Relationship Between Muscle Sympathetic Nerve Activity and Diurnal Blood Pressure Profile

Krzysztof Narkiewicz, Mikolaj Winnicki, Kathleen Schroeder, Bradley G. Phillips, Masahiko Kato, Elzbieta Cwalina, Virend K. Somers

Abstract—The physiological mechanisms mediating the variability and diurnal rhythm of blood pressure are unclear. We tested the hypothesis that resting sympathetic activity is linked to the variability characteristics and 24-hour profile of ambulatory blood pressure measurements. We evaluated the relationship between muscle sympathetic nerve activity (MSNA) and the level, variability, and nocturnal fall of ambulatory blood pressure in 69 normal men. Subjects were subdivided according to the tertiles of MSNA distributions. Mean 24-hour blood pressure was not significantly different across the 3 groups. Compared with subjects in the first tertile (lowest MSNA, <18 bursts/min), subjects in the third tertile (highest MSNA, >25 bursts/min) had significantly greater daytime blood pressure variability, whether expressed as absolute values (10.2±0.5 versus 8.1±0.4 mm Hg for systolic blood pressure and 9.4±0.4 versus 7.2±0.4 mm Hg for diastolic blood pressure; P<0.01 for both comparisons) or as variation coefficients (8.1±0.4% versus 6.6±0.3% for systolic blood pressure and 12.7±0.7% versus 10.1±0.6% for diastolic blood pressure; P<0.01 for both comparisons). Subjects in the third tertile also had a more striking absolute and percentage fall in systolic blood pressure from daytime to nighttime than subjects in the first tertile (17±2 versus 10±2 mm Hg, P=0.02, or 13±1% versus 8.2±1.4%, P=0.02). In conclusion, higher resting measurements of sympathetic traffic are associated with greater daytime blood pressure variability and a more marked nocturnal decline in blood pressure in normal subjects. These findings suggest that sympathetic neural mechanisms may contribute importantly to the regulation of blood pressure over the 24-hour period. (Hypertension. 2002;39:168-172.)

Key Words: circulation • hypertension • atherosclerosis • risk factors

There is increasing evidence that overactivity of the sympathetic nervous system plays a role in the development of hypertension.1,2 Surprisingly, previous studies found no direct relationship between muscle sympathetic nerve activity (MSNA) and office blood pressure in normal subjects.3–5 Ambulatory monitoring provides a more accurate estimate of the true blood pressure than office (casual) measurements. This has been attributed both to the greater number of readings and to the fact that they are taken under more representative circumstances than the clinic setting.5,7

Ambulatory monitoring has demonstrated that the 24-hour blood pressure profile is characterized by considerable variability and a marked diurnal rhythm.6–8 A substantial component of blood pressure variability during ambulatory monitoring can be accounted for by changes in activity.7,9 However, the physiological mechanisms responsible for the variability and diurnal rhythm of blood pressure are unclear.

There is precedent for supposing that sympathetic mechanisms may be linked to both blood pressure variability and the diurnal change in blood pressure.2,10 The sympathetic system is the primary mechanism mediating rapid and short-term changes in blood pressure. Furthermore, the decrease in blood pressure from wake to sleep is associated with clear and substantial decreases in direct measurements of sympathetic nerve traffic.11

Indeed, prior studies are supportive of the concept that sympathetic neural mechanisms contribute to the characteristics of the 24-hour blood pressure profile. First, animal studies have shown that prazosin but not captopril or hydralazine eliminates the diurnal blood pressure profile in spontaneously hypertensive rats.12,13 Second, in studies of patients with progressive autonomic failure resulting from familial amyloid polyneuropathy, the progression of the impairment of autonomic nervous function correlates with a gradual blunting of the circadian blood pressure rhythm.14 Third, the nocturnal blood pressure dipping status is markedly affected by α-adrenergic blockade in hypertensive patients.15 Fourth, endurance training, which is known to reduce sympathetic activity,16 can lower daytime blood pressure but not sleep blood pressure.17 Finally, a study based on spectral analysis
of heart rate (HR) variability has shown that the diurnal blood pressure pattern is linked to autonomic nervous function in hypertensive patients.\(^{18}\)

The relationship between direct measures of sympathetic traffic and the ambulatory blood pressure profile has not been previously studied. We tested the hypothesis that baseline direct measures of intraneural sympathetic nerve activity taken at rest may be linked to the level, variability, and nocturnal fall of 24-hour blood pressure measurements.

