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Influence of Sex and Age on Muscle Sympathetic Nerve Activity of Healthy Normotensive Adults

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Abstract —As with blood pressure, age-related changes in muscle sympathetic nerve activity (MSNA) may differ nonlinearly between sexes. Data acquired from 398 male (age: 39±17; range: 18–78 years [mean±SD]) and 260 female (age: 37±18; range: 18–81 years) normotensive healthy nonmedicated volunteers were analyzed using linear regression models with resting MSNA burst frequency as the outcome and the predictors sex, age, MSNA, blood pressure, and body mass index modelled with natural cubic splines. Age and body mass index contributed 41% and 11%, respectively, of MSNA variance in females and 23% and 1% in males. Overall, changes in MSNA with age were sigmoidal. At age 20, mean MSNA of males and females were similar, then diverged significantly, reaching in women a nadir at age 30. After 30, MSNA increased nonlinearly in both sexes. Both MSNA discharge and blood pressure were lower in females until age 50 (17±9 versus 25±10 bursts·min^{-1}; $P<1\times10^{-19}$; 106±11/66±8 versus 116±7/68±9 mm Hg; $P<0.01$) but converged thereafter (38±11 versus 35±12 bursts·min^{-1}; $P=0.17$; 119±15/71±13 versus 120±13/72±9 mm Hg; $P>0.56$). Compared with age 30, MSNA burst frequency at age 70 was 57% higher in males but 3-fold greater in females; corresponding increases in systolic blood pressure were 1 (95% CI, −4 to 5) and 12 (95% CI, 6–16) mm Hg. Except for concordance in females beyond age 40, there was no systematic change with age in any resting MSNA-blood pressure relationship. In normotensive adults, MSNA increases after age 30, with ascendance steeper in women. **(*Hypertension*. 2020;76:997-1005. DOI: 10.1161/HYPERTENSIONAHA.120.15208.)** ● **Data Supplement**

Key Words: blood pressure ■ body mass index ■ healthy aging ■ norepinephrine ■ sympathetic nervous system

Resting blood pressure increases with age,[1] with a nonlinear time course from the onset of adulthood that differs between women and men.[2] By stimulating sympathetic neurotransmitter release to the heart, kidneys, resistance and capacitance vessels, the noradrenergic nervous system participates in short- and long-term regulation of cardiac output and total peripheral resistance.[3] In healthy normotensive individuals, both sympathetic discharge directed at skeletal muscle vasculature[4–9] and plasma norepinephrine concentrations[10] increase with age. However, whether males and females differ with respect to such age-related changes and the extent to which progressive augmentation of sympathetic outflow drive parallels the rise in blood pressure with healthy aging are relatively unknown.

To date, only 2 studies have examined sex- and age-specific changes in muscle sympathetic nerve activity (MSNA).[8,9] Both reported steeper age-related rises in MSNA in women than in men but differed in their interpretation of the impact of menopause. Matsukawa et al[8] concluded, from sub-analysis of 22 of their Japanese women, that menopause increased MSNA discharge frequency, whereas in a larger cohort of American and Polish women, the onset of menopause had no evident effect.[9] In both sexes, there was a positive relationship between MSNA and mean arterial pressure, but only above the age of 40.[9] Neither group reported relationships between MSNA and either systolic or diastolic blood pressure.[8,9]

These studies were relatively modest in size (145 and 216 participants, respectively),[8,9] included few older adults, applied only linear analyses, and grouped age categorically by decade. Classifying a 39 year old, for example, as someone who is identical to 30 but different from an individual aged 40 can misrepresent associations between covariates (eg, age and sex), as well as outcome measures (eg, MSNA), and risks attenuation of statistical power and inflation of type I error rates.[11] To acquire more confident characterization of norms for MSNA, relative to sex and age, we assembled a data set of 658 healthy volunteers (398 males, 18–78 years; 260 females, 18–81 years), in whom resting MSNA, blood pressure, and heart rate had been measured. We then employed analyses allowing for nonlinear relationships with continuous covariates to (1) characterize sex-specific relationships between resting MSNA

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and age; (2) investigate potential relationships between age-related changes in MSNA and blood pressure; (3) determine whether men and women differ with respect to such characteristics; and (4) acquire sex- and age-based normative values for MSNA. We hypothesized that (1) MSNA increases nonlinearly with age; (2) the MSNA-age relationship differs between the sexes; and (3) age-related changes in MSNA relate similarly to changes in blood pressure in females and males.

