Relationship Between Central Sympathetic Drive and Magnetic Resonance Imaging–Determined Left Ventricular Mass in Essential Hypertension

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Background—Sympathetic activation has been implicated in the development of left ventricular hypertrophy (LVH). However, the relationship between sympathetic activation and LV mass (LVM) has not been clearly defined across a range of arterial pressure measurements. The present study was planned to determine that relationship, using cardiac magnetic resonance imaging to accurately quantify LVM, in hypertensive patients with and without LVH and in normal subjects.

Methods and Results—Twenty-four patients with uncomplicated and untreated essential hypertension (LVH[−]) were compared with 25 patients with essential hypertension and left ventricular hypertrophy (LVH[+]) and 24 normal control subjects. Resting muscle sympathetic nerve activity was quantified as multiunit bursts and single units. Cardiac magnetic resonance imaging–determined LVM was indexed to body surface area (LVM index); in the LVH[−] group, LVM index was 67 ± 2.1 g/m^2, a value between those of the LVH[+] (91 ± 3.4 g/m^2) and normal control (57 ± 2.2 g/m^2) groups, respectively. The sympathetic activity in the LVH[−] group (53 ± 1.3 bursts per 100 cardiac beats and 63 ± 1.6 impulses per 100 cardiac beats) was between (at least $P<0.001$) those of the LVH[+] (66 ± 1.7 bursts per 100 cardiac beats and 77 ± 2.2 impulses per 100 cardiac beats) and normal control (39 ± 3.0 bursts per 100 cardiac beats and 45 ± 3.4 impulses per 100 cardiac beats) groups. Significant positive correlation existed between sympathetic activity and LVM index in the LVH[−] and LVH[+] groups (at least $r=0.76$, $P<0.0001$) but not in the normal control group. However, no consistent relationship existed between arterial blood pressure and sympathetic activity or LVM index.

Conclusions—These findings further support the hypothesis that central sympathetic activation is associated with the development of LVH in human hypertension. **(*Circulation*. 2007;115:1999-2005.)**

Key Words: action potentials ■ nervous system, sympathetic ■ hypertension ■ hypertrophy ■ magnetic resonance imaging

Although the development of left ventricular hypertrophy (LVH) in essential hypertension (EHT) has been attributed to many factors, such as hemodynamic and humoral effects,[1–5] sympathetic activation also has been implicated in the occurrence of LVH.[6,7] Consistent with this implication has been the finding of augmented sympathetic drive in EHT patients with LVH as categorized by echocardiography relative to those without LVH.[8,9] However, these findings alone cannot sufficiently support the hypothesis that sympathetic activation increases LV mass (LVM) in human hypertension, not least because a correlation between LVM and either peripheral or cardiac sympathetic drive has so far been found only in EHT groups having categorical LVH, not in those without LVH.[8,9] Furthermore, to confound the issue, human studies have indicated that the occurrence of clinically discernible LVH can blunt sympathoinhibitory reflexes in its own right, leading to increased sympathetic drive.[10,11]

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Therefore, the present investigation was designed to determine whether the magnitude of sympathetic nerve hyperactivity was related to LVM in subjects who had a broad range of both arterial blood pressures and LVM. For this purpose, we quantified central sympathetic nerve activity (SNA) by microneurography and LVM by cardiac magnetic resonance imaging (MRI) in EHT patients with and without LVH compared with age-, body weight–, and body surface area–matched normal control subjects.

Methods

Subjects

A total of 73 white subjects were prospectively examined (Table 1). The subjects included 49 patients with untreated EHT: 24 patients without LVH (LVH[−]) and 25 patients with LVH (LVH[+]). In

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TABLE 1. Demographic Details of the 3 Subject Groups

Subjects	LVH [−]	LVH [+]	Normal Control Subjects
Subjects, n (men, n)	24 (14)	25 (17)	24 (11)
Age, y	52±1.5	52±2.2	49±2.5
Body weight, kg	81±2.8	85±3.0	77±2.4
Body mass index, kg/m^2	29±0.9	28±0.8	27±0.7
Body surface area, m^2	1.92±0.04	1.99±0.04	1.90±0.05
Heart rate, bpm	72±1.9	68±1.8	64±1.8

Data presented as mean±SEM. Analyses were performed with ANOVA post hoc tests, except for gender difference, for which Fisher exact test was used. All group comparisons were not significantly different ($P>0.05$).

