Relation Between Cardiac Sympathetic Activity and Hypertensive Left Ventricular Hypertrophy

Markus P. Schlaich, MD; David M. Kaye, MBBS, PhD; Elisabeth Lambert, PhD; Marcus Sommerville; Flora Socratous; Murray D. Esler, MBBS, PhD

Background—Left ventricular (LV) hypertrophy is an independent risk factor for cardiovascular morbidity and mortality in hypertensive subjects. Sympathetic activation has been suggested to contribute to LV hypertrophy, but this has not yet been conclusively validated in humans.

Methods and Results—We comprehensively assessed total systemic and regional sympathetic activity by radiotracer dilution methods and microneurography in 15 untreated hypertensive subjects with echocardiographic evidence of LV hypertrophy (EH+), 11 hypertensive subjects with similar blood pressure but without LV hypertrophy (EH−), and 10 age-matched normotensive control subjects (NT). LV mass index was 87±15 g/m² in NT, 106±11 g/m² in EH−, and 138±17 g/m² in EH+ (P<0.001). Total body and renal norepinephrine spillover were higher in both hypertensive groups compared with NT (total norepinephrine spillover, NT 223±145 versus EH− 418±135 versus EH+ 497±303 ng/min; renal norepinephrine spillover, NT 38.8±25.3 versus EH− 88.6±58.0 versus EH+ 103.4±56.2 ng/min; both P<0.05). However, muscle sympathetic nerve activity (NT 25±6 versus EH− 38±20 versus EH+ 57±19 bursts per 100 heartbeats; P<0.01) and cardiac norepinephrine spillover (NT 11.7±6.2 versus EH− 13.1±7.2 versus EH+ 28.6±17.4 ng/min; P<0.01) were only increased in EH+. Cardiac norepinephrine spillover correlated positively with LV mass index in all subjects (r=0.52; P<0.001).

Conclusions—Our findings demonstrate that hypertensive LV hypertrophy is associated with increased sympathetic activity largely confined to the heart, suggesting that increased cardiac norepinephrine release is related to the development of LV hypertrophy. (Circulation. 2003;108:560-565.)

Key Words: hypertrophy ▪ hypertension ▪ nervous system ▪ sympathetic ▪ norepinephrine

Left ventricular (LV) hypertrophy is an independent risk factor for cardiovascular morbidity and predicts cardiovascular complications in patients with hypertension. Numerous studies investigated the mechanisms underlying hypertensive LV hypertrophy, initially with a primary focus on hemodynamic factors. There is increasing evidence for a considerable contribution of nonhemodynamic stimuli to LV hypertrophy. Although experimental and animal studies suggest a role for norepinephrine (NE) as a myocardial hypertrophic neurohormone, such a relation has not yet been conclusively validated in humans. It has recently been demonstrated that the presence of LV hypertrophy is related to increased muscle sympathetic nerve activity in hypertensive subjects. However, to adequately assess whether sympathetic activation promotes LV hypertrophy, regionalization of sympathetic outflow to various organs needs to be taken into account and thus sympathetic tone must be studied in the heart directly.

To additionally investigate the contribution of blood pressure and regional sympathetic activation to hypertensive LV hypertrophy, we applied microneurography and isotope dilution methodology to comprehensively study sympathetic activity in hypertensive subjects with and without echocardiographic evidence of LV hypertrophy. In parallel, we studied 10 normotensive control subjects with normal ventricular mass.

Methods

Subjects

The study cohort consisted of 26 patients with essential hypertension (EH) and 10 normotensive control subjects (NT). None of the patients had accelerated hypertension, clinical coronary heart disease, heart failure, a history of stroke, renal insufficiency, or diabetes. Previous use of antihypertensive therapy was reported in 11 of 26 hypertensive subjects (4 in EH− and 7 in EH+). Antihypertensive therapy was discontinued for at least 4 weeks before the study. Normotensive control subjects underwent careful clinical evaluation and serum biochemistry measurements to exclude renal and hepatic disease. Respondents with a history of incidental disease, alcohol intake >2 standard drinks per day were excluded. Blood pressure (BP) readings were taken according to World Health Organization recommendations.

