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Selective Cardiac Neuroadrenergic Abnormalities in Hypertensive Patients with Left Ventricular Hypertrophy

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Background. Increased sympathetic drive to the heart might contribute to the development and progression of myocardial damage in hypertensive patients (HTs). This study assessed the possible presence of abnormalities in myocardial uptake of ^{123}I-metaiodobenzylguanidine (MIBG), a marker of sympathetic activity, in HTs with left ventricular hypertrophy (LVH).

Methods. Eleven HTs with LVH and 10 matched normotensive controls underwent clinical and laboratory examination, as well as LVH determination by echocardiography. The presence of myocardial ischemia was ruled out by exercise stress testing. Global and regional myocardial uptake of ^{123}I-MIBG was determined in both groups using planar and single proton emission tomography scintigraphy. In addition, thallium-201 (Tl-201) myocardial scintigraphy was performed in HTs. The heart/mediastinum (H/M) ratio on planar ^{123}I-MIBG images at different time points was compared between HTs and controls. Moreover, regional cardiac uptake of ^{123}I-MIBG was compared between groups and, within the HTs group, with regional Tl-201 uptake.

Results. At all study times, the H/M ratio was lower in HTs than in controls (all $p < 0.05$). A significant reduction in ^{123}I-MIBG uptake in the mid-inferolateral and mid-inferior segments was observed in HTs compared to controls. Also, a significant reduction in ^{123}I-MIBG uptake compared to Tl-210 uptake was observed in non-septal segments of HTs.

Conclusions. Cardiac abnormalities in global and regional uptake of ^{123}I-MIBG, as well as impaired ^{123}I-MIBG compared to Tl-201 uptake, are present in HTs with LVH. Given the effect of sympathetic nervous system on the heart, these abnormalities might play a role in hypertension-related cardiac damage.

Key Words: Essential hypertension, Left ventricular hypertrophy, Scintigraphy, Metaiodobenzylguanidine.

Introduction

The use of ^{123}I- or ^{131}I-labeled metaiodobenzylguanidine (MIBG) scintigraphy has been reported since the early 1980s for the diagnosis and therapy of neural crest-derived tumors, mainly pheochromocytoma and neuroblastoma. Because of its peculiar properties, this tracer, an analogue of guanetidine provided with structural similarities to norepinephrine (1,2), is taken up by peripheral sympathetic nerves. Therefore, MIBG is now considered an established sympathetic neuronal imaging agent, and its diagnostic applications include cardiac and pulmonary adrenergic imaging (3,4).

The adrenergic nervous system plays a critical role in the regulation of cardiac size and function in various cardiovascular diseases, including essential hypertension (EH)

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(5−7). In particular, abnormalities of the sympathetic tone are commonly included among the main pathogenetic factors of left ventricular hypertrophy (LVH) in patients with EH (8). More importantly, LVH is known to be a very strong predictor of poor cardiovascular outcome in these patients (9,10). Also, studies looking at the effects of antihypertensive therapy on left ventricular mass have clearly shown that regression of hypertrophy can be achieved only by those agents that either decrease or do not increase sympathetic activity (11). For these reasons, the availability of a methodology allowing direct assessment of sympathetic drive to the heart may provide important prognostic and therapeutic indications. Scintigraphic abnormalities of adrenergic innervation/function at MIBG scanning have been previously reported in hypertensive patients (12,13). A limitation of these studies, however, is that they also included hypertensive patients with angina pectoris, so that the observed MIBG defects might be due to myocardial ischemia rather than hypertension and left ventricular hypertrophy per se.

Therefore, the present study was designed to assess global and regional uptake of MIBG in the heart of patients with EH and LVH in whom myocardial ischemia has been carefully excluded.

Patients and Methods

Eleven patients with EH [stage I or II JNC 7 (14)] and LVH (group H) and 10 normotensive controls (group C) were recruited for this prospective study. All patients underwent complete biochemical examination, chest X-ray and standard ECG recording. Diagnosis of EH was established after secondary forms of hypertension were ruled out by detailed clinical exam, laboratory and imaging testing.