addition, a control group of 24 normal subjects were examined who were recruited from hospital staff, volunteer subjects, and relatives, on the basis of ages and body weights that were comparable to those of the hypertensive patients. All individuals had similar occupational status and dietary habits (including a sodium intake of ≈400 mmol/d), and none were actively engaged in exercise training. Patients were screened by history and by physical and laboratory examinations. Patients were excluded if they had evidence of secondary hypertension, peripheral vascular disease, renal insufficiency, diabetes mellitus, cardiac arrhythmias, or other chronic disease that may influence the autonomic nervous system or any contraindication to MRI scanning such as a permanent pacemaker in situ or intracranial aneurysm clips.

Arterial blood pressure was defined as the average of at least 3 readings taken on separate occasions, and the occurrence of hypertension was accepted if the systolic or diastolic arterial pressures were ≥140 or ≥90 mm Hg, respectively.[12] Both patient groups had diagnosed hypertension for ≤12 months, and none received antihypertensive therapy during the study. Drug therapy was stopped temporarily for at least 4 weeks before the investigation in 5 and 6 patients of the LVH[+] and LVH[−] groups, respectively. The investigation was carried out with the approval of the St James's University Hospital Ethics Committee, and all subjects provided informed written consent.

General Protocol

Each patient underwent 2 independent investigative sessions within 1 week of each other. They comprised microneurographic and MRI assessments. The microneurographic and hemodynamic measurements were obtained in an identical manner during each session, details of which have been published previously.[8,13,14] In brief, microneurography was performed between 9 AM and midday. Patients were asked to have a light breakfast and to empty their bladder before beginning the study. The patients were instructed to maintain a normal dietary intake of sodium and to avoid nicotine, caffeine, and alcohol for 12 hours before the investigation, as well as strenuous exercise for the preceding 24 hours. During each session, subjects were studied in the semisupine position and when the data had attained steady state for at least 30 minutes. Measurements were made in a darkened laboratory in which the temperature was constant at 22°C to 24°C. Resting arterial pressure was measured in the arm with a mercury sphygmomanometer. Changes in heart rate and arterial pressure were monitored and recorded with a standard ECG and a Finometer device (Finometer Medical Systems BV, Arnhem, the Netherlands).

Microneurography

Postganglionic muscle SNA (MSNA) was recorded from the right peroneal nerve.[8,13,14] The neural signal was amplified (×50 000), and for the purpose of generating bursts representing multiunit discharge, the signal was filtered (bandwidth, 700 to 2000 Hz) and integrated (time constant, 0.1 second). The output of action potentials and bursts from this assembly were passed to a personal computer–based data acquisition system (LabView, National Instruments Corp, Austin, Tex) that digitized the acquired data at 12 000 samples per second (16 bits).

Single units (s-MSNA) in the raw-action-potential neurogram were obtained by adjusting the electrode position while using fast monitor sweep and an online storage oscilloscope to confirm the presence of a consistent action potential morphology, as previously described.[8,13–15] Only vasoconstrictor units were accepted and examined; the criteria for acceptance were appropriate responses to spontaneous changes in arterial pressure, the Valsalva maneuver, and isometric handgrip exercise. In addition, simultaneous measurement of calf vascular resistance confirmed the vasoconstrictor function of the observed neural activity. During the Valsalva maneuver, sympathetic activity increased during the latter part of phase II and/or III and decreased during phase IV (increase and overshoot of blood pressure). Isometric handgrip exercise, performed with a dynamometer, produced a late increase in arterial blood pressure and sympathetic neural activity.

An electronic discriminator window was used objectively to count the spikes of s-MSNA, which were quantified in terms of mean frequency of impulses per minute and as impulses per 100 cardiac beats to avoid any possible interference caused by the length of the cardiac cycle.[16] The MSNA bursts were identified by inspection when the signal-to-noise ratio was >3 and were quantified in a similar manner. Data were acquired over 5 minutes when the measured variables had attained steady state for at least 30 minutes. The variability of repeated measurements of s-MSNA units and MSNA bursts over a period of 30 minutes or those of 2 impalements performed within 60 minutes did not exceed 10% in terms of twice the 95% confidence intervals around individual differences relative to the mean of the repeated measurements.[13]

MRI Studies

Quantification of LVM by MRI occurred independently of the microneurography acquisition and analysis sessions by blinded investigators and was performed using an identical protocol in all subjects. MRI studies were performed on a 1.5-T Philips Intera CV MRI system (Philips Medical Systems, Best, the Netherlands) equipped with Master gradients (maximum gradient amplitude, 30 mT/m; maximum slew rate, 150 mT · m^{-1} · ms^{-1}). Patients were scanned in the supine position with a 5-element cardiac phased-array coil and vectorcardiographic method for ECG gating as in routine clinical cardiac MRI.[17,18] Total scan acquisition time was short, with all data sets obtained within 30 minutes.