### Methods

#### Subjects

We studied 69 normal white male subjects 31.0±9.2 (mean±SD) years of age. Body mass index, calculated as weight (in kilograms) divided by height (in meters) squared, was 25.7±3.8 kg/m\(^2\), and waist-to-hip ratio was 0.86±0.08. All subjects were normotensive (office blood pressure <140/90 mm Hg) and free of any diseases. None of the subjects was taking any medication. Written, informed consent was obtained from all subjects. The study was approved by the institutional Human Subjects Review Committee.

#### Measurements

Measurements of MSNA, blood pressure, and HR were obtained in the morning or early afternoon. Sympathetic nerve activity was recorded continuously by obtaining multiunit recordings of postganglionic sympathetic activity to muscle, measured from a nerve fascicle in the peroneal nerve with tungsten microelectrodes (shaft diameter, 200 μm, tapering to an uninsulated tip of 1 to 5 μm).\(^{19}\) A subcutaneous reference electrode was inserted 2 to 3 cm from the recording electrode. Sympathetic bursts were identified by inspection of the mean voltage neurogram. MSNA was recorded in subjects while awake and during 10 minutes of undisturbed supine rest and was expressed as bursts per minute. Mean blood pressure was measured every minute with a Physio-Control Lifestat 200 sphygmomanometer. HR was measured by ECG.

Twenty-four-hour ambulatory blood pressure and HR monitoring was performed with the Spacelabs 90202 recorder (Spacelabs Inc). The recorders were programmed to obtain measurements every 15 minutes from 6 AM to 10 PM and every 20 minutes from 10 PM to 6 AM. Subjects were asked to continue their regular activities during the recordings and to go to bed no later than 11 PM. The daytime period was defined as the interval from 8 AM to 10 PM; nighttime, from midnight to 6 AM.\(^{9}\) The nocturnal fall was defined as the difference between the average daytime and nighttime values. The nocturnal fall was also calculated as a percentage change. Standard deviation and coefficient of variation of daytime and nighttime values were calculated to assess blood pressure and HR variability.

#### Statistical Analysis

Results are expressed as mean±SEM. Subjects were subdivided according to tertiles of MSNA distributions. Comparisons between tertiles were made by analysis of variance (ANOVA) and analysis of covariance (ANCOVA), followed by pairwise comparison with the use of Scheffé’s test. A value of \(P<0.05\) was considered significant.

### Results

Table 1 presents demographic data, blood pressure, and HR of subjects subdivided into 3 groups according to the tertiles of MSNA (first tertile, <18 bursts/min; second tertile, 18 to 25 bursts/min; and third tertile, >25 bursts/min; 23 subjects in each tertile). Age, body mass index, waist-to-hip ratio, and supine office blood pressures were similar across the MSNA tertiles. Subjects with higher MSNA had faster HRs.

Subjects in the third tertile (high MSNA) had greater daytime systolic blood pressure (SBP) variability than subjects in the first tertile (low MSNA) (Figure 1). In contrast, nighttime SBP variability was similar in the 3 groups (Figure 1). Daytime diastolic blood pressure (DBP) variability was also significantly different across the MSNA tertiles (7.2±0.4, 8.6±0.4, and 9.4±0.4 mm Hg in the first, second, and third tertiles, respectively; \(F=7.10; P=0.002\)). There was no difference in nighttime DBP variability (data not shown).

### Figure 1

SBP variability during daytime (left) and nighttime (right) in subjects grouped according to tertiles of MSNA (tertile I, <18 bursts/min; tertile II, 18 to 25 bursts/min; and tertile III, >25 bursts/min). SBP variability was significantly different across the MSNA tertiles during daytime (\(F=6.74, P=0.002\) by ANOVA) but not during nighttime (\(F=0.49, P=0.60\)). Data are mean±SEM. Probability values were calculated by pairwise comparison with the use of Scheffé’s test.

| Table 1. Demographic Data, Blood Pressure, and HR in Subjects Grouped According to Tertiles of MSNA Muscle Sympathetic Nerve Activity |
|---------------------------------|---------------------------------|---------------------------------|
| Measurement                     | Tertile of MSNA | ANOVA |
| Age, y                          | (<18 bursts/min) | (18–25 bursts/min) | (>25 bursts/min) | F      | P      |
| BMI, kg/m\(^2\)                 | 24.9±0.4        | 26.2±1.1          | 26.0±0.8         | 0.73   | 0.48   |
| Waist-to-hip ratio              | 0.85±0.01       | 0.86±0.02         | 0.87±0.01        | 0.40   | 0.67   |
| Supine SBP, mm Hg              | 116.1±1.8       | 115.9±2.4         | 116.8±2.1        | 0.05   | 0.95   |
| Supine DBP, mm Hg              | 66.7±1.9        | 67.8±2.1          | 67.0±1.9         | 0.09   | 0.91   |
| Supine HR, bpm                 | 58.4±1.6        | 63.5±2.5          | 65.9±1.8*        | 3.57   | 0.03   |

*SEM. BMI indicates body mass index. Values are mean±SEM.