Patients eligible for this study had their previous antihypertensive medications withdrawn at least 15 days before the study day. None of the patients had a history of myocardial infarction or angina, as well as ECG signs of ischemic heart disease, either at rest or during exercise. Patients with atrial fibrillation, bundle-branch block, Wolff-Parkinson-White syndrome, pacemakers, valvular heart disease, severe renal and/or chronic heart failure, diabetes mellitus, cardiomiopathy, cerebral vascular disease or any other relevant disease were also excluded from this study. Secondary forms of hypertension were ruled out by clinical and laboratory examination. The study protocol was approved by the local Ethical Committee and all patients provided written informed consent.

^{123}I-metaiodobenzylguanidine (MIBG) and Tl-201 Myocardial Scintigraphy

Patients of group H underwent both ^{123}I-MIBG and Tl-201 scintigraphy. In these patients Tl-201 was performed at least 1 week before the Tl-201 single photon emission tomography (SPET) by IV injection of 3 mCi (111 MBq) of Tl-201 at rest. Image acquisition was started within 3−4 h after the injection using a rotating single head gamma camera (Elscint 409 ECT) with a 40-cm field view, equipped with low-energy general-purpose parallel hole collimator. Energy discrimination was achieved by a 25% window, centered over the 69 KeV x-ray peak of Tl-201; the zoom factor was ×1.2; the acquisition matrix was 64 × 64. The camera was rotated at 6° increments, collecting 30 views for 45 sec each. Image reconstruction was accomplished by filtered back-projection using a Butterworth filter with a cut-off frequency of 0.35 cycles/pixel and a power factor of 5. No attenuation correction was performed.

^{123}I-MIBG planar scintigraphy and SPET were performed in both groups by IV injection of 5 mCi (185 MBq) of MIBG (Sorin Biomedica, Saluggia, Italy) in 1 min, after at least 1-h rest. Patients were instructed to have no breakfast and to continue fasting up to 4 h following the injection. No patient or subject was taking any drug known or suspected to interfere with MIBG uptake. Planar scintigraphic images of the chest were recorded in the anterior view at 0.5, 1, 2, 3, and 18 h following injection. The acquisition time was 5 min, the matrix size was 256 × 256, the zoom factor was ×1. At the end of 3 h acquisition of the 3 planar scans, a SPET acquisition was performed, using the same camera, configuration and computer setting as described for the Tl-201 studies (the energy window was centered over the 159 KeV peak of ^{123}I; the window width was 20%). Acquisition time and image reconstruction procedure were identical to those used for the Tl-201 SPET.

Study of Global Adrenergic Function

For the ^{123}I-MIBG planar scintigraphy, a heart/mediastinum (H/M) ratio was calculated, using a region of interest (ROI) manually drawn around the heart. The H/M ratio of ^{123}I-MIBG was considered an index of global cardiac uptake, indicative of adrenergic function. A lung/mediastinum (L/M) ratio was also calculated on ^{123}I-MIBG images, using a ROI manually drawn on both lungs (the mean lung counts were used as the ratio numerator). Mean H/M ratio and L/M ratio values of group H were compared with those of group C.

Salivary gland uptake (SGU) was qualitatively evaluated on planar 4-h MIBG scintigraphies and classified according to the following score: SGU 0 = no visualization; SGU 1 = mild visualization; SGU 2 = intense visualization.

Study of Regional Adrenergic Function (^{123}I-MIBG) and Regional Perfusion (Tl-201)

From the transverse slices of ^{123}I-MIBG and Tl-201 SPET studies, short axis slices of the left ventricle were obtained. Slice thickness was normalized in order to obtain a total of

15 short axis slices and Bull's Eye polar maps were derived by standard software using the maximum pixel value for each 6° angle. In order to evaluate regional tracer uptake, each polar map was divided into 16 segments, according to ASE segmentation, and the mean count in each segment was computed as an index of ^{123}I-MIBG and Tl-201 uptake (15).

