Interactive Effect of Heart Rate and Muscle Sympathetic Nerve Activity on Blood Pressure

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Background—Sympathetic traffic to the peripheral vasculature and sympathetic discharge to the heart have complementary effects on blood pressure. Although faster heart rates have been linked to higher blood pressures, the relationship between muscle sympathetic nerve activity (MSNA) and long-term regulation of blood pressure is not clear. We tested the hypothesis that MSNA and heart rate are linked to blood pressure levels in normotensive subjects.

Methods and Results—We studied normal young male (n=120) and female (n=48) subjects subdivided according to tertiles of heart rate and MSNA distributions. Systolic, diastolic, and pulse pressures were significantly different across the heart rate tertiles in male subjects, with the highest blood pressure values in the upper tertile of heart rate. No significant differences in blood pressure across the tertiles of MSNA were found. The relationship between MSNA and blood pressure, however, was affected by heart rate. MSNA did not influence blood pressure in the first and second heart rate tertiles. However, within the upper heart rate tertile, subjects with higher levels of MSNA had significantly higher systolic (P=0.02) and pulse (P=0.004) pressures than subjects with lower levels of MSNA. In female subjects, blood pressure was not different across the tertiles of heart rate or MSNA.

Conclusions—MSNA and heart rate have interactive effects on systolic blood pressure and pulse pressure in normotensive male but not female subjects. No relationship between MSNA and blood pressure or pulse pressure is evident in subjects with slower heart rate. In male subjects with faster heart rates, higher levels of MSNA are associated with higher systolic and pulse pressures. (Circulation. 1999;100:2514-2518.)

Key Words: nervous system, autonomic ■ nervous system, sympathetic ■ heart rate ■ blood pressure

The sympathetic nervous system is an integral mechanism for the overall regulation of blood pressure and can increase peripheral vascular resistance, cardiac output, and sodium reabsorption to raise blood pressure.1–4 Arteriolar vasoconstriction as well as sympathetic–mediated venuconstriction (with consequent central redistribution of blood and increased cardiac output) both act to increase blood pressure. Cardiac sympathetic chronotropic and inotropic effects also increase blood pressure, particularly in the setting of increased vascular resistance. Thus, sympathetic traffic to the peripheral vasculature and sympathetic discharge to the heart have complementary effects on blood pressure.

The relationship between direct intraneural measurements of muscle sympathetic nerve activity (MSNA) and blood pressure is controversial. In patients with hypertension, MSNA has been reported to be higher than5–7 or similar to8–10 measurements in normotensive control subjects. Studies in normal subjects have reported that MSNA is linked to heart rate (HR)11 but is unrelated to blood pressure.12,13 The link between HR and blood pressure is more compelling. Faster resting HRs are associated with higher blood pressures in normotensive male but not female subjects.14–16 Normotensive subjects with faster HRs17,18 and male subjects with sympathetic predominance in HR variability19 are more prone to develop hypertension. Early hypertension is characterized by increased cardiac sympathetic activity.20

Sympathetic traffic to the muscle circulation contributes importantly to short-term changes in blood pressure.21 It is therefore surprising that no clear relationship between MSNA and resting blood pressure is apparent. HR may be implicated in the link between MSNA and blood pressure. Any interactive influence of HR and MSNA on blood pressure has not been previously studied. We therefore evaluated the relationship between MSNA, HR, and blood pressure in homogenous groups of normal young male and female subjects and tested the hypothesis that HR and MSNA are linked to blood pressure levels in normotensive subjects.

Methods

Subjects
We studied 168 normal white subjects of normal weight (120 men and 48 women). Normal weight was defined as body mass index (BMI) ≤25 kg/m². The mean BMIs of male and female subjects were 23.3±1.2 and 22.0±2.0 kg/m² (mean±SD), respectively. The mean ages for male and female subjects were 25.6±6.5 and 27.9±8.0 years. All subjects were normotensive (blood pressure always <140/90 mm Hg) and free of any diseases. The subjects were taking
no medications, except for 7 women using oral contraceptives. Current cigarette smoking was reported by 16% of the subjects. Participants did not have any history of excessive alcohol use. Eighty-five percent of the subjects undertook regular leisure-time exercise. None of the subjects participated in professional sports. All participants were studied on their normal diets without salt restriction. Subjects were recruited from the University of Iowa and the Iowa City community. Written informed consent was obtained from all subjects. The study was approved by the Institutional Human Subjects Review Committee.

