Evidence Against Elevated Sympathetic Vasoconstrictor Activity in Borderline Hypertension

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Abstract. The relationship between sympathetic nerve activity and BP in the early stages of essential hypertension remains unclear. To investigate this relationship further, this study measured resting muscle sympathetic nerve activity (MSNA; representing peripheral vasoconstrictor activity), plasma catecholamines, BP, central venous pressure, and heart rate in 20 young (24 ± 2 SD yr), lean (body mass index, 24.2 ± 3.0 kg/m²), male subjects with borderline hypertension (BHT) and in 21 male normotensive (NT) control subjects matched for age and body mass index. A cold pressor test was also performed to evaluate sympathetic reflex responsiveness. Resting mean BP and heart rate were significantly higher in the BHT subjects compared with NT subjects (113 ± 9 versus 89 ± 9 mmHg; 74 ± 8 versus 62 ± 8 bpm; P < 0.0001 each) with no difference in central venous pressure. Resting MSNA levels tended to be lower in the BHT versus the NT group (12 ± 6 versus 14 ± 9 bursts/min, P = NS; 16 ± 8 versus 22 ± 13 bursts/100 heartbeats, P = 0.05) and did not correlate with either BP or body mass index. Significant positive correlations were found between resting MSNA and plasma norepinephrine levels in both groups (P < 0.05). Hemodynamic and sympathetic nerve responses to the cold pressor test were similar between the BHT and NT subjects. It is concluded that resting MSNA and plasma norepinephrine levels are correlated in young lean NT and BHT men; however, neither of these variables is correlated with BP. Because MSNA was similar in the two groups, the concept that augmented resting MSNA is important in the early developmental phase of essential hypertension must be reevaluated.

Borderline hypertension (BHT) represents an early stage in the development of established essential hypertension (1,2). Studying the pathophysiology of BHT may provide important insight into the pathogenesis of essential hypertension. Reports on increased plasma catecholamine levels and responsiveness to adrenergic agonists and antagonists (3–5) provided initial evidence for increased sympathetic drive in young mildly hypertensive humans. However, these studies could not show whether the increased plasma norepinephrine levels resulted from facilitated neurotransmitter release, from impaired norepinephrine reuptake at the peripheral nerve endings, or from increased sympathetic nerve fiber firing. To elucidate these mechanisms, investigators have applied direct microneurographic measurements of intraneural vasoconstrictor sympathetic activity to muscle (MSNA) in young mildly hypertensive and borderline hypertensive humans (6–14). Nevertheless, the results were conflicting. The majority of studies demonstrated increased basal MSNA; however, age and body mass index, which are now known to affect MSNA (15–23), were not controlled. In addition, patients with more advanced stages of essential hypertension were included (8,11). Furthermore, two studies (13,14) that found no increased basal MSNA nevertheless identified an elevated cardiac output with normal peripheral resistance (24,25). To reexamine this issue, we quantified resting levels of MSNA and plasma catecholamine concentrations in a larger group of young, lean, male BHT subjects and in normotensive (NT) male control subjects well matched for age and body mass index. Because cardiovascular regulatory dysfunction may occur not only at rest but also more commonly during stress, we also performed a cold pressor test as a nonspecific sympathoexcitatory stimulus.

Materials and Methods

Subjects

We studied 20 young male lean borderline hypertensive subjects and 21 male normotensive control subjects well matched for age, weight, height, and body mass index (Table 1). All subjects were university students and were recruited by advertisement. The subjects reported similar levels of physical activities and general level of physical fitness. They ingested no special diet and generally ate regularly at the campus cafeteria.

Subjects were classified as NT or BHT after at least four screening sessions more than 1 wk apart in which BP measurements were obtained from the arm with a standard mercury sphygmomanometer. During measurements, subjects sat quietly for 15 min and then three readings were taken during 6 min. Korotkoff Phase V was used as the diastolic BP value. Subjects whose systolic BP values were intermittently ≥140 mmHg and/or whose diastolic BP readings were intermittently ≥90 mmHg on one or more other visits, yet whose BP values were below 140/90 mmHg on one or more other visits, were
considered to have BHT. NT subjects had BP values of <140 mmHg systolic and <90 mmHg diastolic on all screening measurements.

No subject ingested any medications or had ever been treated for hypertension. Except for histories of intermittent BP elevations in the BHT subjects, the medical history and physical examinations of all subjects were normal. Sixteen BHT subjects and one NT subject had a family history of hypertension. Informed written consent was obtained before the study, and the protocol was approved by the Human Subjects Review Committee of the University of Erlangen-Nürnberg.