Echocardiographic Measurements

Echocardiographic studies were carried out in all patients after the preliminary workup, using a Hewlett-Packard ultrasound unit (model 77020A). All examinations were performed and blindly interpreted by an experienced physician. Standard M-mode echocardiograms were recorded in all subjects and parasternal long- and short-axis 2/D imaging were performed to provide reference points for the M-mode examination. M-mode measurements of the left ventricle, including left ventricular diastolic diameter, left ventricular systolic diameter, left ventricular posterior wall thickness and interventricular septum thickness, were calculated as the average of three consecutive cardiac cycles, in accordance with the American Society of Echocardiography recommendations and the Penn Convention (16,17).

Echocardiographic left ventricular mass was then calculated using the Devereux and Reichek formula (16):

$$\mathrm{LVM\,(g)} = 1.04\,([\mathrm{IVS} + \mathrm{PW} + \mathrm{DD}]^3 - [\mathrm{DD}]^3) - 13.6\,\mathrm{g}$$

where IVS = interventricular septum thickness; PW = posterior wall thickness; and DD = left ventricular diastolic diameter.

LVM was then indexed to the body surface area to obtain a left ventricular mass index (LVMI). LVH was defined by values exceeding 134 g/m^2 for males or 110 g/m^2 for females. Left ventricular ejection fraction (EF) was calculated as follows:

$$\mathrm{LVEF} = (\mathrm{DD}^3/\mathrm{SD}^3) \times 100$$

where SD = left ventricular systolic diameter.

Plasma Renin Activity (PRA)

PRA was determined in both clinostatic and orthostatic position by radioimmunoassay of the angiotensin I generated during incubation of plasma (pH 6) at 37°C, using a commercial kit (Angiotensin I RIA kit, Sorin, Italy).

Urinary Catecholamines (UCTH)

UCTH (epinephrine and norepinephrine) were determined by chromatography method (HPLC Bio-Rad, Munchen, Germany).

Statistical Analysis

Statistical analysis was performed using Sigma-Stat 2.03 Statistical Software (SPSS Inc., Chicago, IL). Data are expressed as means ± SEM.

Differences between groups were analyzed by ANOVA and Student's *t*-test, as appropriate. In order to correct for multiple comparisons, Bonferroni's post-hoc test was used, setting the level of significance to α/k, where α is 0.05 (the desired significance level) and k is the number of comparisons performed.

Results

As shown in Table 1, there was no significant difference between groups in demographic features, smoking habit, laboratory parameters and EF. As expected, hypertensive patients had higher systolic and diastolic blood pressure values and LVMI; plasma renin activity was also significantly higher in hypertensive patients than in controls.

Planar ^{123}I-MIBG Studies

Figure 1 shows the H/M and L/M ratios in the two groups, whereas Figure 2 reports individual data for the H/M ratio 1 h following injection of MIBG. At all study times, H/M values in group H were significantly lower than in group C (top panel). In contrast, no significant difference was