Participants were classified by

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as normotensive if the average of 4 casual BP measurements taken in our outpatient clinic was <140 mm Hg systolic and <90 mm Hg diastolic on at least 2 different occasions and as hypertensive if the mean of 4 casual BP measurements taken in our outpatient clinic was >140 mm Hg systolic or >90 mm Hg diastolic on at least 2 different occasions. These were confirmed by measurements with a Finapres BP monitor (Datex-Ohmeda 2300) during microneurography and by intra-arterial BP measurements during the catheter study. Written informed consent was obtained before the study. The study protocol was approved by the Alfred Hospital Ethics Review Committee.

**General Procedure**

The study commenced in the morning after an overnight fasting period with abstinence from smoking, alcohol, tea, and coffee for >12 hours before the experiment. Echocardiography, microneurography, and catheterization were performed on the same day if possible and otherwise on separate days less than 1 week apart.

**Echocardiography**

Two-dimensional guided M-mode echocardiography was performed in all subjects (M2424A [Sonos5500], Agilent Technologies). LV dimensions were measured according to the recommendations of the American Society of Echocardiography. LV mass was calculated according to the recommendations of the American Society of Echocardiography and corrected following the suggestions of Devereux et al. LV mass index (LVMI) was derived with normal limits defined as ≤125 g/m² for men and ≤110 g/m² for women. Accordingly, 15 of 26 hypertensive subjects had evidence of LV hypertrophy. The remaining 11 hypertensive subjects and all normotensive subjects had LVMI within normal limits.

**Microneurography**

Multunit postganglionic sympathetic nerve activity was recorded in the peroneal nerve, as described previously. The nerve signal was amplified (×50 000), filtered (bandpass, 700 to 2000 Hz), and integrated. BP, ECG, and muscle sympathetic nerve activity (MSNA) were digitized with a sampling frequency of 1000 Hz (PowerLab recording system, model ML785/8SP, ADI Instruments). After an acceptable nerve-recording site was obtained, which was possible in 30 of the 36 participants (NT 8 of 10; EH− 9 of 11; and EH+ 13 of 15 subjects), MSNA was recorded for 20 minutes.

**Catheterization Protocol**

Participants received a tracer infusion of [3 H]-labeled NE (specific activity of 11 to 25 Ci/mmol; New England Nuclear) via a peripheral vein at 0.6 to 0.8 μCi/min, after a priming bolus of 12 μCi to measure NE kinetics by isotope dilution. The radial artery was cannulated (3F, 5 cm, Cook) for arterial pressure monitoring and blood sampling. A venous introducer sheath was placed in the antecubital fossa. Subsequently, a coronary sinus thermodilution catheter (Webster CCS 7/8U90A, Webster Laboratories) was introduced via the venous sheath and placed under fluoroscopic control in the region of interest for blood sampling and determination of blood flow by thermocardiography. Catheterization of the coronary sinus was not possible in 1 subject (EH+), and catheterization of the renal vein was performed successfully in 28 of 36 subjects (NT 9 of 10; EH− 9 of 11; and EH+ 10 of 15 subjects). Renal plasma flow was determined from the steady-state clearance and renal extraction of p-aminohippurate.

**Biochemical Analysis**

Plasma concentrations of neurochemicals were determined by high-performance liquid-chromatography with electrochemical detection. Timed collection of eluate leaving the detection cell with a fraction collector enabled collection of the [3 H]-labeled NE for subsequent counting by liquid scintillation spectroscopy. Calculation of NE kinetics was performed using equations previously described.

**Statistical Analysis**

Results are presented as mean±SD. Two-sided probability values are given throughout the text. Two-sided P<0.05 was considered to indicate statistical significance. Multigroup comparisons of variables were carried out by one-way ANOVA followed by the Bonferroni correction. Relations between variables were determined by linear regression analysis. The data were processed using the software package SigmaStat for Windows 2.03 (SPSS Inc).

**Results**

Characteristics of the study cohort are summarized in Table 1. Body mass index (BMI) tended to be higher in hypertensive
TABLE 2. Total Systemic and Cardiac NE Plasma Kinetics