Localizing survey scans were followed by breathhold (in expiration) cine acquisitions in the ventricular long-axis and horizontal long-axis planes to ensure accurate planning of the true short axis. LV volume data sets comprising multiple slices were acquired parallel to the mitral valve, covering the heart from the apex to the base in 10 to 14 short-axis slices. A standard steady-state free-precession pulse sequence was used, one for which a normal range has been established by researchers in our department[18]; this sequence has been validated in animal studies.[19] The parameters of this steady-state free-precession pulse sequence were as follows: repetition time, 3.34 ms; echo time, 1.67 ms; flip angle, 55°; bandwidth, 1042 Hz/pixel; acquisition matrix, 192×163; field of view, 360×288 mm; half-Fourier acquisition; slice thickness, 6 mm; interslice gap, 4 mm; and phases per cardiac cycle, 18, with 2 slices acquired per 10- to 12-second breathhold.

Image analysis was performed offline with commercially available analysis software (MASS version 5.0, Medis, Leiden, the Netherlands). Standard criteria, which have been previously described, were used to delineate the cardiac borders (Figure 1).[20] End-diastolic and end-systolic contours were drawn for each slice from the apex to the base of the heart. Two papillary muscles were outlined separately and included in the myocardial mass analysis. Importantly, at the base of the heart, slices were included for quantification if the blood pool was surrounded by ≥50% ventricular myocardium as previously described.[20] LVM was calculated by modified Simpson's rule: LVM=1.05×(epicardial volume−endocardial volume). Left ven-