\(P<0.05\) vs tertile I by pairwise comparison with the use of Scheffé’s test.
TABLE 2. Ambulatory Blood Pressure and HR in Subjects Grouped According to Tertiles of MSNA

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Tertile of MSNA</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I (&lt;18 bursts/min)</td>
<td>II (18–25 bursts/min)</td>
</tr>
<tr>
<td>24-Hour SBP, mm Hg</td>
<td>120.2±1.1</td>
<td>124.5±2.0</td>
</tr>
<tr>
<td>Daytime SBP, mm Hg</td>
<td>122.6±1.2</td>
<td>128.1±2.1</td>
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<tr>
<td>Nighttime SBP, mm Hg</td>
<td>112.4±1.7</td>
<td>112.0±1.6</td>
</tr>
<tr>
<td>24-Hour DBP, mm Hg</td>
<td>69.8±1.2</td>
<td>74.0±1.4</td>
</tr>
<tr>
<td>Daytime DBP, mm Hg</td>
<td>72.3±1.4</td>
<td>77.1±1.3</td>
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<tr>
<td>Nighttime DBP, mm Hg</td>
<td>61.4±1.3</td>
<td>62.7±1.6</td>
</tr>
<tr>
<td>24-Hour HR, bpm</td>
<td>67.1±1.6</td>
<td>71.4±2.5</td>
</tr>
<tr>
<td>Daytime HR, bpm</td>
<td>69.5±1.6</td>
<td>74.5±2.8</td>
</tr>
<tr>
<td>Nighttime HR, bpm</td>
<td>59.8±2.2</td>
<td>60.7±2.0</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

Compared with subjects in the first tertile, subjects in the third tertile had greater daytime blood pressure variability even when variability was expressed as a variation coefficient (8.1±0.4% versus 6.6±0.3% for SBP and 12.7±0.7% versus 10.1±0.6% for DBP; P<0.01 for both comparisons). The differences in daytime blood pressure variability remained significant even after adjustment for daytime HR (8.1% versus 6.7% for SBP, P=0.02; 12.7% versus 10.2% for DBP, P=0.01).

Table 2 shows ambulatory blood pressure and HR. Mean 24-hour blood pressure and HR were similar across the 3 groups (Table 2). However, the nocturnal SBP fall was significantly different across the MSNA tertiles (Figure 2). Subjects in the third tertile (highest MSNA, >25 bursts/min) had greater day-night SBP differences than subjects in the first tertile. Similar results were obtained when the nocturnal SBP fall was expressed as a percent change from daytime values. The SBP fall in the third MSNA tertile (13.1±1.1%) was greater (P=0.02) than that in the first MSNA tertile (8.2±1.4%). The day-night SBP difference was closely correlated with the day-night fall in HR (r=0.64, P<0.001). However, even after adjustment for the HR change, subjects in the third tertile of MSNA had a more marked SBP fall (13.0% versus 8.3% in the first tertile; P=0.04). Thus, the interaction between MSNA and day-night SBP difference was independent of the change in HR.

The trend in day-night DBP differences across the MSNA tertiles (10.9±1.5, 14.4±1.4, and 14.7±1.2 mm Hg in the first, second, and third tertiles) did not achieve statistical significance (F=2.55, P=0.09).

Discussion

In this study, we sought to determine the relationship between resting measures of sympathetic neural activity and the diurnal blood pressure profile in normal humans. The main findings are (1) that there is a significant positive interaction between sympathetic traffic and daytime blood pressure variability and (2) that the day-night blood pressure difference is linked to MSNA recorded during wakefulness.

Previous studies of normotensive subjects found no direct relationship between MSNA and office blood pressure.3–5 In the present study, we were also not able to demonstrate an independent link between MSNA and office blood pressure. However, MSNA interacted significantly with the variability characteristics and diurnal blood pressure profile recorded in the ambulatory setting. Higher MSNA was associated with greater daytime blood pressure variability and a steeper decline in blood pressure from day to night.

Prior studies have shown that increased blood pressure variability is associated with an increased likelihood of target organ damage, independent of the absolute blood pressure level.20–23 Furthermore, in a longitudinal study,24 greater blood pressure variability was associated with a faster progression of end organ damage. Thus, excessive blood pressure variability may constitute an independent risk factor for cardiovascular disease. The mechanisms underlying blood pressure variability are not completely understood. An important study by Parati et al25 speaks directly to our findings. These investigators demonstrated that administration of atropine reduced HR variability but did not affect the variability of blood pressure. Thus, blood pressure variability cannot be attributed only to variations in HR and cardiac output,6,25 suggesting that sympathetic traffic to blood vessels may be

Figure 2. Nighttime fall in SBP in subjects grouped according to tertiles of MSNA (tertile I, <18 bursts/min; tertile II, 18 to 25 bursts/min; and tertile III, >25 bursts/min). SBP fall was significantly different across the MSNA tertiles (F=4.05, P=0.02 by ANOVA). Data are mean±SEM. Probability values were calculated by pairwise comparison with the use of Schefé’s test.
the primary determinant of short-term variations in blood pressure.