Table 1. Patients' characteristics

	Group H	Group C	*p* values
Patients (*n*)	11	10	NS
Sex (M/F)	7/4	6/4	NS
Age (years)	52 ± 7	53 ± 5	NS
BSA (m^2)	1.84 ± 0.04	1.81 ± 0.06	NS
Smokers (*n*)	7	6	NS
Casual SBP (mmHg)	170 ± 6	125 ± 5	0.0001
Casual DBP (mmHg)	108 ± 3	75 ± 5	0.0001
Duration hypert. (years)	10 ± 4		
Cholesterol (mg/dL)	182 ± 24	176 ± 30	NS
Triglycerides (mg/dL)	125 ± 16	130 ± 18	NS
Fibrinogen (mg/dL)	320 ± 18	328 ± 10	NS
Hematocrit (%)	44 ± 3	42 ± 4	NS
PRA c (pg/mL)	3.6 ± 1.1	1.8 ± 0.2	0.02
PRA o (pg/mL)	8.8 ± 2.7	3.5 ± 0.4	0.008
*U*E (μg/24 h)	42.4 ± 4.6	22.8 ± 2.8	0.0001
*U*NE (μg/24 h)	75.07 ± 8.4	30.6 ± 3.05	0.0001
LVMI (g/m^2)	166.01 ± 23.2	87.6 ± 15.1	0.0001
LVEF (%)	61 ± 5	62 ± 4	NS
DRUG administration			
ACE inhibitors	11		
Calcium antagonist	11		

NS, not significant; BSA: body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; PRAc, plasma renin activity clino. PRAo, plasma renin activity ortho; *U*E, urinary epinephrine; *U*NE, urinary norepinephrine.

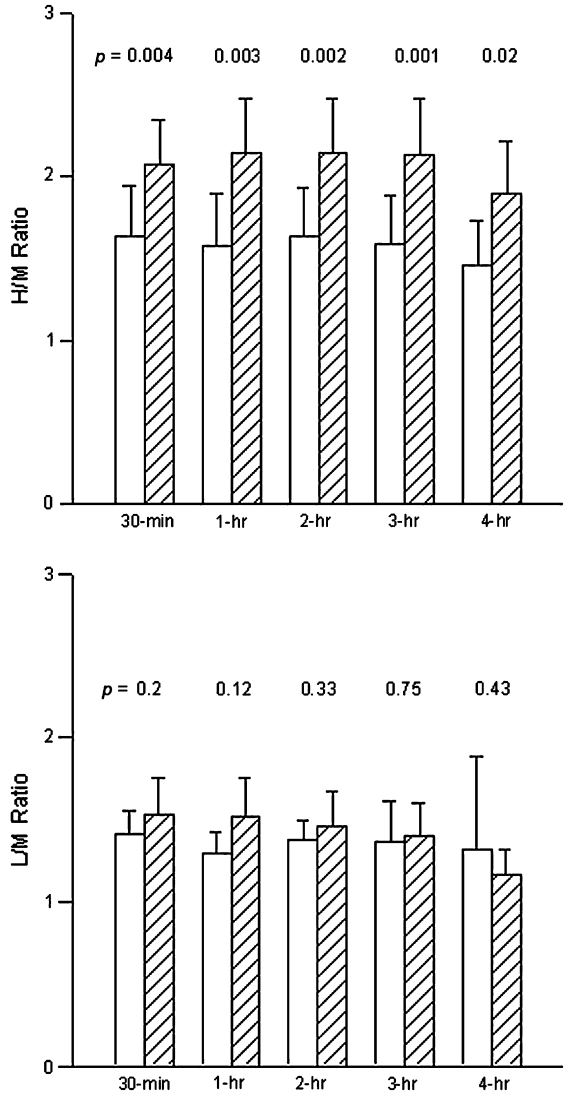

Figure 1. Bars show the H/M ratio (top panel) and the L/M ratio (bottom panel) in hypertensive patients (open bars) and normotensive controls (hatched bars) at different time-points during ^{123}I-MIBG scintigraphy. The *p* values refer to the comparison between hypertensive and controls at each time-point by ANOVA.

observed in the L/M ratio between groups (bottom panel). SGU values were comparable between groups; thus, all patients showed a SGU score of 2, indicative of intense salivary gland visualization, without differences between groups.

SPET Studies

A significant reduction of ^{123}I-MIBG myocardial uptake was observed in the mid-inferolateral (ILM) and in the mid-inferior (IM) segments in group H compared to group C.

