Hypertensive Left Ventricular Hypertrophy: Relation to Peripheral Sympathetic Drive

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OBJECTIVES  This study was designed to examine whether the occurrence of left ventricular hypertrophy (LVH) in moderate to severe essential hypertension (EHT) was associated with alteration in peripheral sympathetic drive.

BACKGROUND  In hypertension, LVH is an independent predictor of increased morbidity and mortality. The reported mechanisms leading to LVH remain unclear but include hemodynamic and humoral factors. The sympathetic nervous system may be important, particularly as catecholamines have been shown to have trophic properties. We tested the hypothesis that sympathetic activity measured using microneurography could be different in patients with hypertension depending on the presence of LVH.

METHODS  We examined 28 subjects with moderate to severe EHT (stages 2 to 3; Joint National Committee [JNC]-VI classification). Fourteen had echocardiographic evidence of LVH (EHT + LVH), while the other 14 subjects (EHT) did not. Subjects were matched in terms of age, body mass index and levels of arterial blood pressure. Peripheral muscle sympathetic nerve activity was measured from both multiunit bursts (MSNA) and single unit (s-MSNA) vasoconstrictor impulses via the peroneal nerve.

RESULTS  The mean frequency of s-MSNA and MSNA was greater in the EHT + LVH group than it was in the EHT group (mean ± SEM; 75.9 ± 6.9 impulses/100 beats vs. 52.1 ± 2.9 impulses/100 beats, p < 0.001 and 64.2 ± 5.7 bursts/100 beats vs. 48.9 ± 2.8 bursts/100 beats, p < 0.05).

CONCLUSIONS  These results indicate that, in subjects with moderate to severe hypertension, the presence of LVH is associated with higher sympathetic discharge, evidenced by an increase in unitary firing frequency and also by fiber recruitment. (J Am Coll Cardiol 2001;38:1711–7) © 2001 by the American College of Cardiology

In patients with hypertension, the occurrence of left ventricular hypertrophy (LVH) has been associated with an increase in mortality from all cardiovascular causes (1–4). However, not all subjects go on to develop LVH, and the reasons for this remain undetermined. The development of LVH has been attributed to many factors, including raised arterial pressure levels (resulting in increased myocardial workload) and growth-promoting substances such as angiotensin II, insulin-like growth factor-1 and circulating catecholamines (5–10).

In essential hypertension (EHT), the elevated arterial pressure has been associated with increased central sympathetic output to the heart, kidney and skeletal muscles (11–13). In humans, a direct assessment of sympathetic activity can be performed using the technique of microneurography. This technique measures muscle sympathetic nerve activity (MSNA) via the assessment of the mean frequency of multiunit MSNA bursts (14,15) or from single unit vasoconstrictor activity (s-MSNA) (16,17).

It has been suggested that the severity of hypertension is related to the magnitude of increased sympathetic drive (15). However, other studies have not demonstrated this relationship (18,19), and, more recently, we have shown that, in stage 1 hypertensive disease, the peripheral sympathetic drive is, in fact, higher than that found in the more severe degrees of hypertension (16). In accounting for these differences, one should bear in mind that in the earlier study (15) the presence LVH was not taken into account.

Thus, it remains unknown whether hypertensive patients who have developed LVH have altered sympathetic drive compared with those without LVH who have similar blood pressure levels. Indeed, it is known that patients with hypertension who have peripheral vascular disease have a greater degree of LVH than those without LVH (20) and that increased sympathetic drive enhances vascular hypertrophy (10). This supports the hypothesis that patients with hypertension and end-organ damage may have evidence of more severe and widespread sympathetic hyperactivity.

Therefore, this investigation was designed to see whether in EHT the presence of LVH was associated with altered central sympathetic drive to the periphery at rest. In addition to multiunit microneurographic recordings, single
unit discharge was obtained as this allows further insight into the mechanisms of central autonomic control. Two groups of patients with hypertension were examined, either with or without LVH, and they were closely matched in terms of age, body weight and, in particular, arterial blood pressure levels.

**METHODS**

**Subjects.** The study involved Caucasian patients with newly diagnosed EHT who were examined between January 1998 and May 1999. The study group was recruited from among 34 patients; in 6 patients it was not possible to obtain stable microneurographic data. All patients were screened for repeated baseline resting measurements of arterial blood pressure values, based on the average of at least three readings taken on separate occasions, indicated a severity of hypertension within stage 2 or 3 of the Joint National Committee (JNC)-VI classification (21), as summarized in the following text.