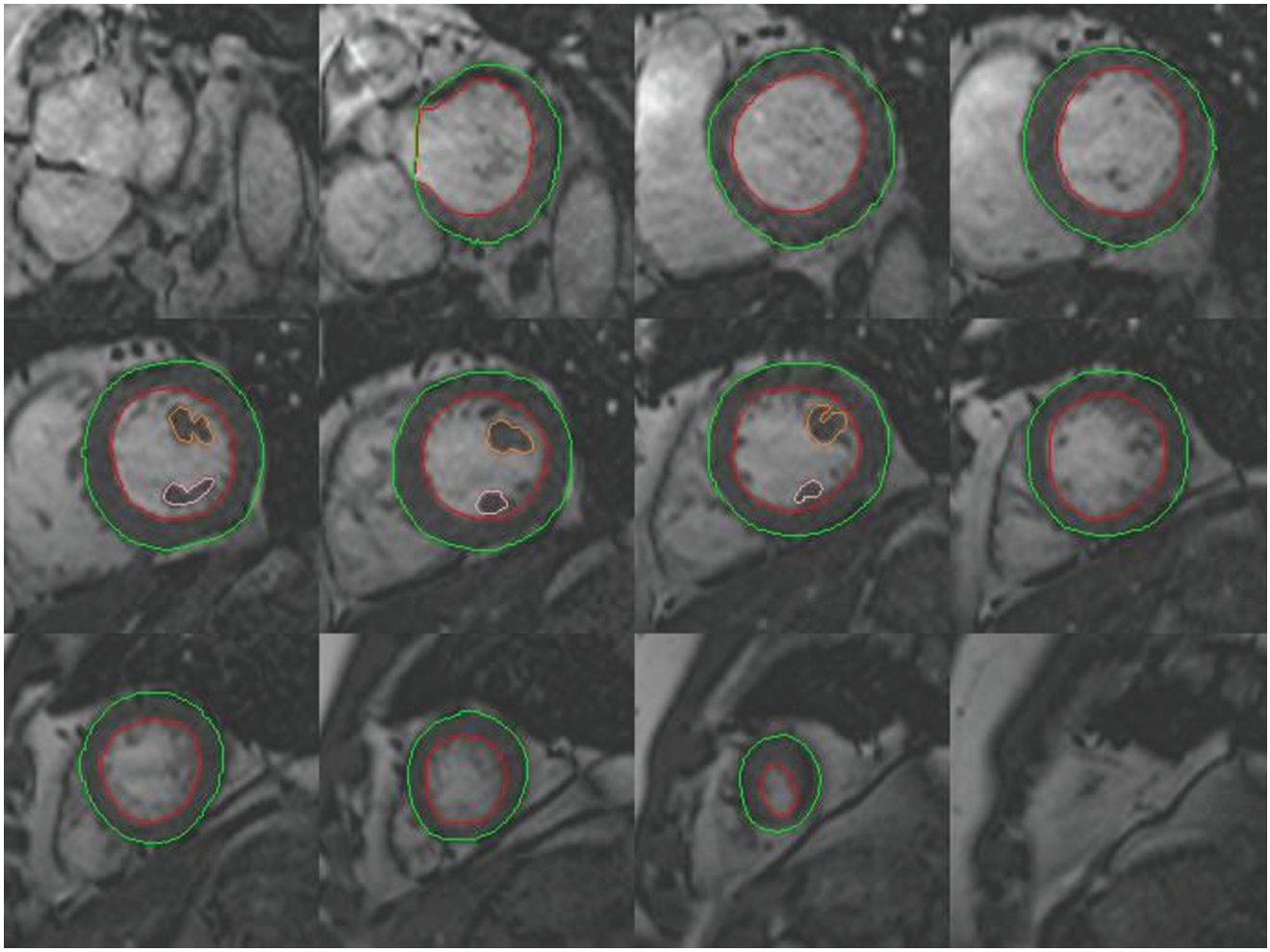

Figure 1. LV short-axis images taken from the base of the heart to the apex using a standard steady-state free-precession multiphase, multislice MRI sequence. Endocardial and epicardial contours are shown outlined in end diastole, enabling accurate calculation of LVM.

tricular mass index (LVMI) was subsequently calculated by dividing LVM by body surface area, using the Mosteller equation.

Normal LVM and LVMI ranges already established by others (using larger groups of an age similar to that used in this study) were used to categorize patients.[18] These normal ranges expressed over a range of 2 SD from the mean equated to 85 to 181 g or 46 to 83 g/m^2 for men and 66 to 114 g or 37 to 67 g/m^2 for women, respectively.[18] LVH was defined as >2 SD above the mean normal range; thus, these ranges were used to categorize the hypertensive patients into LVH[+] or LVH[−]. LVM measurements made with cardiac MRI have been shown to be more accurate and reproducible than M-mode and 2-dimensional echocardiography measurements,[21–23] and the technique is highly reproducible, with extremely favorable intrastudy and interstudy variability of <3%.[24]

Statistical Analysis

One-way ANOVA with Newman-Keuls' post hoc tests were used to compare data between the 3 groups of subjects. The least-squares technique was used to assess the linear relationship between variables. Multiple regression analysis was used to examine the relationship of measured variables to LVMI. Values of $P<0.05$ were considered statistically significant, and data are presented as mean±SEM.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

The 3 groups of subjects were not significantly different with respect to age, body weight, body mass index, heart rate, and body surface area (Table 1). In addition, no significant differences existed in the gender ratio between the 3 groups ($\chi^2=2.47$; $P>0.20$). In the 2 hypertensive groups (LVH[−] and LVH[+]), the indices of arterial blood pressure (systolic, diastolic, and mean) were similar (161±2.4, 97±4.0, and 118±1.7 mm Hg versus 170±4.7, 98±2.5, and 121±3.0 mm Hg, respectively), and as expected, they were greater than those of the normal control group (127±2.5, 79±1.4, and 95±1.7 mm Hg).

As a result of the nature of the study design, the measures of LVM and LVMI were greater in the LVH[+] (182±8.6 g and 91±3.4 g/m^2) than in the LVH[−] group (131±6.1 g and 67±2.1 g/m^2). However, the LVH[−] group also had significantly greater LVM ($P<0.05$) and LVMI ($P<0.05$) compared with the normal control group (107±5.8 g and 57±2.2 g/m^2). Group analysis of the microneurographic data revealed that all indices of SNA were significantly greater in the hypertensive groups relative to the control group and were greater in the LVH[+] compared with the LVH[−] group (Table 2).