**Measurements**

A direct writing, multichannel physiologic recorder (Gould, Oxnard, CA) was used to simultaneously record arterial and central venous pressures, heart rate, respiratory activity, and MSNA. Systolic, diastolic, and mean arterial pressure were measured noninvasively "beat-to-beat" by a photo-plethysmographic finger device (FINAPRES; Ohmeda, Englewood, CO) as described in detail elsewhere (18). Central venous pressure was determined with an 18.5-gauge, polyethylene catheter inserted in a right medial antecubital vein, and advanced to an intrathoracic vein. An indwelling cannula was inserted into a right forearm vein for drawing plasma catecholamine samples. Heart rate and rhythm were recorded continuously by electrocardiogram, and respiratory activity was recorded by a strain gauge pneumograph. Zero reference point for all hemodynamic measurements was defined at the phlebostatic axis in the midaxillary position.

Multunit recordings of postganglionic sympathetic nerve activity were obtained with unipolar tungsten microelectrodes inserted selectively into muscle nerve fascicles of the peroneal nerve posterior to the fibular head by the microneurographic technique of Valbo et al. (19). The electrodes were connected to a preamplifier, and the nerve signal was fed through a bandpass filter and routed through an amplitude discriminator to a storage oscilloscope and loudspeaker. For recording and analysis, the filtered neurogram was fed through a resistance-capacitance integrating network to obtain a mean voltage display of the neural activity. A recording of sympathetic activity was considered acceptable when the neurogram revealed spontaneous, pulse-synchronous bursts of neural activity, with the largest bursts showing a minimal signal-to-noise ratio of 3:1. In each study, we also confirmed that we were recording the sympathetic outflow to skeletal muscle rather than sympathetic discharge to skin by demonstrating that the neural activity did not respond to arousal stimuli or a pinch of the skin but showed a characteristically biphasic response to the Valsalva maneuver. For analysis, sympathetic bursts were identified by inspection of the filtered and mean voltage neurograms. The rate of sympathetic nerve discharge was expressed as the number of bursts per minute (burst frequency). Sympathetic activity was also corrected for heart rate and expressed as bursts per 100 heart beats (burst incidence). All nerve recordings were analyzed by two investigators who were unaware of the group assignment of the subjects. The data of sympathetic nerve activity as given in the text and figures represent the mean of the two observers. Results and conclusions were not different between observers. Similar to previous studies (20,21), the intraobserver and interobserver variability in identifying bursts were 5% and less than 10%, respectively.

**Protocol**

All studies were performed at the same time of day, starting at 2 p.m., with the subjects supine in the postabsorptive state (i.e., at least 90 min after the ingestion of a light meal), in a warm (22 to 24°C) and quiet room. Subjects were instructed to maintain their usual diet, but to avoid alcohol, caffeine-containing beverages, and tobacco during the 12 h before the study. To ensure that all baseline variables were stable, all subjects rested quietly for 20 min after the nerve electrode had been inserted and the other monitoring devices had been applied. Hemodynamic parameters and MSNA at rest were then recorded continuously for at least 15 min. The reported values represent the mean for this period. Blood was withdrawn into ice-cooled tubes at the end of this resting period, and was stored at −21°C for later plasma norepinephrine and epinephrine determinations (radioenzymatic assay). After registration of baseline data, a cold pressor test was performed. One of the subject’s hands was immersed up to the wrist in ice water for 2 min. Control and recovery periods for the cold pressor test were also 2 min in duration. The average response during each period of control, cold pressor test, and recovery was then determined.

**Statistical Analyses**

All data are presented as mean ± SD. Two-tailed t test for unpaired data was used to compare MSNA, hemodynamic parameters, and plasma catecholamines at rest and in response to the cold pressor test between NT and BHT subjects. The relationships between MSNA, norepinephrine levels, body mass index, and BP were assessed with multiple regression analysis. A value of P < 0.05 was considered significant.

**Results**

Characteristics of the subjects are given in Table 1. The groups did not differ by age, weight, height, and body mass index. The values for mean arterial pressure and heart rate (113 ± 9 mmHg and 74 ± 8 bpm) were significantly higher in the BHT group compared with the NT group (89 ± 9 mmHg and 62 ± 8 bpm, respectively; P < 0.0001). Central venous pressure levels (7 ± 3 mmHg and 8 ± 3 mmHg) did not differ between the groups.