**Measurements**

Measurements were obtained in the morning or early afternoon ≥3 hours after the last meal. Subjects abstained from any cigarettes and from beverages containing caffeine and alcohol for ≥12 hours before the study. MSNA was recorded continuously by multunit 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). A subcutaneous reference electrode was inserted 2 to 3 cm away from the recording electrode. Sympathetic bursts were identified by inspection of the mean voltage neurogram. Sympathetic activity was recorded while the subject was awake during 10 minutes of undisturbed supine rest and expressed as bursts per minute. Mean blood pressure was measured every minute with a Physio-Control Lifesat 200 sphygmomanometer. HR was measured by an ECG. Reproducibility of the measurements was assessed in 22 male subjects who were studied twice. The 2 studies were performed 30±5 days (mean±SEM) apart.

**Statistical Analysis**

Results are expressed as mean±SEM. Comparisons between male and female subjects were made by use of an unpaired t test. Male and female subjects were subdivided according to the tertiles of HR and MSNA distributions. Comparisons between groups were made by 1- and 2-way ANOVA, followed by Bonferroni’s test for multiple comparisons. Reproducibility of HR, MSNA, and blood pressure was assessed by use of the Bland-Altman approach. Changes between sequential measurements were calculated by subtracting the first from the second recording, taking into account the sign of the difference. Consistency was obtained by calculating the difference between the first and second measurements, disregarding the sign of the difference. Repeatability was defined as twice the SD of the difference. Reproducibility was defined as twice the SD of the between the first and second measurements, disregarding the sign of the difference. Consistency was obtained by calculating the difference between the first and second recordings, disregarding the sign of the difference. A value of P<0.05 was considered significant.

**Results**

**Male Subjects**

Mean systolic blood pressure (SBP) for all 120 male subjects was 118±1 mm Hg; mean diastolic blood pressure (DBP) was 65±1 mm Hg; and mean pulse pressure was 54±1 mm Hg. Pulse pressure was positively correlated with HR (r=0.69, P<0.001) and negatively correlated with DBP (r=−0.32, P<0.001). HR averaged 62±1 bpm, and MSNA averaged 21±1 bursts/min.

Figure 1 presents the SBP, DBP, and pulse pressure of male subjects subdivided into 3 groups according to the tertiles of HR (left) and MSNA (right). ANOVA revealed that SBP, DBP, and pulse pressure were significantly different across the HR tertiles (F=13.38, P<0.001; F=5.84, P=0.004; and F=4.78, P=0.01, respectively). SBP and pulse pressure in the highest HR tertile (range, 66.1 to 84.7 bpm) were greater than in the first (range, 41.0 to 57.3 bpm) or second (range, 57.7 to 66.0 bpm) HR tertile (Figure 1). DBP in the highest HR tertile was higher than in the first tertile (Figure 1). MSNA was similar across the tertiles of HR and averaged 20±1 bpm in the first, 22±1 bpm in the second, and 22±2 bpm in the third HR tertile (P=0.53 by ANOVA).

MSNA ranged from 2.0 to 16.6 bursts/min in the first MSNA tertile, from 16.7 to 24.0 bursts/min in the second tertile, and from 24.3 to 44.3 bursts/min in the third MSNA tertile. ANOVA did not reveal any significant differences in blood pressure across the tertiles of MSNA (P=0.29 for SBP, P=0.76 for DBP, and P=0.20 for pulse pressure) (Figure 1).

To evaluate whether MSNA and HR may have any interactive effect on blood pressure and pulse pressure, within each tertile of HR, subjects were subdivided into 2 equal groups: those with MSNA below the median (low MSNA) and those with MSNA above the median (high MSNA) for the given tertile (Figure 2). Two-way ANOVA revealed that HR and MSNA had an interactive effect on SBP (F=5.15, P=0.007 for the HR and MSNA interaction) and pulse pressure (F=6.89, P=0.001 for the HR and MSNA interaction) (Figure 2). This HR-MSNA interaction was evident even when MSNA was expressed as bursts/100 heartbeats. MSNA did not relate to SBP or pulse pressure in the first and second HR tertiles (Figure 2). However, within the third HR tertile, ie, in those 40 subjects with the fastest HRs, subjects with higher levels of MSNA had significantly higher SBPs (P=0.02) and greater pulse pressure (P=0.004) than subjects with lower levels of MSNA (Figure 2). MSNA and HR had no significant interactive effect on DBP (data not shown).