<table>
<thead>
<tr>
<th></th>
<th>NT (n=10)</th>
<th>EH-LVH (n=11)</th>
<th>EH+LVH (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial NE plasma conc.</td>
<td>181±66</td>
<td>229±76</td>
<td>274±109</td>
</tr>
<tr>
<td>Coronary sinus conc.</td>
<td>211±122</td>
<td>250±111</td>
<td>425±214†</td>
</tr>
<tr>
<td>Fractional transcardiac</td>
<td>70.2±11.7</td>
<td>62.2±9.6</td>
<td>57.0±14.8</td>
</tr>
<tr>
<td>Coronary sinus flow</td>
<td>81.4±17.9</td>
<td>81.1±20.7</td>
<td>91.2±29.3</td>
</tr>
<tr>
<td>Cardiac NE spillover</td>
<td>11.7±6.2</td>
<td>13.1±7.2</td>
<td>28.6±17.4†</td>
</tr>
<tr>
<td>Total systemic spillover</td>
<td>223±145</td>
<td>418±135*</td>
<td>497±303*</td>
</tr>
<tr>
<td>NE clearance, ml/min</td>
<td>1519±335</td>
<td>1602±445</td>
<td>1443±349</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD. To convert from ng/min to pmol/min, multiply by 5.91.

*P<0.05 vs NT; †P<0.05 vs EH-LVH.

compared with normotensive subjects (P=0.09). Intra-arterial blood pressures directly recorded at rest in the cardiac catheterization laboratory were higher in hypertensive subjects. Both hypertensive groups had similar systolic and diastolic blood pressure.

Posterior wall and interventricular septal wall thickness were higher in EH+ compared with EH− and NT. LV internal diameter was similar in both hypertensive groups but higher in EH+ compared with NT. The estimated LV mass was 238±39 g in EH+, 176±47 g in EH−, and 139±28 g in NT, and the values for LVMI were 138±17, 106±11, and 87±15 g/m², respectively (ANOVA, P<0.001) (Table 1). There was a trend toward higher LVMI in EH+ compared with NT (P=0.056).

Total systemic and cardiac NE kinetics are detailed in Table 2. Mean arterial plasma NE concentration was similar in all 3 groups. Total body NE spillover was similar in the 2 hypertensive groups but significantly higher compared with NT (both P<0.05). However, NE spillover from the heart was only increased in EH+ (more than 2-fold), whereas no difference in cardiac NE spillover was evident between EH− and NT (NT 11.7±6.2 versus EH− 13.1±7.2 versus EH+ 28.6±17.4 ng/min; P<0.01) (Figure 1A). The higher cardiac NE spillover in EH+ was not attributable to a reduction in cardiac neuronal NE reuptake or alterations in myocardial blood flow, because fractional transcardiac extraction of tritiated NE across the heart and coronary sinus plasma flow were similar in all 3 groups (Table 2). Increased cardiac sympathetic outflow was most likely attributable to increased cardiac NE release, as reflected by significantly higher mean NE concentrations in coronary sinus plasma in EH+ compared with EH− and NT (P<0.05) (Table 2).

Similarly, resting MSNA was only increased in EH+ but not in EH− compared with NT (burst frequency, NT 16±4 versus EH− 24±13 versus EH+ 33±12 bursts/min; P<0.05; burst incidence, NT 25±6 versus EH− 38±20 versus EH+ 57±19 bursts/100 heartbeats; P<0.01) (Figure 1B).

Conversely, total systemic (Table 2) and renal sympathetic nervous activity (NT 38.8±25.3 versus EH− 88.6±58.0 versus EH+ 103.4±56.2 ng/min) did not differ between EH+ and EH− but were higher in both hypertensive groups compared with NT (both P<0.05) (Figure 1C). There was a positive correlation between LVMI and cardiac NE spillover (r=0.52; P<0.001), whole-body NE spillover (r=0.50; P<0.01), and MSNA (r=0.50; P<0.01) for hypertensive and normotensive subjects combined but not for renal NE spillover (r=0.41; P=NS) (Figure 2). When only the 2 hypertensive groups were considered, a positive correlation between NE spillover and LVMI was found (r=0.41; P=NS) (Figure 2).

Figure 1. Cardiac NE spillover rates (A), MSNA (B), and NE spillover rates from the kidney (C) in NT, EH−, and EH+. *P<0.05 vs NT; **P<0.01 vs NT and EH−.
correlation was evident only between LVMI and cardiac NE spillover ($r=0.44$; $P=0.05$).

**Discussion**

This study comprehensively investigated the relation between regional sympathetic tone and hypertensive LV hypertrophy in humans. For the first time we demonstrate that hypertensive LV hypertrophy is correlated with increased sympathetic activity in the heart. Estimates of sympathetic tone in the kidneys and for the whole body were unrelated to the presence of LV hypertrophy in EH. Coupled with the observation that central sympathetic outflow was only increased in those hypertensive subjects with increased LV mass, our data strongly suggest that trophic effects of increased cardiac sympathetic nerve firing and NE release are directly related to the development of hypertensive LV hypertrophy.