TABLE 2. LVM, Blood Pressure, and Microneurographic Data From the 3 Subject Groups

Subjects	LVH [−] (A)	LVH [+] (B)	Normal Control Subjects (C)	*P*, A vs B	*P*, A vs C	*P*, B vs C
MSNA, bursts/min	38±1.3	45±1.6	25±2.1	<0.01	<0.001	<0.001
MSNA, bursts/100 beats	53±1.3	66±1.7	39±3.0	<0.001	<0.001	<0.001
s-MSNA, impulses/min	45±1.6	52±1.9	29±2.2	<0.05	<0.001	<0.001
s-MSNA, impulses/100 beats	63±1.6	77±2.2	45±3.4	<0.001	<0.001	<0.001
LVM, g	131±6.1	182±8.6	107±5.8	<0.001	<0.05	<0.001
LVMI, g/m^2	67±2.1	91±3.4	57±2.2	<0.001	<0.05	<0.001
Systolic BP, mm Hg	161±2.4	170±4.7	127±2.5	NS	<0.001	<0.001
Diastolic BP, mm Hg	97±4.0	98±2.5	79±1.4	NS	<0.001	<0.001

BP indicates blood pressure. Data presented as mean±SEM. Analyses were performed with ANOVA post hoc tests.

Considering the 3 study groups (normal control subjects, LVH[-], and LVH[+]) separately, no significant correlations existed between sympathetic activity and arterial blood pressure (always $P>0.05$) (Figure 2A and 2B). However, individual group analysis revealed that the measures of LVMI in the 2 hypertensive groups were significantly and positively related to measures of SNA (Figure 2C and 2D). Specifically, in the LVH[+] group, the correlation coefficient and linear regression analysis values were $r=0.91$, $P<0.0001$ and $r^2=0.83$, $P<0.0001$ (for s-MSNA; Figure 2C) and $r=0.86$, $P<0.0001$ and $r^2=0.73$, $P<0.0001$ (for MSNA; Figure 2D). In LVH[−], this significant positive relationship also was apparent, with correlation coefficient and linear regression analysis values of $r=0.76$, $P<0.0001$ and $r^2=0.58$, $P<0.0001$ (for s-MSNA; Figure 2C) and $r=0.76$, $P<0.0001$ and $r^2=0.57$, $P<0.0001$ (for MSNA; Figure 2D). On the contrary, in the normal control group, no relationship existed between LVMI and measures of SNA (s-MSNA or MSNA, $r=-0.03$, $P>0.93$ and $r^2=0.0009$, $P>0.94$). In addition, considering the 3 study groups separately, no significant correlation existed between any of the indices of arterial blood pressure and LVMI (always $r<0.2$, $P>0.32$; Figure 3).

Finally, the measures of LVMI in both hypertensive groups were positively related to body surface area (at least $r=0.37$, $P<0.04$), although they were not correlated to age or heart rate. In the normal control group, the measures of LVMI were not related to body surface area, age, or heart rate. After age, body mass index, body surface area, arterial pressure, and SNA data were included in the multiple regression analyses, the measures of LVMI always remained significantly related to those of SNA (always $P<0.005$ in LVH[−] and always $P<0.0001$ in LVH[+]).