Methods

The authors declare that all supporting data are available within the article.

Participants

We assembled resting hemodynamic and MSNA data from healthy adult volunteers enrolled in research studies undertaken at 4 Canadian institutions: University Health Network (n=309), University of Western Ontario (n=169), University of Guelph (n=148), and Dalhousie University (n=32; Table S1 in the Data Supplement). All protocols received institutional Research Ethics Board approval; all participants provided written informed consent. At the time of screening, all participants were healthy (absent any acute or chronic medical condition) nonobese nonsmokers with systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg. With the exception of oral contraceptives, none was taking medication known to influence blood pressure or cardiovascular autonomic function.

Protocol

All sympathetic nerve recordings and concurrent blood pressure and heart rate data were acquired in climate-controlled laboratories after abstention for 12 hours or more from caffeine, alcohol, and vigorous exercise. After a high-quality nerve recording was secured, participants rested quietly supine or semi-recumbent for a minimum of 5 minutes. Once MSNA, blood pressure, and heart rate stabilized, data were recorded during quiet rest for at least 5 minutes.

Measurements

Similarly trained, experienced investigators, working in comparably equipped laboratories, acquired multi-unit efferent postganglionic MSNA signals from the common fibular nerve using a 2 or 10 mΩ tungsten microelectrode, as previously described.[12–15] Neural signals were amplified (30 000–100 000×), band-pass filtered (700–2000 Hz), rectified and integrated (time constant 0.1 s) to obtain a mean voltage neurogram of MSNA (Nerve Traffic Analyzer, University of Iowa, Iowa City, IA). Systolic and diastolic blood pressure were measured concurrently, either on a minute-by-minute basis manually or by automated sphygmomanometry and upper arm cuff (Dinamap Pro 100; Critikon, Tampa, FL or model BPM-200, BpTRU, Coquitlam, BC) or continuously, using photoplethysmography (Finometer and Portapres; Finapres Medical Systems, Amsterdam, the Netherlands). Heart rate was derived from lead II of the ECG. Data were digitized and stored using LabView (National Instruments, Austin) or PowerLab (AD Instruments Pty Ltd, NSW, Australia) software platforms.

From the integrated mean voltage neurogram, bursts of pulse-synchronous MSNA were identified and confirmed according to standard published criteria common to all 4 participating laboratories.[16,17] Resting blood pressure and heart rate values were computed as the mean of the sampling period. Nerve firing was quantified as MSNA burst frequency (bursts·min^{-1}), the principal correlate of neural norepinephrine release rate.[18] To adjust for between-participant differences in heart rate, MSNA burst incidence (bursts·100 heartbeats^{-1}) also was calculated.

Statistical Analysis

Group mean (eg, female-male) comparisons were made using unpaired *t* tests. Age related trends in mean MSNA burst frequency, MSNA burst incidence, systolic and diastolic blood pressure, pulse pressure, and heart rate were estimated using natural cubic splines with knots at the upper limit of the first (24 years) and second (46 years) tertiles[11] to allow for nonlinearity in the age-MSNA relationship. These trends, with 95% CIs, were estimated and plotted for the whole sample and for males and females separately. Sex-specific inference was based on models that accounted for potential confounding of the age-MSNA relationship by blood pressure[6,8,9] and body mass index (BMI)[4,8,19] by including these variables as covariates (also using natural cubic splines). The relative importance of all variables was quantified by their contribution to the total model R^2.[20,21]