Figure 1 shows representative experimental recordings from two subjects to illustrate resting hemodynamic activity and MSNA. The BHT subjects had higher BP and heart rate levels but similar levels of central venous pressure and sympathetic nerve activity, compared with the NT subjects. The group resting sympathetic activities are shown in Figure 2 (top panel). Resting MSNA was similar in BHT and NT subjects when expressed as burst frequency (12 ± 6 versus 14 ± 9 bursts/}

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NT (n = 21)</th>
<th>BHT (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>25 ± 3</td>
<td>24 ± 2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78 ± 10</td>
<td>80 ± 8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>183 ± 5</td>
<td>182 ± 7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.3 ± 2.4</td>
<td>24.2 ± 3.0</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>89 ± 9</td>
<td>113 ± 9b</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>8 ± 3</td>
<td>7 ± 3</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>62 ± 8</td>
<td>74 ± 8b</td>
</tr>
</tbody>
</table>

* NT, normotensive; BHT, borderline hypertension; BMI, body mass index; MAP, mean arterial pressure; CVP, central venous pressure; HR, heart rate.

b P < 0.0001.
min; \( P = \text{NS} \); however, due to the higher heart rate in the BHT subjects, MSNA tended to be lower in this group compared with the NT subjects when expressed as burst incidence (16 ± 8 versus 22 ± 13 bursts/100 heart beats; \( P = 0.05 \)). In Figure 2 (bottom panel), group mean catecholamine values are shown. Plasma norepinephrine levels (295 ± 132 versus 270 ± 133 pg/ml; \( P = \text{NS} \)) and epinephrine concentrations (57 ± 25 versus 56 ± 20 pg/ml; \( P = \text{NS} \)) were similar between the BHT and NT subjects.

A correlation matrix for MSNA (burst incidence), norepinephrine, body mass index, and mean arterial BP is shown in Table 2. MSNA was correlated with norepinephrine in the entire group (\( r = 0.45, P = 0.005 \)), as well as in the BHT subjects (\( r = 0.50, P < 0.05 \)) and in NT subjects (\( r = 0.54, P < 0.05 \)), when the groups were considered separately. These relationships are shown in Figure 3. However, MSNA did not correlate with body mass index or mean arterial BP. Body mass index correlated weakly with norepinephrine in the entire study group (\( r = 0.34, P = 0.045 \)).

In Table 3, the hemodynamic and MSNA responses to the cold pressor test are compared. The increases in mean arterial BP, central venous pressure, heart rate, and MSNA were similar between the borderline hypertensive and the normotensive subjects.

Discussion

The main finding of our study is that no significant difference in resting levels of MSNA or plasma catecholamines was found between young lean BHT and NT men, matched for age, height, weight, and body mass index. If anything, resting MSNA tended to be lower in this large group of BHT subjects. Thus, the concept of an elevated MSNA in the early developmental stage of essential hypertension should be revised. Because hemodynamic and sympathetic nerve responses to the cold pressor test did not differ between the BHT and the NT subjects, BHT is not necessarily characterized by a nonspecific sympathetic hyper-reactivity to stress.

It has been suggested that increased activity of the sympathetic nervous system, or an imbalance between the sympathetic or vagal tone, may be at least partially responsible for the hemodynamic alterations in the early phase of essential hypertension (1,26). Thus, elevated plasma norepinephrine levels have been found in young mildly hypertensive patients (3–5). However, venous norepinephrine levels reflect the amount of neurotransmitter release from all body organs. Thus, no specific conclusions can be drawn concerning the level of cardiac, renal, or muscle sympathetic activity, all of which are particularly important for the regulation of BP. In contrast, assessment of sympathetic nerve activity to muscle by microneurography uniquely provides direct insight into the central sympathetic outflow directed to muscle vascular beds, a region where peripheral vascular resistance is largely determined.

Most investigators who previously investigated resting MSNA in subjects with BHT reported an increased nerve activity (6–12); however, some did not (13,14). In the majority of studies, body mass index was not controlled (6,7,9–11).
Figure 2. Bar graphs compare group values for resting levels of MSNA and plasma catecholamines between the normotensive (NT) and the borderline hypertensive (BHT) subjects. Except for a tendency to lower values for burst incidence in the BHT group ($P = 0.05$), resting levels of burst frequency and plasma catecholamines were similar between both groups.

### Table 2. Correlation matrix showing pairwise associations of relevant variables for entire study group and separately for NT and BHT subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>MSNA Value</th>
<th>MSNA $P$</th>
<th>NE Value</th>
<th>NE $P$</th>
<th>BMI Value</th>
<th>BMI $P$</th>
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<td></td>
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<tr>
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<td></td>
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<td></td>
</tr>
<tr>
<td>BHT</td>
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<td>$&lt;0.05$</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>entire group</td>
<td>0.09</td>
<td>NS</td>
<td>0.34</td>
<td>$&lt;0.05$</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>NS</td>
<td>0.36</td>
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</tr>
<tr>
<td>BHT</td>
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<td>NS</td>
<td>0.30</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
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</tr>
<tr>
<td>entire group</td>
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<td>NS</td>
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<tr>
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<td>NS</td>
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<td>NS</td>
</tr>
<tr>
<td>BHT</td>
<td>$-0.27$</td>
<td>NS</td>
<td>0.01</td>
<td>NS</td>
<td>$-0.20$</td>
<td>NS</td>
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</table>

*MSNA, muscle sympathetic nerve activity (bursts/100 heart beats); NE, norepinephrine (pg/ml); BMI, body mass index (kg/m²); MAP, mean arterial pressure (mmHg).