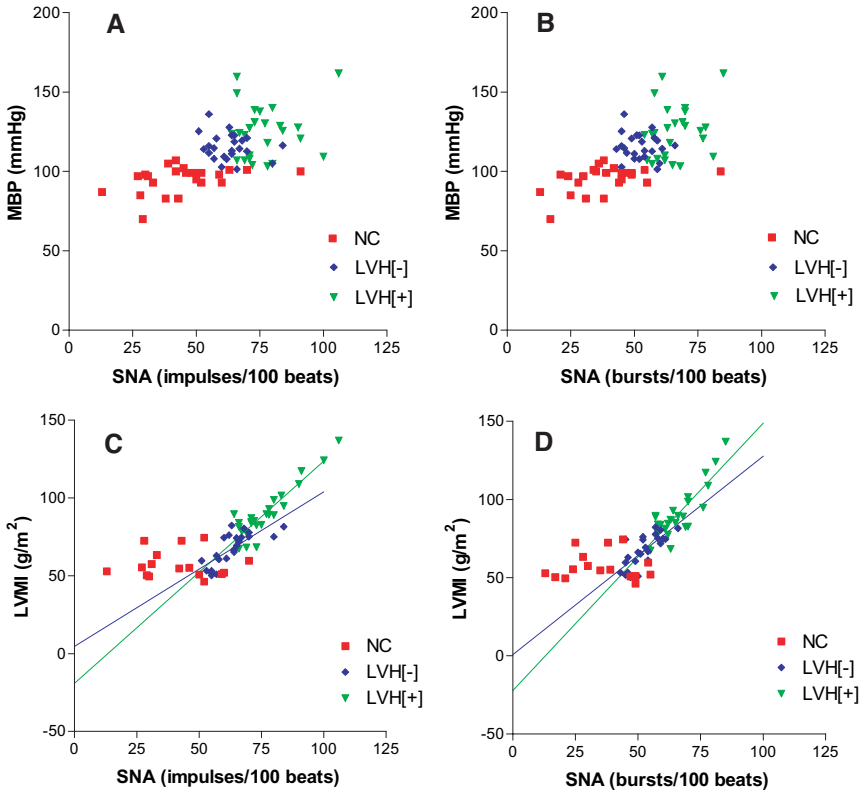

Figure 2. Within subject groups, no direct relationship exists between SNA and mean arterial pressure (MBP) (A, B). In normal control subjects (NC), a relationship also does not exist between SNA and LVMI (C, D). However, in LVH[−] and LVH[+], a direct linear relationship exists between SNA and LVMI (C, D).

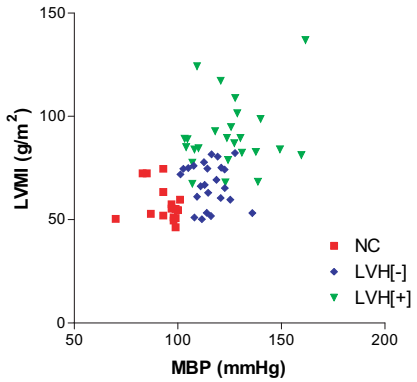

Figure 3. For any of the individual subject groups (normal control subjects [NC], LVH[−], and LVH[+]), no direct relationships exist between mean arterial pressure (MBP) and LVMI.

Discussion

The present investigation has shown for the first time in patients with EHT that LVM is significantly related to central sympathetic nerve hyperactivity regardless of whether associated clinical LVH exists. These findings indicate that sympathetic activation found in EHT may be an important determinant of the growth of human LV myocardium because the 2 variables are related to each other even in the absence of categorical LVH.

Importantly, as in any investigation of the autonomic nervous system, all subjects in this study were examined under identical laboratory conditions to avoid confounding influences related to circadian variation,[25] alcohol intake,[26] and visceral distension.[27,28] In addition, all groups were closely matched to avoid confounding factors such as age and gender,[29] race,[30] body weight,[31] and heart rate.[16] Unavoidably, the levels of arterial pressure in the 2 hypertensive groups were greater than in the normal control group. However, we found no correlation between SNA and indexes of arterial pressure as we have reported previously in hypertensive and normotensive subjects,[13] supporting the proposal that chronic sympathetic excitation was independent of baroreceptor reflex function.[32] Furthermore, the 2 hypertensive groups were closely matched with respect to all other measured variables except for the quantified LVM and sympathetic activity. These considerations make it likely that the observed similarity in progression of LVMI and sympathetic activity from normal control to LVH[−] and then to LVH[+] was not significantly affected by known confounding factors.