Stage 1: Systolic blood pressure of 140 to 159 mm Hg or diastolic blood pressure of 90 to 99 mm Hg.

Stage 2: Systolic blood pressure of 160 to 179 mm Hg or diastolic blood pressure of 100 to 109 mm Hg.

Stage 3: Systolic blood pressure of $\geq 180$ mm Hg or diastolic blood pressure of $\geq 110$ mm Hg.

Over the same period of time, a second group of 14 patients (9 male) with EHT without signs of LVH were studied, and these were matched in terms of age, body weight, body mass index and levels of arterial blood pressure.

Electrocardiographic voltage criteria were used to identify subjects with suspected LVH, and left ventricular dimensions were measured using two-dimensional M-mode echocardiography (Toshiba Powervision SSA-380A, Toshiba Corp., Japan). Using American Society of Echocardiography recommendations (22), measurements of end-diastolic posterior wall thickness (PW), left ventricular internal diameter (LVID) and intraventricular septal thickness (IVS) were determined and considered to represent LVH if measures of PW or IVS exceeded 11 mm. Left ventricular mass (LVM) was calculated according to the Penn convention (23) using the equation: 

$$LVM(g) = 1.04 \left[ (IVS + LVID + PW)^3 - (LVID)^3 \right] - 13.6$$

and, to account for body surface area, left ventricular mass index (LVMI) was derived.

Of the 14 patients with EHT + LVH, 8 had stage 2 and 6 had stage 3 disease. Due to the severity of disease, some individuals had already been commenced on oral antihypertensive therapy (between two and four months) before taking part in the study. It was felt unethical to perform a prolonged washout period before these studies, so treatment was only omitted on the study day. Of these 14 patients, 6 were receiving treatment that consisted of diuretics ($n = 2$), the beta-blocking agent atenolol ($n = 2$), angiotensin-converting enzyme inhibitors ($n = 3$) and calcium antagonists ($n = 1$). The 14 patients with EHT (seven each with stage 2 and stage 3 disease) who did not have evidence of LVH were examined before commencing antihypertensive therapy.

**General protocol.** Under the approval of St. James’s University Hospital Ethics Committee, subjects provided informed written consent to the investigation. All subjects were studied between the hours of 9 AM and 12:00 midday and were asked to avoid nicotine and caffeine products for 12 h and alcohol and strenuous exercise for 24 h before the investigation. Subjects maintained a normal dietary intake of sodium, and they were requested to have had a light breakfast and to empty their bladder before commencing the study.

During each session, subjects were studied in the semisupine position. Measurements were made in a darkened laboratory in which the temperature was constant at 22 to 24°C. Heart rate and arterial blood pressure were monitored and recorded using a standard electrocardiogram and a Finapres device (Model 2300; Ohmeda, Hatfield, Herts, United Kingdom) applied to the middle finger at the level of the heart. A pneumograph consisting of a corrugated rubber tube connected to a pressure transducer was used to monitor and record respiration. Subjects were asked to relax and not speak for 10 min so as to reach a steady state, after which time hemodynamic and microneurographic data were obtained for repeated baseline resting measurements of at least 5-min duration.

**Microneurography.** Postganglionic muscle sympathetic nerve activity was recorded from the right peroneal nerve as previously described in detail (14,16). Briefly, the neural signal was amplified ($\times 50,000$), and, for the purpose of generating bursts representing multiunit discharge, the signal was filtered (bandwidth of 700 to 2,000 Hz) and integrated (time constant 0.1 s). The output of action potentials and bursts from this assembly were passed to a
data-acquisition system (FASTDAQ, Lectromed UK Ltd., Letchworth Garden City, Herts, United Kingdom) for on-line monitoring and storage using a minicomputer (Elonex UK Ltd., Bradford, United Kingdom). The FASTDAQ system digitized the action potentials at 12,000 samples/s and all other data channels at 2,000 samples/s (8 bits). Long-term storage was achieved using a high-capacity drive (Iomega zip drive, Iomega Europe GmbH, Freiburg, Germany).

With the exploring electrode in the nerve, electrical stimulation (0.1 to 1.0 V, 1 Hz, 0.2 ms) caused muscular twitches without paraesthesia. Multunit muscle sympathetic nerve activity was differentiated from skin sympathetic activity and afferent activity by previously accepted criteria (14). Single units were sought by repeatedly making tiny adjustments to the exploring electrode position. When a unit was identified in the raw action potential neurogram as being different in height from other concomitant units (if present), it was further scrutinized to confirm it had vasoconstrictor properties, as described in the section entitled “Other procedures.” Fast monitor sweep and an on-line storage oscilloscope were then used to confirm the presence of a single unit by demonstrating consistency in action potential morphology as previously described (16,17).