The mean uptake values of ^{123}I-MIBG in each myocardial segment are reported in Table 2. In group H, a significant reduction in the apical lateral (LA), apical inferior (IA), apical anterior (AA), mid-inferolateral (ILM), mid-inferior (IM) and mid-anterolateral (ALM) segments was observed in ^{123}I-MIBG uptake compared to Tl-201 uptake. The mean uptake of ^{123}I-MIBG and Tl-201 in each myocardial segment is reported in Table 3.

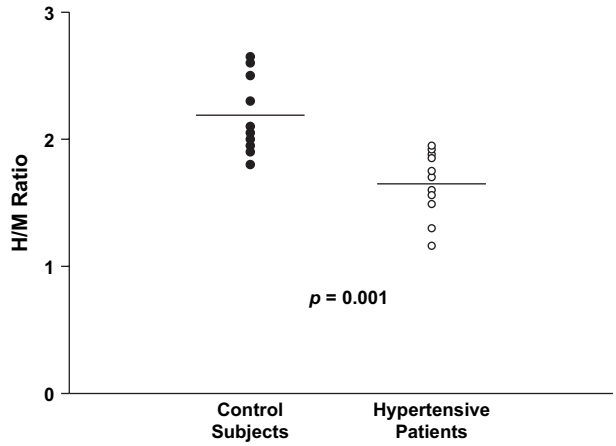

Figure 2. Scatterplot shows individual values of the H/M ratio in hypertensive patients (open circles) and normotensive controls (filled circles) 1 h after ^{123}I-MIBG injection. The *p* value refers to the comparison between the 2 means (lines) by Student's *t*-test for unpaired data.

Discussion

The present study shows that HTs with LVH without signs of myocardial ischemia have impaired global cardiac uptake of ^{123}I-MIBG compared to matched normotensive controls. Moreover, this group of HTs showed segmental abnormalities in cardiac uptake of ^{123}I-MIBG compared to Tl-201 uptake. Together these findings clearly indicate the presence of an abnormal sympathetic drive to the heart in patients with essential hypertension associated with LVH.

In the hypertensive population recruited for this study, we obtained H/M ratio values for ^{123}I-MIBG uptake between 1.64 (30 min post-injection) and 1.48 (18 h post-injection), which are definitely abnormal compared to the age-matched population. Furthermore, normal lung and salivary gland ^{123}I-MIBG uptake demonstrates the cardiac selectivity of the neuroadrenergic derangement, since those organs are richly innervated by sympathetic nerve terminals.

Abnormality in one or more indices of global cardiac MIBG uptake and/or clearance reflects an abnormal ''neuroadrenergic heart function.'' This rather generic term hides the still insufficient knowledge about the precise mechanisms determining abnormal MIBG uptake in the heart *in vivo*. According to previous studies (18,19), the most likely cause is damage in norepinephrine uptake mechanism in

Table 2. ^{123}I-MIBG group H vs. ^{123}I-MIBG in group C

Segment	^{123}I-MIBG (Group H)	^{123}I-MIBG (Group C)	*p* values
LA	164.16 ± 18.39	201.57 ± 9.09	NS
IA	153.17 ± 25.58	189.77 ± 19.91	NS
AA	178.44 ± 21.27	200.20 ± 11.29	NS
SA	178.83 ± 25.20	193.82 ± 16.74	NS
ILM	172.01 ± 18.48	209.18 ± 11.72	>0.003
ASM	201.61 ± 19.07	197.95 ± 16.43	NS
ISM	201.46 ± 33.99	194.10 ± 19.86	NS
AM	199.18 ± 23.76	207.82 ± 9.57	NS
IM	156.32 ± 15.91	172.34 ± 13.34	0.04
ALM	204.04 ± 19.58	233.42 ± 6.81	NS
AB	155.83 ± 19.79	148.17 ± 16.88	NS
IB	121.72 ± 24.81	123.89 ± 8.37	NS
ALB	163.80 ± 20.81	167.31 ± 14.68	NS
ASB	126.87 ± 23.14	119.39 ± 17.72	NS
ISB	113.21 ± 26.44	108.91 ± 16.52	NS
ILB	140.07 ± 25.07	154.27 ± 16.31	NS