Although regional differences exist in sympathetic output,[33] reported evidence indicates that resting sympathetic drive to the periphery correlates well with that to the heart in normal subjects[34] and that both are increased in hypertension.[35,36] Both peripheral drive and cardiac sympathetic drive have been shown to be abnormally increased in EHT patients with categorical LVH,[8,9] and this has been confirmed by our present findings. However, unlike previous studies using echocardiography, the use of cardiac MRI, a more accurate and reproducible tool for the quantification of LVM,[21–23,37] has allowed us to show an increase in sympathetic drive in hypertensive patients without categorical LVH (LVH[−]). The previously reported absence of correlation between sympathetic drive and LVMI in LVH[−] patients, although not proven, could be related to limitations in the accuracy of the chosen measurement technique (echocardiography).[9] It is well accepted that echocardiographic estimation of LVM, calculated from equations involving LV wall thickness and cavity dimensions, can be inaccurate as a result of mathematical assumptions that cannot allow adequately for the complex LV geometry. The present study also includes limitations. Our design used office arterial pressure, measured as the average of at least 3 readings at rest,[12] and this could be argued not to reflect the 24-hour arterial pressure profile. However, this design made it possible to match the 2 hypertensive groups in the resting state with respect to arterial pressure values and heart rate. Although the group mean systolic arterial pressure in LVH[+] was slightly greater than that of LVH[−], this was not likely to be a significant confounding factor because no significant correlation existed between arterial pressure indices and LVM. At the same time, SNA was significantly correlated to LVM in the 2 hypertensive groups. In addition, in our group comparisons, no significant differences existed in systolic arterial pressure levels between the 2 hypertensive groups, whereas the group values of SNA and LVM were significantly different.

From the group analyses, the present investigation has shown for the first time that central sympathetic drive is closely linked to LVMI when quantified by MRI in patients without LVH. Previously, in human hypertension, a link between LVMI and sympathetic drive has been reported only in patients with LVH[8,9]; this link has been confirmed in this study. Previous findings were therefore not able to support the hypothesis that sympathetic activation might be a significant mechanism in its own right in increasing LVM. This inability was accentuated by the fact that LVH itself has been found to increase sympathetic drive, possibly through blunting sympathoinhibitory reflexes from the heart.[10,11] Our findings in LVH[−] patients, however, are entirely consistent with the theory that central sympathetic activation in EHT is a significant mechanism leading to increased LVM in humans. The present findings then support the growing body of evidence that sympathetic activation in EHT is one mechanism instrumental to the development of target organ damage, including LVH.[6,7,35,38] Indeed, the findings from this study in human hypertension are supported by animal data in that catecholamines have been shown experimentally to have trophic properties both on cardiac myocytes[39] and in the intact animal heart.[40]

That central sympathetic activation is linked to increased LVM in human hypertension, regardless of whether this increase is clinically categorized as LVH, could have therapeutic and prognostic implications. Hypertension, sympathetic activation, and clinical LVH are recognized as independent cardiovascular risk factors,[6,7,41,42] and regression of LVM in hypertension has been associated with a reduction in this risk.[43–45] Therefore, it is reasonable to expect that sympatholytic antihypertensive agents could help to prevent the development of clinically recognized LVH. Although sympathetic activation, hypertension, and LVH have complex interacting mechanisms, the data from this study show a clear

relationship between sympathetic activity and LVM across a range of arterial blood pressure levels. Interestingly, no relationship existed between sympathetic activity and blood pressure or between blood pressure and LVMI within individual groups, suggesting that sympathetic hyperactivity may have an independent effect on LVM in addition to that associated with raised blood pressure (afterload). Although in a human biological system it is not possible to study these interacting mechanisms in isolation during the development of LVH, it may be possible in future studies of hypertensive LVH regression to determine whether mechanisms in addition to blood pressure (afterload) lowering are important in LVM reduction.

Conclusions

The present study has shown that central sympathetic activation is associated with an increased LVM in human hypertension, regardless of whether this increase is categorized as definitive LVH. The findings are consistent with the theory that sympathetic activation in hypertension is a significant mechanism leading to increased LVM.

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Disclosures

None.

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CLINICAL PERSPECTIVE

In patients with essential hypertension, the detection of left ventricular hypertrophy (LVH) by ECG or echocardiography has long been recognized as an independent cardiovascular risk factor. Clinical LVH has previously been associated with central sympathetic activation. The present study found that the magnitude of sympathetic activation in essential hypertension is significantly related to left ventricular mass, as quantified by cardiac magnetic resonance imaging, and that this relationship existed regardless of whether LVH was present. These findings support the hypothesis that central sympathetic activation is associated with both a subclinical and an overt pathological increase in left ventricular mass. Because regression of LVH in hypertension has been associated with reductions in cardiovascular risk, it is possible that sympatholytic antihypertensive agents could be particularly beneficial in promoting the regression of any increased left ventricular mass and may even prevent the development of LVH. Better understanding of these mechanisms may allow us to test the hypothesis that the development of clinical LVH is not simply a consequence of the increased arterial pressure (afterload).