Other procedures. Only vasoconstrictor activity was accepted and examined, the criteria of acceptability being appropriate responses to spontaneous changes in arterial blood pressure, the Valsalva maneuver and isometric hand-grip exercise, as previously described (16,17). Briefly, during Valsalva, sympathetic activity increased during the latter part of phase II or phase III and decreased during phase IV (increase and overshoot of blood pressure). Isometric hand-grip exercise, performed using a dynamometer (MIE Medical Research Ltd., Leeds, United Kingdom) produced a late increase in arterial blood pressure, sympathetic neural activity and calf vascular resistance. Calf vascular resistance was determined from the product of mean arterial pressure on the mean of at least six measurements of calf blood flow in the left leg using strain-gauge plethysmography (DE Hokansen Inc., Bellevue, Washington). In each subject the resting mean frequencies of s-MSNA impulses and MSNA bursts were obtained simultaneously.

Data analysis. Without knowledge of the patient diagnosis, data analysis was performed off-line by a single experienced operator using signal-processing software (FASTDAQ, Lectromed UK Ltd.). Mean data from at least three baseline time periods were analyzed. An electronic discriminator was used to count the spikes of s-MSNA and the R-wave of the electrocardiogram (Fig. 1). The former was quantified as mean frequency of impulses/min and impulses/100 cardiac beats. The bursts of MSNA on the mean voltage neurogram were identified by inspection, being defined by amplitude when the signal-to-noise ratio was >3, and they were quantified as mean number of bursts/min and bursts/100 cardiac beats. Neural activity was expressed both per min and per 100 cardiac beats as it is understood that there is a complex relationship between heart rate and sympathetic discharge frequency, and the latter expression avoids any interference by the length of the cardiac cycle (24).

Statistics. Two-way analysis of variance (ANOVA) with Bonferroni multiple post-test comparisons were used to compare data between the two groups. The least square technique was used for assessing the linear relationship between variables. Values of p <0.05 were considered statistically significant. Data were presented as mean ± SEM.

RESULTS

The demographic details of the two matched groups are shown in Table 1. There was no significant difference in age, body weight, body mass index, heart rate or arterial blood pressure between the groups.

Table 1. Demographic Details of the Two Subject Groups

| Subjects             | EHT   | EHT + LVH | p Value*
|----------------------|-------|-----------|----------
| Number (men)         | 14 (9)| 14 (6)    |          |
| Disease stage 2 (stage 3) | 7 (7) | 8 (6)  |          |
| Age (yrs)            | 55 ± 1.8 | 55 ± 2.4 | NS       |
| Weight (kg)          | 84 ± 4.0 | 84 ± 3.3 | NS       |
| Body mass index (kg/m²) | 30 ± 1.0 | 30 ± 1.3 | NS       |
| Heart rate (beats/min) | 74 ± 2.6 | 67 ± 2.1 | NS       |
| Arterial pressure (mm Hg) | 128 ± 3.4 | 125 ± 3.2 | NS       |
| Mean                 | 173 ± 4.5 | 174 ± 6.6 | NS       |
| Systolic             | 107 ± 4.1 | 101 ± 2.6 | NS       |

*Two-way analysis of variance (Bonferroni post-test analysis), no significant interaction (p > 0.7).

EHT = essential hypertension; LVH = left ventricular hypertrophy; NS = nonsignificant.
As expected, there was a significant positive correlation (r) for resting s-MSNA and MSNA with the subjects' age (r at least 0.42 and at most 0.59; p < 0.0002). However, there was no significant correlation within any group (consistently r < 0.38, p > 0.09) between resting sympathetic discharge (s-MSNA or MSNA) and the levels of resting arterial blood pressure (systolic, diastolic or mean pressure) or heart rate.

Respectively, for the EHT + LVH and the EHT groups, posterior wall thickness was 13 ± 0.8 mm and 10 ± 0.3 mm (p < 0.05); interventricular septal thickness was 12 ± 0.8 mm and 10 ± 0.3 mm (p > 0.05), and end-diastolic volumes were 124 ± 12.4 ml and 127 ± 15.8 ml (p > 0.8). The estimated LVM in the EHT + LVH group was 301 ± 26.6 g and in the EHT group was 215 ± 19 g (p < 0.05), and the values for LVMI when indexed by body surface area were 155 ± 13 g/m² and 113 ± 10.9 g/m² for the two groups, respectively (p < 0.05). Using two-way ANOVA, no significant interaction was found between any of these variables (p > 0.3).