NS, not significant; LA, apical lateral; IA, apical inferior; AA, apical anterior; SA, apical septal; ILM, mid-inferolateral; ASM, mid-anteroseptal; ISM, mid-inferoseptal; AM, mid-anterior; IM, mid-inferior; ALM, mid-anterolateral; AB, basal anterior; IB, basal inferior; ALB, basal anterolateral; ASB, basal anteroseptal; ISB, basal inferoseptal; ILB, basal inferolateral.

Table 3. ^{123}I-MIBG SPET vs. Tl-210 in group H

Segment	^{123}I-MIBG (Group H)	^{201}Tl (Group H)	*p* values
LA	164.16 ± 18.39	177.41 ± 14.86	0.0001
IA	153.17 ± 25.58	175.01 ± 22.46	0.008
AA	178.44 ± 21.27	175.48 ± 15.22	0.03
SA	178.83 ± 25.20	187.72 ± 10.95	NS
ILM	172.01 ± 18.48	200.00 ± 18.47	0.0001
ASM	201.61 ± 19.07	201.11 ± 17.58	NS
ISM	201.46 ± 33.99	192.96 ± 16.35	NS
AM	199.18 ± 23.76	199.44 ± 17.89	NS
IM	156.32 ± 15.91	175.58 ± 24.08	0.04
ALM	204.04 ± 19.58	218.99 ± 14.76	0.002
AB	155.83 ± 19.79	151.88 ± 15.96	NS
IB	121.72 ± 24.81	129.73 ± 19.54	NS
ALB	163.80 ± 20.81	166.05 ± 14.71	NS
ASB	126.87 ± 23.14	121.05 ± 17.89	NS
ISB	113.21 ± 26.44	112.39 ± 15.90	NS
ILB	140.07 ± 25.07	155.00 ± 12.15	NS

NS, not significant; LA, apical lateral; IA, apical inferior; AA, apical anterior; SA, apical septal; ILM, mid-inferolateral; ASM, mid-anteroseptal; ISM, mid-inferoseptal; AM, mid-anterior; IM, mid-inferior; ALM, mid-anterolateral; AB, basal anterior; IB, basal inferior; ALB, basal anterolateral; ASB, basal anteroseptal; ISB, basal inferoseptal; ILB, basal inferolateral.

the adrenergic nerve endings (‘‘uptake-1’’); other possible causes, however, might include an excess of circulating norepinephrine (which competes with MIBG at uptake-1 sites) or the presence of drugs interfering with MIBG uptake (mainly reserpine, imipramine, desipramine and several sympatomimetic substances). Because this latter mechanism can be ruled out in our study, both remaining possibilities support the notion of an increased availability of norepinephrine at the receptor level in the heart of patients with hypertension and LVH.

