertensive patients.

Regional Reduction of Iodine-123-Metaiodobenzylguanidine Uptake

The regional uptake of ^{123}I-MIBG was decreased significantly in the inferior and lateral regions in hypertensive patients with LVH; however, the exact cause of this result remains uncertain. We previously reported that the prevalence of the negative T wave was observed mainly in the lateral portion of the left ventricle and, partly, in the inferior in essential hypertensive patients with LVH (*25*). In view of this finding, our result may reflect a difference in the severity of myocardial hypertrophy in the left ventricle.

Systolic Function and Cardiac Sympathetic Nerve Activity

Left ventricular ejection fractions of the patients with LVH were normal, despite the abnormal ^{123}I-MIBG distribution and kinetics. We did not find any correlation between the ejection fraction and ^{123}I-MIBG scintigraphic data, as had been reported in the patients with dilated cardiomyopathy (*26*). Although the cause of this finding is not clear, cardiac sympathetic nervous activity may be influenced by the several myocardial conditions.

Study Limitation

A limitation of this study is that 36 of the hypertensive patients (74%) had received antihypertensive therapy, although the discontinuation of the therapy was at least 1 wk before the evaluation. Despite this problem, a highly significant association was observed between myocardial sympathetic nervous activity and the LVMI. In addition, there was no difference in the previous medications between the non-LVH and LVH groups. Thus, we conclude that the influence of previous medication on the relationship between cardiac sympathetic innervation and LVH is not significantly high.

CONCLUSION

Cardiac sympathetic innervation was impaired in hypertensive patients with LVH, predominantly located in the inferior and lateral regions of the left ventricle. In addition, hypertensive patients had a decreased accumulation and an increased MWR of ^{123}I-MIBG in proportion to the degree of LVH.

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