Gender-Selective Interaction Between Aging, Blood Pressure, and Sympathetic Nerve Activity


Abstract—The mechanisms mediating the more striking age-related increase in cardiovascular disease in women than in men are poorly understood. We tested the hypothesis that aging has a greater impact on sympathetic traffic in women than in men. Muscle sympathetic nerve activity (MSNA), blood pressure, and heart rate were measured in 120 healthy males and 96 healthy females aged 20 to 72 years. MSNA increased with age in both sexes, but age explained 53% of MSNA variance in female subjects and only 8% of MSNA variance in male subjects. Both the slope and intercept of the regression lines were significantly different between male and female groups (P<0.01 and P<0.001, respectively). For each decade of life, women showed an increase of 6.5 bursts/min in comparison to an increase of 2.6 bursts/min in males. Menopause did not explain the age-related increase in sympathetic traffic. For every 10-burst/min increment in MSNA in subjects older than 40, mean blood pressure increased by 2.7 mm Hg in men and by 6.1 mm Hg in women. Aging is accompanied by a greater increase in sympathetic traffic in women than in men, independent of menopausal status. Sympathetic neural mechanisms may contribute importantly to the more marked influence of age on blood pressure and cardiovascular disease in women. (Hypertension. 2005;45:522-525.)

Key Words: age ■ cardiovascular diseases ■ gender ■ heart rate ■ hypertension ■ sympathetic nervous system

Although cardiovascular risk increases with age in both sexes, this increase is sharper in women. More women than men have congestive heart failure and, overall, more women than men die from cardiovascular disease in the US. This gap continues to widen. The mechanisms underlying this differential age effect are not well understood. Changes in serum total cholesterol level, body mass index, and diabetes prevalence explain only 50% of the age-related increase in cardiovascular morbidity and mortality among women. Thus, other factors are implicated in the high prevalence of cardiovascular disease in older women.

The sympathetic nervous system contributes importantly to cardiovascular disease manifestations. It is generally accepted that sympathetic activity increases progressively with aging. However, little is known of the effects of gender on age-related changes in sympathetic traffic, and the existing evidence is conflicting.

We measured sympathetic traffic, blood pressure, and heart rate in a large sample of normal white subjects. We tested the hypothesis that aging has a greater impact on sympathetic traffic in women than in men. Furthermore, we evaluated the relative influence of age versus menopause per se on sympathetic activity, and we examined whether there is any gender differential in the interaction between sympathetic traffic and blood pressure.

Methods

Subjects
We studied 216 normal white subjects (120 males and 96 females). Mean age was 39.1 years (range, 20 to 72 years) for males, and 40.1 years (range, 20 to 71 years) for females. Body mass index was similar in the 2 groups and averaged 25.8 kg/m² (range, 19 to 39 kg/m²) in males, and 25.0 kg/m² (range, 19 to 40 kg/m²) in females. In all obese (body mass index >30 kg/m²) subjects (n=31), occult obstructive sleep apnea was ruled out by overnight polysomnographic study. All subjects were normotensive (blood pressure <140/90 mm Hg) and free of any diseases, and none was using any medication, including hormone replacement therapy. Menopausal status was assessed by menstrual history. All women younger than 40 years were premenopausal and all women older than 56 years were postmenopausal. Sixteen of 35 women aged 40 to 56 years were postmenopausal.

Subjects were recruited from the Iowa City (n=124) and Gdansk (n=92) communities. The US and Polish subjects were comparable for age (39±1 versus 41±2 years, respectively) and body mass index (25.4±0.4 versus 25.4±0.4 kg/m², respectively). The study was approved by the Institutional Human Subjects Review Committees.

Measurements
Intraneural measurements of muscle sympathetic nerve activity (MSNA) from a nerve fascicle in the peroneal nerve, blood pressure, and heart rate were obtained in the morning or early afternoon. MSNA was recorded while awake, during 10 minutes of undisturbed supine rest, and expressed as bursts per minute.
pathetic bursts were identified by inspection of the mean voltage neurogram according to previously published criteria by an investigator blinded to the subjects’ group assignment. Only bursts with a minimal signal-to-noise ratio of 3:1 were counted. Mean blood pressure was measured every minute with a Physio-Control Lifestat 200 sphygmomanometer. Heart rate was measured by electrocardiography. The same system of data acquisition (PowerLab from ADInstruments Pty Ltd) was used in Iowa City and Gdansk.