Despite some limitations, determination of global MIBG heart uptake has been demonstrated to be very useful in several clinical settings. Thus, it has been shown that it is the most powerful independent predictor of mortality in patients with chronic heart failure (20,21). Similarly, MIBG heart uptake has been demonstrated able to predict and monitor the response to therapy with β-blockers (22,23). In addition to global cardiac uptake, it is also possible to evaluate regional left ventricle MIBG uptake by use of the SPET imaging. Regional abnormalities in MIBG myocardial uptake and/or clearance, with or without global MIBG uptake changes, have been previously reported in patients with coronary heart disease, cardiomyopathy, and several other heart conditions. The most typical case in which it is possible to observe these abnormalities is in patients with previous myocardial infarction. In these patients, an area of ‘‘denervation’’ corresponding to the infarcted area (where neurons have been irreversibly damaged by the prolonged ischemic insult), is not generally observed, but also a defect in distal areas innervated by sympathetic neurons running through the infarcted area (13,24). Because neurons are more sensitive than myocytes to ischemic damage, patients with coronary artery disease (even without previous myocardial infarction) do usually exhibit MIBG regional defects at rest (25). In our study, we observed regional defects in the inferior and inferolateral left ventricular walls when MIBG distribution of hypertensive patients was compared to controls. A previous report from Kuwahara et al. (12), in which planar and SPET scintigraphies were used to evaluate myocardial uptake of ^{123}I-MIBG, showed that hypertensive patients have decreased H/M ratio, increased myocardial washout rate and inferolateral uptake defects even in the absence of LVH. A decreased H/M ratio and an increased myocardial washout rate of MIBG have also been demonstrated by Sakata et al. (13) in a study comparing normotensives, borderline and mild essential hypertensives. However, the limitation of both these studies is that they included patients with chest pain (12,13). In the present study, by contrast, patients with chest pain were excluded and all study individuals underwent exercise stress testing in order to rule out the possibility of silent myocardial ischemia. It must be acknowledged, however, that owing to the limited predictive value of exercise stress testing, the presence of coronary artery disease in our patients cannot be completely ruled out.

When regional distributions of MIBG and Tl-201 were compared in our group of hypertensive patients, we found several myocardial segments (6/16 segments) where MIBG uptake was reduced compared to Tl-201. These selective abnormalities of MIBG were localized predominantly in

the apical and the inferolateral segments; importantly, they also included those segments (inferomedial and inferolateral) in which hypertensive patients had reduced MIBG uptake compared to control subjects. Abnormalities in MIBG uptake compared to Tl-201 uptake observed in hypertensive patients are not unexpected if one takes into account the physiological dyshomogeneities of MIBG regional distribution. Indeed, whereas in normal subjects the distribution of the perfusion tracers (Tl-201, ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin) in the myocardium of left ventricle is rather homogeneous, some irregularities in MIBG uptake, especially in the apical and inferior wall regions, may already be present in these individuals. This is probably due to a relatively unbalanced equilibrium between sympathetic and parasympathetic fibers, a phenomenon that increases with age (12,16). Comparison between MIBG and Tl-201, therefore, is important to rule that the inferior MIBG defects observed in our group of hypertensive patients might be due to photon attenuation rather than to adrenergic abnormalities. Because Tl-201 signal is much more prone to attenuation than the more energetic ^{123}I emission, the higher Tl-201 uptake in the inferior wall guarantees the specificity of the MIBG inferior defects observed in our study.

It must be noted that previous studies have also reported increased MIBG washout rate in the heart of hypertensive patients, in the presence or even in the absence of LVH (12,13). However, interpretation of increased MIBG washout rate seems to be less clear compared to the decreased MIBG uptake observed in our study. This is because myocardial egress of MIBG may be accelerated in hypertrophic or overloaded hearts due to a disproportionately increased non-neuronal washout, as demonstrated by previous studies (26). For these reasons, we decided not to evaluate MIBG washout rate in our study patients.

In addition to mechanical load, an increased sympathetic nervous activity has been proposed as one of the most important factors in the development and the progression of LVH, based on the observations that catecholamine administration induces LVH, whereas sympatholytic intervention diminishes myocardial hypertrophy (5,6). Another mechanism by which an enhanced sympathetic tone may increase cardiovascular risk in hypertensive patients is by triggering ventricular arrhythmias and sudden death (10). Based on these considerations, our findings of global and regional abnormalities in neuroadrenergic activity in the heart of hypertensive patients with LVH might have relevant clinical implications. Thus, MIBG cardiac imaging might be useful in the early stages of the hypertensive process to identify those patients at increased risk of developing LVH. Importantly, this methodology might also help monitoring whether a reduction in cardiac sympathetic hyperactivity by antihypertensive therapy is associated with the regression of LVH. However, prospective trials with long-term follow-up are needed to test these attractive hypotheses.

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