Measurement of sympathetic activation in humans is challenging, particularly so if regional activation is to be assessed. The use of radiotracer dilution methods provides the most accurate estimation of regional sympathetic activation in cardiovascular disease, where the sympathetic outflow may be selectively activated to some organs but unchanged or inhibited in others. Other potential aspects of dysfunction of NE disposition, such as reduced capacity for neuronal NE reuptake and metabolism, were assessed and did not seem to be primarily involved.

NE has been identified as a myocardial hypertrophic hormone in several experimental and animal studies. However, such a role for NE has not yet been conclusively validated in humans. Our results provide the most direct evidence yet available to support the hypothesis of a trophic effect of NE on the myocardium in hypertensive humans in that cardiac sympathetic tone was only increased in those hypertensive subjects with evidence of LV hypertrophy. Of note, although not statistically significant, LV mass was substantially higher in EH than in NT ($P=0.054$), in keeping with the well-described impact of increased afterload on LV structure in hypertension and indicating that a component of the increase in LV mass in both hypertensive groups is attributable to increased blood pressure. On the basis of the correlation shown in Figure 2A, cardiac NE spillover only explains $\approx 25\%$ of the variation in LV mass. Therefore, LV hypertrophy cannot be attributed solely to cardiac NE release and stresses the importance of other contributing factors. For example, both systolic LV dysfunction and diastolic filling abnormalities could also contribute to an increase in cardiac NE spillover via variations in intracardiac pressures. However, ejection fraction and the ratio of the velocity time integral of the A/E wave were similar between all 3 groups, although there was a trend toward increased velocity time integral A/E in hypertensive patients with LV hypertrophy. Additional studies are necessary to adequately address this issue as a potential mechanism for increased cardiac NE spillover in hypertensive LV hypertrophy. Furthermore, LV hypertrophy and cardiac sympathetic activation in heart failure patients has been suggested to be associated with diminished reflex vagal heart rate regulation. The increase in cardiac NE spillover in our hypertensive subjects with LV hypertrophy might therefore be a consequence of the effects of LV hypertrophy, leading to a reflex reduction in cardiac vagal tone and increase in NE release through an escape from cholinergic sympathetic neuromodulation. Against this argument, however, it is noteworthy that even in borderline hypertension cardiac vagal tone is reduced.

Our study does not allow discrimination between hypertrophy of myocytes or hypertrophy caused by an increase in cardiac fibrosis in our hypertensive patients with LV hypertrophy. However, a previous study in patients with hypertensive heart disease and a LVMI of 175.6$\pm$14.6 g/m$^2$ revealed that the collagen volume fraction was 6.9$\pm$0.6%. Thus, although we cannot provide data to indicate the extent to which LV hypertrophy evident in some of our hypertensive patients may be caused by cardiac fibrosis, myocyte hyper-
trophy seems to be the major determinant of LV hypertrophy in hypertensive heart disease.

Antihypertensive therapy may have possibly influenced LV mass in our study. Four of 11 patients in the EH− group and 7 of 15 patients in the EH+ group previously were taking medication, which was discontinued at least 4 weeks before the study, making a significant contribution of drug effects on sympathetic tone during the study unlikely. Such a possibility, however, cannot definitely be ruled out. In 8 of 11 previously treated subjects, the regimen consisted of an ACE inhibitor or AT1-receptor blocker, with a similar distribution in both groups (EH− 3; EH+ 5). Thus, potential long-term effects of previous therapy most likely did not influence the overall difference in NE spillover between the 2 hypertensive groups.

Both hypertensive groups were well matched for factors known to impact LV mass and sympathetic activity, including age, obesity, and severity of hypertension, suggesting that our finding of an interrelationship between LV mass and cardiac sympathetic activity was not confounded by them. However, mean BMI for both hypertensive groups was in the overweight range compared with the normotensive control group. Lean hypertensive subjects are characterized by increased cardiac sympathetic activity, whereas cardiac NE spillover in obese hypertensive subjects does not differ from that of their normotensive obese counterparts. If at all, the higher BMI in both of our hypertensive groups therefore could be expected to ameliorate cardiac NE spillover, making the marked differences between EH+ and the 2 other groups even more striking. Similarly, MSNA is increased in obesity, whereas no difference exists between normotensive and hypertensive obesity. Thus, whereas the relatively high BMI in both hypertensive groups may have contributed to their higher MSNA (although not statistically significant for EH−), it cannot account for the marked difference in MSNA between the 2 hypertensive groups.