Resting s-MSNA in EHT + LVH was greater than that in EHT; on average this represented a 34% and a 46% increase when activity was expressed per minute and per 100 cardiac beats (Fig. 2). The group mean frequency of s-MSNA in EHT + LVH versus EHT was 51.1 ± 5.3 impulses/min versus 38.1 ± 2.4 impulses/min (p > 0.05) and 75.9 ± 6.9 impulses/100 beats versus 52.1 ± 2.9 impulses/100 beats (p < 0.001). In addition, the group of EHT + LVH had greater resting MSNA than the EHT group (Fig. 3), respectively; on average this represented a 14% and 31% increase when activity was expressed per minute and per 100 cardiac beats. The group mean frequency of MSNA in EHT + LVH versus EHT was 40.6 ± 2.5 bursts/min versus 35.5 ± 2.1 bursts/min (p > 0.05) and 64.2 ± 5.7 bursts/100 beats versus 48.9 ± 2.8 bursts/100 beats (p < 0.05). Two-way ANOVA of these variables showed there was no significant interaction (p > 0.15). When only the 22 untreated patients were considered (8 in the EHT + LVH group vs. 14 in the EHT group), the overall findings were unaltered in that the LVH group still had significantly greater sympathetic discharge compared with the non-LVH group. Within the group of EHT + LVH, there was no significant difference in any measure of sympathetic discharge between those who were treated and those untreated (Figs. 2 and 3). Finally there was a significant correlation between both s-MSNA and MSNA (quantified per 100 cardiac beats) and LVMI (always p < 0.05; r = 0.48 and r = 0.46, respectively).

**DISCUSSION**

This is the first evidence that the mean resting frequency of peripheral sympathetic vasoconstrictor discharge in moderate to severe hypertension was greater in those patients with LVH compared with those without LVH. This relative sympathetic hyperactivity reflected an increased central output at rest and was not caused by differences in arterial blood pressure, age or body weight. These findings allow us to hypothesize that patients with relatively higher central sympathetic output may be more likely to develop LVH than those with equivalent severity of hypertension who have lower sympathetic output.

**Microneurography.** Microneurography is a well-established technique that has been used successfully in the assessment of peripheral sympathetic activity (14). Previous studies have examined the frequency and incidence of MSNA bursts derived from multiunit recordings but have not been specific to any of the individual action potentials that constitute the burst. Despite the difficulty of establishing that every unit within a burst has a vasoconstrictor role, there is a wealth of evidence to
suggest that patients with hypertension have a greater frequency of MSNA bursts than properly matched normotensive subjects (15, 25–27).

More recently, recordings of single unit muscle sympathetic discharge have been obtained from normotensive and hypertensive subjects (16, 17). Though more difficult to obtain than MSNA bursts, the advantage of directly measuring the mean frequency of a single unit discharge is that it may be a reflection of the true resting central sympathetic output to the periphery. This is because it allows quantification from specific units with demonstrable vasoconstrictor function without interference from other uncharacterized units. In addition, it can avoid the inclusion of recruited units, which could otherwise be counted during the recording of MSNA bursts. Finally, although the technique of microneurography is selective for the particular unit(s) studied, under resting conditions the variability between repeat recordings of both s-MSNA and MSNA is <8% (16).

In this study we measured both the resting mean frequency of multiunit MSNA bursts and single unit discharge. Qualitatively, both measures responded to reflex maneuvers in a manner that reflected their involvement in peripheral vascular control. The results obtained from MSNA recordings in this study were similar to those previously published in age-comparable hypertensive subjects (15, 16, 25, 26, 28). This can be considered a reflection of the stringent study protocol and the attempts to avoid confounding factors. As previously discussed (16), it is known that many biological factors can influence sympathetic output such as age, obesity and severity of hypertension, as well as environmental factors including dietary sodium intake, alcohol, nicotine and exercise. Thus subjects in the two groups were closely matched for biological variables and were studied under the same laboratory conditions. Although there was a significant difference in LVM between the two groups, there was a degree of overlap in the data. This relates, in part, to the variability of left ventricular internal diameter and the requirement of an increase in wall thickness for a patient to be considered as having LVH. This overlap could not be avoided, as it was important that subjects were matched for biological variables and not excluded on the basis of cavity or wall dimensions. However, even if we hypothesize that the EHT group had some degree of LVH (to explain the overlap), it remains valid that the EHT + LVH group with a greater degree of LVH have greater sympathetic activation. In fact, this is further supported by the fact that there was a positive correlation between LVMI and sympathetic nerve activity.