This factor may be a crucial. Recent observations indicate that body mass index is correlated with MSNA (17) and that obesity is associated with increased MSNA (22,23). We did not study obesity-related hypertension. It may well be that hypertension in the obese involves increased sympathetic tone. In previous studies involving BHT, conceivable mechanisms related to obesity-associated hypertension were being examined. Our study is the largest to date involving homogeneous groups
of young lean BHT and NT men, carefully matched for body mass index. Thus, by eliminating age, gender, and body mass index as MSNA confounding variables, we found that neither sympathetic nerve activity nor plasma catecholamines were increased in the early phase of essential hypertension. Our data are therefore in accord with recent findings by Noll et al. (27), who demonstrated that under baseline conditions MSNA tended to be lower in offspring of hypertensive parents compared with offspring of normotensive parents. On the basis of their results and our data, it seems likely that the initial phase of essential hypertension does not involve an increase in basal MSNA. Nevertheless, resting MSNA may conceivably increase at a later time point, when BP is persistently but still mildly elevated (8,9–12), and subsequently may return to normal levels in the more advanced stages of established hypertension (28,29).

The fact that we did not find augmented hemodynamic and sympathetic nerve responses to the cold pressor test in our BHT subjects does not exclude the possibility that an increase in sympathetic nervous system activity in response to stress other than the one we applied could be causative for hypertension in some patients. In this regard, Noll et al. (27) suggested that hyper-reactivity to mental stress represents a rather specific abnormality in the early stages of hypertension. This notion is supported by observations that sympathetic hyper-reactivity in BHT occurred only in association with tasks that elicited active behavioral coping responses, in contrast to passive tolerance of aversive stimulation (30–32).

Together with the observation of an increased heart rate in the BHT subjects, our data are in accord with the hyperdynamic findings described for BHT, namely increased cardiac output and normal total peripheral resistance (24,25). Although cardiac sympathetic drive seems to be augmented in young patients with BHT, sympathetic vasoconstrictor activity reflected by our MSNA data is unaltered. These findings are in accord with Guyton's theory of total body autoregulation (33). In terms of BP and family history, our BHT subjects have substantial greater risk of developing essential hypertension than the NT subjects. We regard the BHT status as pre-essential hypertension (1,2). We would predict that in time, as BP values increase in the BHT subjects, their peripheral vascular resistance will increase and their heart rates will decrease accordingly (33). We have not examined pressure natriuresis; however, a large body of literature strongly suggests that our BHT subjects have already developed a rightward shift, compared with NT subjects (34).
Our data extend earlier findings that showed significant linear relationships between resting MSNA levels and plasma norepinephrine concentrations in normotensive subjects and in subjects with established hypertension (35,36). We showed that this relationship is also valid for subjects with BHT. Since we identified no correlation between MSNA levels and BP, and since plasma norepinephrine concentrations are largely determined by MSNA levels, resting venous norepinephrine levels probably offer only a limited insight into hypertensive mechanisms.

Because sympathetic nerve activity was measured with the subjects in the supine position, we cannot address the question of whether upright posture would have unmasked a heightened central sympathetic neural drive when the increased buffering influences of the cardiopulmonary baroreceptors were removed, as has been suggested by Mark (37). The concept of increased cardiopulmonary baroreflex control of sympathetic nerve activity (14) and forearm vascular resistance (38) in BHT has recently been demonstrated. Another limitation in our study is that the subjects were not controlled for salt intake. In view of the findings by Anderson et al. (6), our results of attenuated resting MSNA in the BHT subjects could theoretically be explained by differences in dietary salt intake. We have no reason to believe that BHT subjects ate more salt than NT subjects. They were exposed to the same food sources and had central venous pressure levels no different from NT subjects.

In conclusion, our data showed that resting MSNA levels and plasma norepinephrine concentrations were correlated in NT and BHT men. However, neither of these variables was correlated with BP. We were very careful to eliminate confounding factors such as age, body mass index, and gender. Under these conditions, BHT subjects did not appear to exhibit an increase in sympathetic vasoconstrictor activity during supine resting conditions. Similarly, no sympathetic hyperreactivity to the cold pressor stress occurred in BHT subjects. Taken together, these findings question the notion that during supine resting, MSNA is important in the early developmental stage of essential hypertension.

References
25. Messerli FH, Frohlich ED, Suarez H, Reisin E, Dreslinski GR,