For all 120 male subjects, MSNA did not correlate significantly with HR (r=0.16, P=0.085), SBP (r=0.16, P=0.08) or pulse pressure (r=0.16, P=0.08). However, within the upper tertile of HR, MSNA was correlated with HR (r=0.37, P=0.02), SBP (r=0.39, P=0.01) and pulse pressure (r=0.42, P=0.007).
To evaluate further the interaction of MSNA and HR, we performed additional analyses across the quartiles of HR. ANOVA revealed that SBP and pulse pressure were significantly different across the HR quartiles (F = 11.12, P < 0.001; F = 3.79, P = 0.01; respectively). Two-way ANOVA revealed that HR and MSNA had an interactive effect on SBP (F = 3.95, P = 0.01 for the HR-MSNA interaction) and pulse pressure (F = 2.89, P = 0.03 for the HR-MSNA interaction).

Within the fourth HR quartile, subjects with higher levels of MSNA had on average SBPs that were 12 mm Hg higher (P = 0.008) and pulse pressures that were 10 mm Hg (P = 0.04) greater than those of subjects with lower levels of MSNA. The corresponding differences within the third HR quartile were only 3 mm Hg for SBP and 6 mm Hg for pulse pressure (P = NS).

Female Subjects
For all 48 women, mean SBP was 110 ± 2 mm Hg, mean DBP was 65 ± 1 mm Hg, and mean pulse pressure was 45 ± 1 mm Hg. HR averaged 62 ± 1 bpm, and MSNA averaged 18 ± 1 bursts/min.

SBP, DBP, and pulse pressure of female subjects were not different across the tertiles of HR or MSNA (Figure 3). One-way ANOVA revealed no significant differences in SBP, DBP, and pulse pressure across HR or MSNA tertiles. Values are mean ± SEM.

Comparison Between Men and Women
Male subjects had slightly higher MSNA burst frequency (P = 0.02) and had higher SBPs and pulse pressures compared with female subjects (both P < 0.001; Table 1). HR and DBP were similar in both groups (Table 1).

Reproducibility of HR, MSNA, and Blood Pressure
Changes in and correlation coefficients, consistency, and repeatability of HR, MSNA, and blood pressure in 22 male subjects are reported in Table 2. Measurements were very similar on the first and second recordings.

Discussion
In this study, we sought to determine the relationship between HR, MSNA, and blood pressure in normotensive humans. Our novel finding is that MSNA and HR in normotensive male subjects have an interactive effect on SBP and pulse pressure. In men with faster HRs, higher levels of MSNA are associated with higher SBP and greater pulse pressure. No relationship between MSNA and blood pressure is evident in male subjects with slower HRs or in female subjects overall.

Our data are consistent with the positive relationship between resting HR and blood pressure observed in epidemiological studies.
et al. have recently observed that although pulse pressure cardiovascular mortality may also be sex dependent. Benetos speculation that the absence of an HR–blood pressure interaction in women may be explained in part by the lower MSNA influence blood pressure at higher HRs, it is tempting to intriguing. In view of our observation that MSNA may between HR and blood pressure in men but not women is stronger for SBP and pulse pressures than for DBP, and (3) the HR–blood pressure interaction is present in male but not female subjects.

Previous studies in smaller samples of normotensive subjects found no relationship between MSNA and blood pressure. In our larger sample, we still were not able to demonstrate an independent link between MSNA and blood pressure across all subjects. The relationship between MSNA and blood pressure, however, was affected by HR. Higher MSNA was associated with higher SBP and greater pulse pressure only in male subjects with faster HRs. Thus, the combination of faster HR and increased MSNA identifies subjects with highest SBP and greatest pulse pressure. It may be that some individuals are able to “buffer” the blood pressure effect of sympathetic activation to the heart by decreasing sympathetic drive to another region. Hence, an individual with a fast HR may maintain normotension by inhibiting sympathetic vasoconstriction. Alternatively, effects of higher sympathetic vasoconstrictor traffic (perhaps genetically determined) on blood pressure may be blunted by slowing of HR through an increase in vagal tone.