Impaired neuronal NE reuptake has been suggested to contribute to the increased spillover of NE from the heart in hypertension. Interestingly, we observed a tendency toward higher burst incidence in EH− compared with NT (38±20 versus 25±6 bursts per 100 heartbeats, P=0.11). Therefore, similar MSNA in NT and EH− is most likely related to the relatively small subject number. If both hypertensive groups are combined, MSNA differs significantly from the normotensive group (52±21 versus 25±6 bursts per 100 heartbeats; P<0.01).

There would be potential value in studying cardiac NE spillover in normotensive variants of LV hypertrophy. This could help to establish whether LV hypertrophy causes increased cardiac NE spillover and provide an indication of the relative capacities of high blood pressure and high cardiac sympathetic tone to contribute to LV hypertrophy development. An example of increased LV mass of normotensive subjects is normotensive obesity. BMI is clearly related to LV mass. In a recent study in normotensive obese subjects, we have demonstrated that normotensive obese subjects are characterized by increased renal NE spillover but low cardiac sympathetic tone. Therefore, increased cardiac NE spillover is not caused by LV hypertrophy in this population. Another group of normotensive subjects with LV hypertrophy is athletes. Neri Serneri et al have demonstrated that cardiac NE spillover is increased in athletes with LV hypertrophy compared with a sedentary control group, suggesting that a selective increase in cardiac sympathetic drive is associated with cardiac hypertrophy in athletes. The heterogeneity of data obtained from various normotensive groups with evidence of increased LV mass supports the notion that LV hypertrophy is a complex phenotype and that investigation of special groups such as these will not necessarily allow discrimination between the blood pressure and cardiac sympathetic stimuli to LV mass index.

In consideration of the available evidence, a possible sequence of events to induce hypertensive LV hypertrophy could include the following: cardiac, renal, and muscle sympathetic nerve activity is increased, particularly in young hypertensive subjects, leading to a hemodynamic profile characterized by an increase in heart rate, cardiac output, renal vascular resistance, and blood pressure. The increase in LV workload induces adaptive cardiac structural changes, which are additionally potentiated in the presence of high cardiac NE levels or other humoral factors such as angiotensin II and finally culminate in a phenotype resembling LV hypertrophy. Established target-organ structural changes maintain the severity of hypertension and may subsequently lead to a downregulation of sympathetic drive.

This notion may, at least in part, also help to explain the overt discrepancy between the suggested importance of NE for the development of LV hypertrophy and the variable effects of antihypertensive therapy with antiadrenergic drugs on regression of LV hypertrophy beyond blood pressure–related effects, ranging from complete absence of effect to a pressure-unrelated reversal of LV hypertrophy. Animal studies revealed the significance of α1-receptor blockers for catecholamine-induced cardiac hypertrophy. The use of α1-receptor blockers in hypertensive subjects indeed demonstrated favorable effects on reversal of LV hypertrophy.
although such an effect was not evident in all studies. Of note, however, α₁-adrenergic blockade may well have clinical implications beyond the reduction of LV mass, with the recent demonstration of an increased risk for the development of heart failure during treatment of hypertension with doxazosin in the Antihypertensive and Lipid-Lowering Treatment To Prevent Heart Attack Trial study. Most studies including β-receptor blockers revealed the ability of this drug class to reduce hypertensive LV hypertrophy beyond blood pressure–related effects. Furthermore, a meta-analysis examining the ability of the major antihypertensive drug classes to reduce hypertensive LV hypertrophy additionally substantiated the notion of beneficial effects of antiadrenergic therapy on reversal of LV hypertrophy.

In conclusion, our study provides the most direct evidence to date for an association between increased cardiac sympathetic activity and hypertensive LV hypertrophy in humans. Although such an association is not necessarily indicative of a cause and effect relationship, which could only be determined by a series of experiments spread over several years, the available evidence from experimental, animal, and human studies strongly suggests that increased cardiac NE release is related to the development of hypertensive LV hypertrophy.

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References
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