**Statistical Analysis**

Results are means ± SEM. Statistical analysis included an unpaired *t*-test, analysis of variance, and analysis of covariance. Relationships between demographic, autonomic, and hemodynamic measurements were assessed by single and multiple linear regressions. In both genders, the estimated slopes of regression lines were calculated for age in predicting MSNA and for MSNA in predicting mean arterial pressure. The interaction between age and gender was assessed by 2-way analysis of variance with age category (decade of life) and gender as grouping factors. The key variable was the age-by-gender interaction. *P* < 0.05 was considered significant.

**Results**

**Mean Arterial Pressure, Heart Rate and MSNA Were Similar in Males and Females**

MSNA correlated weakly with body mass index in females (*r* = 0.25; *P* < 0.01) but was unrelated to body mass index in males (*r* = 0.12). MSNA was not related to waist-to-hip ratio for either gender (*r* = 0.21 for males and *r* = 0.17 for females), but correlated with age in both male and female subjects. The correlation between age and MSNA was much stronger in females (*r* = 0.73; *P* < 0.0001) than in males (*r* = 0.31; *P* = 0.003). Age explained 53% of MSNA variance in female subjects and only 8% of MSNA variance in male subjects. For each decade of life, women showed on average a 6.5-burst/min increase in comparison to an increase of 2.6 bursts/min in males. Analysis of covariance revealed that both the slope and intercept of the regression lines were significantly different between males and females (*P* < 0.01 and *P* < 0.001, respectively). Similar results were obtained when MSNA was expressed in bursts/100 heart beats (Table).

In younger subjects, MSNA was lower in females than males (Figure 1). The age-related increase in MSNA was strikingly greater in female subjects (Figure 1). There was a significant interaction of gender with age (*P* = 0.02), indicating that the effect of age on MSNA is gender-dependent.

In both males and females, multivariate analysis including age, body mass index, and waist-to-hip ratio as independent variables revealed that only age was independently correlated with MSNA. In women aged 40 to 56 years, MSNA was similar in postmenopausal (31 ± 3 bursts/min; *n* = 16) and premenopausal women (29 ± 2 bursts/min; *n* = 19; *P* = 0.31).

In young (<40 years) male and female subjects, MSNA was not related to blood pressure (Figure 2). By contrast, MSNA correlated significantly with MAP in older male and female subjects (Figure 2). MAP correlated significantly with MSNA only in men (*r* = 0.37; *P* = 0.01) and women (*r* = 0.57; *P* < 0.0001) older than 40 years, but not in younger men (*r* = 0.01; NS) or younger women (*r* = 0.02; NS). For every 10-burst/min increase in MSNA in subjects older than 40, mean arterial pressure increased by 2.7 mm Hg in men and by 6.1 mm Hg in women.

MSNA was similar in the US and Polish female (25 ± 2 versus 27 ± 2 bursts/min; NS) and male subjects (27 ± 2 versus 26 ± 2 bursts/min; NS). The correlation between age and MSNA was stronger in females than in males in the US (*r* = 0.73; *P* < 0.0001 versus *r* = 0.39; *P* < 0.001) and Polish subjects (*r* = 0.72; *P* < 0.001 versus *r* = 0.25; *P* < 0.05).

**Discussion**

The main findings in this study are that aging has a more striking effect on increasing sympathetic traffic in white women than in men. This marked increase is independent of
body mass index and waist-to-hip ratio. Second, menopause per se does not explain the age-related increase in sympathetic traffic. Third, there is a significant positive interaction between sympathetic traffic and blood pressure only in people older than 40 years of age—this interaction is far more striking in women than in men.