Our results show that increased sympathetic drive may indeed be implicated in increased daytime blood pressure variability. We were not able to demonstrate any link between MSNA and blood pressure variability at night, when exogenous influences on blood pressure are eliminated. These data are consistent with the results of Kario et al., who have shown that sympathetic predominance in HR variability is associated with greater blood pressure variability during daytime but not during nighttime. Our findings, together with those by Kario and colleagues, support the concept that sympathetic mechanisms may play a role in mediating the pressor effects of the environmental and behavioral factors operating during wakefulness.

Our data also provide some insight into the day-to-night change in blood pressure. There has been great interest in the mechanisms and clinical significance of the dipper or non-dipper pattern of ambulatory blood pressure profiles. It has been suggested that both nondipping and extreme dipping are associated with more pronounced target organ damage. Previous studies in both animals and humans indicated that the autonomic nervous system may contribute to the diurnal blood pressure rhythm. Animal studies have shown that prazosin but not metoprolol, captopril, or hydralazine eliminated the diurnal blood pressure change. These results suggested that the circadian blood pressure rhythm, at least in animal models, is influenced by sympathetic traffic to the blood vessels but not to the heart.

We found no differences in 24-hour and nighttime blood pressures across the tertiles of MSNA. The greater nocturnal blood pressure fall in the high-MSNA third tertile was explained almost exclusively by higher ambulatory daytime blood pressure in these subjects and not by lower nighttime blood pressure. These findings are consistent with data from previous studies in hypertensives treated with α-receptor blockade and in patients with autonomic dysfunction. In a study by Kario et al., doxazosin lowered daytime blood pressure more than nighttime blood pressure in hypertensive patients and consequently attenuated the nocturnal blood pressure fall. A recent study by Carvalho et al. assessed the relationship between the degree of autonomic dysfunction and circadian blood pressure patterns in patients with progressive autonomic failure caused by familial amyloid polyneuropathy. With the progression of the impairment of the autonomic nervous function, a gradual blunting of the circadian blood pressure variation was observed. Interestingly, nighttime blood pressure did not change. The progressive decline of the day-night difference was solely a result of the lower daytime blood pressure.

The mechanisms responsible for greater day-night blood pressure differences in subjects in the third tertile (those with the highest MSNA) are not clear. Exaggerated blood pressure responses to standing in subjects with high sympathetic traffic might be implicated. Previous studies by Kario et al. and Vriz et al. have suggested that the hemodynamic response to standing is one of the most important determinants of daytime blood pressure. Hyperresponsiveness to standing has been shown to be associated with enhanced sympathetic tone, as indicated by increased levels of 24-hour urinary norepinephrine. A further possibility is that the more marked effects of α-blockade on daytime compared with nighttime blood pressure may be mediated by its action on standing blood pressure.

Classification of dipping status is based on daytime blood pressure. Sleep blood pressure is less likely to be affected by environmental factors. During most of sleep, sympathetic tone is low and blood pressure is at a “floor” level. A persuasive case has been made for taking the sleep blood pressure as the baseline level for analysis of the circadian rhythm. According to this approach, subjects with higher daytime blood pressure might be classified as “peakers.” Our results indicate that such subjects are characterized by higher MSNA during supine resting wakefulness.

A potential limitation is that our study was limited to normal men. In women and in hypertensive subjects, the relationship between sympathetic traffic and diurnal blood pressure profile may be different. Second, because polysomnographic measures were not able to be obtained in the ambulatory setting, we cannot draw conclusions about any sleep-wake changes. Our conclusions are therefore confined to day-night differences in blood pressure. Third, sympathetic drive was assessed by a single measurement of MSNA in the late morning or early afternoon. However, measurements of MSNA show good reproducibility. In particular, Middlekauff et al. have shown no variation in sympathetic nerve traffic during the daytime, demonstrating that MSNA in the morning is very similar to that in early afternoon.

In conclusion, higher sympathetic traffic is associated with increased daytime blood pressure variability and greater day-night blood pressure differences. Our study does not speak directly to any causal nature of the associations we describe. However, these findings suggest that sympathetic neural mechanisms may contribute importantly to daytime blood pressure variability and the diurnal blood pressure profile.

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References


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