Previous studies of HR–blood pressure interactions have reported that faster HRs are linked to higher blood pressure in male but not female subjects. This selective interaction between HR and blood pressure in men but not women is intriguing. In view of our observation that MSNA may influence blood pressure at higher HRs, it is tempting to speculate that the absence of an HR–blood pressure interaction in women may be explained in part by the lower MSNA in female subjects. Interactions between pulse pressure and cardiovascular mortality may also be sex dependent. Benetos et al. have recently observed that although pulse pressure independently predicts cardiovascular mortality in normotensive and hypertensive men, no such association was observed in either normotensive or hypertensive women.

Higher sympathetic drive, as reflected by both faster HRs and increased sympathetic burst frequency, was associated with higher SBP and greater pulse pressure in our male cohort. Our findings in resting subjects support those observed during short-term sympathetic activation. Sympathetic activation during the cold-pressor test or mental stress decreases radial arterial compliance and increases SBP and pulse pressure. The sympathetic nervous system may also contribute to blood pressure levels in the long term by mechanisms other than its effect on vasomotor tone, such as by its effects on the kidney. Wallin et al. have demonstrated that in healthy human subjects, resting sympathetic nerve traffic is proportional in sympathetic nerves to both muscle blood vessels and the kidney.

Tachycardia is linked to increased risk of cardiovascular morbidity and mortality. Subjects with faster HRs are more prone to develop hypertension. We show here that in normotensive male subjects with faster HRs, SBPs and pulse pressures are higher in those subjects with increased MSNA. Both SBP and pulse pressure are important predictors of cardiovascular risk. The probability of individuals with blood pressure in the high-normal range developing hypertension is 2- to 3-fold higher than for those with normal blood pressure. Sympathetic predominance in HR variability and SBP are strong risk factors for future hypertension. Thus, we speculate that increased MSNA may contribute to the development of hypertension in normotensive subjects with faster HRs.

An important strength of this study is the narrow age and BMI ranges of the participants, all of whom were white. Age, BMI, sex, and race may influence measures of MSNA, HR, and blood pressure. Thus, the homogeneity of our study population minimizes any potential confounding influence of these variables on the interactive relationship we describe. However, we cannot absolutely exclude possible influences of such factors as cigarette smoking, physical activity level, and alcohol use on our data. Salt intake, not monitored in our study, may also have direct effects on measurements of sympathetic neural traffic.

Another potential limitation is that we cannot rule out the possibility that our findings may be secondary to a reaction to the measurements being made. Those patients with faster HRs and higher MSNA levels and blood pressures may represent a subgroup of “reactors.” In mitigation, if this were so, MSNA, HR, and blood pressure would be expected to decline with extended duration of a single study or with repeated studies. Neither serial measurements during the same study nor repeated measures on ≥3 separate occasions have shown any progressive reduction in MSNA or hemodynamic measurements. In addition, repeated measures in a subgroup of our population show excellent reproducibility of measurements. A further limitation is the absence of additional measures of sympathetic tone, such as plasma norepinephrine levels. However, the reproducibility and sensitivity of plasma norepinephrine measurements are relatively poor compared with MSNA.

| TABLE 2. Reproducibility of HR, MSNA, and Blood Pressure Measurements in 22 Male Subjects |
|-----------------------------------------------|-----|-----|----------------|----------------|
|                                | Change | P  | r    | Consistency | Repeatability |
| HR, bpm                       | 0.6   | NS  | 0.64*| 5.6        | 13.4          |
| MSNA, bursts/min              | 1.3   | NS  | 0.55*| 5.2        | 13.2          |
| SBP, mm Hg                    | 1.3   | NS  | 0.80†| 5.3        | 12.6          |
| DBP, mm Hg                    | −0.9  | NS  | 0.70†| 5.5        | 13.0          |
| Pulse pressure, mm Hg         | 0.1   | NS  | 0.54*| 5.1        | 13.0          |

*P<0.01; †P<0.001.
In conclusion, MSNA and HR have an interactive effect on SBP and pulse pressure in normotensive male but not female subjects. No relationship between MSNA and blood pressure is evident in male subjects with slower HRs. In male subjects with faster HRs, higher levels of MSNA are associated with higher SBP and pulse pressure. This novel approach, incorporating the interaction between MSNA and HR, may also help clarify the relationship between MSNA and blood pressure in patients with hypertension.

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References
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