The rate of increase in MSNA per decade was 2.5-fold higher in women than in men. The contribution of age to MSNA variance in women was 6-fold greater than that in men. Our findings are in contrast to previous studies in white subjects. Ng et al\textsuperscript{10} studied 17 younger and 15 older subjects. For both younger and older subjects, MSNA was significantly lower in women compared with men of the same age. The results of this previous study might have been confounded by the small sample size and inclusion of older women using hormone replacement therapy.\textsuperscript{10}

Our results are, however, consistent with findings of Matsukawa et al\textsuperscript{9} in Japanese subjects. In this study, MSNA was lower in women than in men among subjects younger than 50 years, and similar for both genders in subjects older than 50 years of age.\textsuperscript{9} Thus, enhanced age-related sympathetic activation in women is not race-specific. In contrast, we found no evidence of any effect of menopause on sympathetic traffic.\textsuperscript{9} An increase in MSNA in men and women after age 40 in both our studies argues further against menopause as a primary cause of age-related increases in MSNA. The age-related menopause-independent increase in sympathetic traffic in women may conceivably be relevant to the absence of any cardiovascular benefit from hormone replacement therapy in postmenopausal women.\textsuperscript{13}

Our findings of a more striking age-related increase in sympathetic activation in women parallels epidemiological data indicating a higher prevalence of hypertension in women by age 60.\textsuperscript{2,3,14} The significant correlation between MSNA and blood pressure, evident especially in older female subjects, provides further support for a possible role of sympathetic activation in the close link between aging and hypertension, particularly in women. Sympathetic activation might also predispose to cardiovascular events by other mechanisms, including metabolic, hemodynamic, trophic, and rheological abnormalities.\textsuperscript{5,6}

The mechanisms underlying the differential relationships between muscle sympathetic nerve activity and blood pressure in younger and older subjects are unknown. The higher sympathetic activity and its more marked influences on blood pressure in older subjects suggests that age-related decreases in compliance may be implicated. These data provide further support for the concepts proposed by Julius et al, namely that hypertension evolves from a high-output state in early hypertension to a condition of vasoconstriction in the later stages.\textsuperscript{5} This evolution of hypertension pathophysiology may reflect, in part, the effects of increasing age.
The strengths of this study include that all participants were healthy and using no medications, including hormone replacement therapy and oral contraceptives. Second, there is a high prevalence of sleep apnea in asymptomatic, apparently normal obese subjects.\textsuperscript{15,16} Subjects with sleep apnea have very high levels of sympathetic traffic.\textsuperscript{16} Therefore, an important and novel strength of our data is that we ruled out sleep related disorders.

Potential limitations of our study include that some young, healthy subjects may become hypertensive. Prospective studies may provide further insights into the link between aging, sympathetic drive, and hypertension. Second, we cannot exclude the possibility that estrogen levels influenced our findings in younger subjects. Our cross-sectional study does not speak directly to causality of associations we describe, nor do we have any information regarding interactions between MSNA and the follicular or luteal phases of the menstrual cycle\textsuperscript{17} in the premenstrual subjects in our study. Our cross-sectional study does not speak directly to causality of associations we describe, nor do we have any information regarding interactions between MSNA and the follicular or luteal phases of the menstrual cycle\textsuperscript{17} in the premenstrual subjects in our study. However, our findings are consistent with experimental studies showing that estrogens may modulate sympathetic nervous system tone.\textsuperscript{18,19} Third, subjects were recruited from 2 different white populations. In mitigation, the US and Polish subjects were comparable for age and body mass index. We used the same method of data acquisition in both centers. Furthermore, the correlation between age and MSNA may thus contribute importantly to the more marked influence of age on blood pressure and cardiovascular disease in women.

**Perspectives**

Aging is accompanied by a greater increase in sympathetic traffic in women than in men. This increase is independent of body mass index, waist-to-hip ratio, and menopausal status. The age-related increase in sympathetic drive is associated with increased blood pressures only in older subjects, and especially in older women. Sympathetic neural mechanisms may thus contribute importantly to the more marked influence of age on blood pressure and cardiovascular disease in women.

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