Main findings. In this study, the resting mean discharge frequency of s-MSNA per 100 cardiac beats in the patients with EHT + LVH was significantly greater (by about 46%) than that in the EHT group. Assessment from multiunit MSNA bursts revealed that the EHT + LVH group still had about 31% greater sympathetic activity than the EHT group. Although there was a similar trend regarding the mean discharge frequency per minute of both measures of sympathetic activity, the differences did not reach statistical significance. This increase in both single unit and multiunit sympathetic discharge demonstrates two potential mechanisms for central sympathetic regulation. First, increased s-MSNA represents a true increase in the discharge frequency of central sympathetic neurons. Second, increased MSNA represents central activation as well as reflex-based increases (fiber recruitment) in sympathetic activity.

In interpreting these results, it is important to take into consideration that some of the subjects with LVH were on antihypertensive medication, some of which can lower heart rate. It is well known that differences in the pulse interval can affect the assessment of mean sympathetic discharge frequency (24). Thus, considering the data over 100 heart beats to allow for differences in resting heart rate, assessment of both MSNA and s-MSNA demonstrated clear differences between the groups. Furthermore, if one considers only those subjects not receiving antihypertensive therapy, then the group resting heart rates were similar, and the overall findings of sympathetic discharge were unaltered. In addition, it has been reported that beta-blockers have a variable effect on sympathetic discharge. Acute intravenous administration can increase sympathetic discharge, presumably as a result of acute blood pressure lowering and baroreceptor reflex activation. However, chronic administration, as in this study, with agents such as atenolol (29) and metoprolol (30) may, respectively, have either no effect or reduce the resting mean frequency of sympathetic discharge in EHT. Also, treatment with angiotensin-converting enzyme inhibitors in hypertension has been shown to have either no effect or decrease sympathetic nerve traffic (31, 32). Therefore, the increased activity in EHT + LVH was not attributable to antihypertensive treatment and, in fact, was still apparent despite the use of agents that may have attenuated the group differences, thus adding further weight to the findings.

Previous investigators have suggested a positive correlation between MSNA and the severity of hypertensive disease (15). More recently, we have shown that patients with moderate to severe hypertension had either lower or equal sympathetic output compared with matched groups with milder hypertension, depending on whether single units or multiunits were examined (16). There are a number of reasons that may account for these different findings. First, blood pressure classification differed between the studies, the former using an arbitrary classification and the latter using the JNC-VI classification (21). Secondly, we have shown that the ability to record neural activity from a single sympathetic unit allows further insight into central command, as it allows a true assessment of central sympathetic discharge frequency. Thus, using a combination of single and multiunit assessment may have allowed for further characterization of the hypertensive subjects. Finally, and perhaps most importantly, subjects with severe hypertension in the former study had a high LVMI, whereas, in the latter
eral sympathetic hyperactivity has also been reported in
structural changes (11,34). On the other hand, marked periph-
maintained, in part, by the occurrence of end-organ struc-
onset of hypertension is associated with sympathetic hyper-
these findings also help to reconcile differing reports on
sympathetic hyperactivity in hypertension. On the one hand
it has been reported that peripheral sympathetic hyperactiv-
this study was performed in the baseline resting state. In
addition, although elegant techniques for the assessment of
cardiac sympathetic function utilizing norepinephrine spill-
over are available, by their invasive nature they still have
methodologic constraints. Importantly, however, evidence
does suggest that measures of cardiac norepinephrine spill-
over do correlate well with recordings of peripheral sympa-
thetic nerve activity (41). One final point to remember is
that this was a cross-sectional study, which, although it
implies an association, gives no direct evidence of causality.
There are many additional factors known to be important in
the development of LVH, but, in light of the current
findings, the occurrence of LVH needs to be considered in
future studies involving sympathetic assessment in hyper-
tensive disease.

Conclusions. This is the first evidence that, in patients
with moderate to severe EHT, the presence of LVH is
associated with higher resting sympathetic discharge, evi-
denced by both an increase in unitary firing frequency and
by fiber recruitment. This supports the hypothesis that
central sympathetic hyperactivity may be a factor in the
development of hypertensive LVH.

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