To assess sex differences with respect to relationships between each MSNA parameter and age, a single regression model was fitted to the entire data set, with separate spline functions fitted to the MSNA-age relationships in men and women. These models allow between-sex differences in MSNA to vary continuously with age and also allow estimation of those differences at specific ages. From the model, the sex-specific difference in mean MSNA between ages 30

Table 1. Participant Characteristics

Variable	All	Women	Men	*P* Value
n	658	260	398	
Age, y	38±17	37±18	39±17	0.14
Height, cm	172±9	164±8	177±6*	<0.001
Mass, kg	74±15	66±14	80±12*	<0.001
BMI, kg·m^{-2}	25±4	24±5	25±3*	0.007
Heart rate, beats·min^{-1}	62±10	64±10	61±10*	<0.001
Systolic blood pressure, mm Hg	114±13	110±14	117±12*	<0.001
Diastolic blood pressure, mm Hg	69±9	67±10	69±9*	0.02
Mean blood pressure, mm Hg	84±10	82±10	85±9*	<0.001
Pulse pressure, mm Hg	45±11	42±11	48±10*	<0.001
MSNA burst frequency, bursts·min^{-1}	26±13	23±13	28±12*	<0.001
MSNA burst incidence, bursts·100 heartbeats^{-1}	43±20	37±21	46±19*	<0.001

Group mean data are displayed as mean±SD. BMI indicates body mass index; and MSNA, muscle sympathetic nerve activity.
*Different from women (*P*<0.05).

(nadir) and 70 (zenith) was estimated, and this difference was compared between males and females.

The dependence of blood pressure on MSNA burst frequency was hypothesized to vary by age in a way that differed by sex. This hypothesis was tested by fitting a linear model with blood pressure as the outcome and MSNA burst frequency, age, and sex and all their interactions as predictors. Sex difference in age-related changes in the blood pressure-MSNA slopes are represented by the 3-way interaction term. The power for identifying such interaction terms is low, so conditioning plots were used as a visual aid to assess the presence of the hypothesized pattern.

Quantile regression[22] was used to estimate the median, fifth, 20th, 80th, and 95th percentiles for MSNA burst frequency and incidence separately for males and females as a function of age. Briefly, quantiles were parameterized as functions of age by both a 1- or 2-term fractional polynomial model with power selected from a ladder of values (−2, −1, −0.5, 0, 0.5, 1, 2, 3).[23] An iterative fitting approach was then applied to the MSNA and age data to determine the fractional coefficients and the combination of values for the 2 powers from the ladder that provided the best goodness of fit (ie, lowest χ^2).

Results

Data were derived from 658 protocol participants, 398 male (mean age±SD: 39±17 years; range: 18 to 78 years) and 260 female (mean age: 37±18 years; range: 18 to 81 years; Table 1). In the pooled cohort, MSNA burst frequency and burst incidence doubled between the ages of 20 and 80 years; the relationship between MSNA and age was sigmoid, rather than linear (Figure 1A and 1B). Average systolic and diastolic blood pressures were highest in the middle age range (40–65 years; Figure 1C and 1D) whereas mean heart rate and pulse pressure remained relatively constant across these 6 decades (Figure 1E and 1F).

In females, age accounted for 41.1% of the variance in MSNA burst frequency and 41.6% of the variance in burst incidence. Corresponding values for males were 22.6% and 30.2% (P<0.001 for between-sex differences). Measured by relative importance, in females, BMI was a significant predictor of burst frequency (R^2=11.4%, P=0.01). This was not the case for males (R^2=1.3%, P=0.78). However, adding BMI to age did not improve the prediction of burst incidence of either women (R^2=8.8%, P=0.30) or men (R^2=1.0%, P=0.33).

Importantly, MSNA burst frequency and incidence did not increase linearly with age in either sex (Figure 2A and 2B). At age 20, the mean MSNA burst frequency of males and females was similar, then diverged significantly, falling in women to a nadir at age 30. After age 30, MSNA increased, nonlinearly, in both sexes. The difference in mean MSNA from nadir (≈30

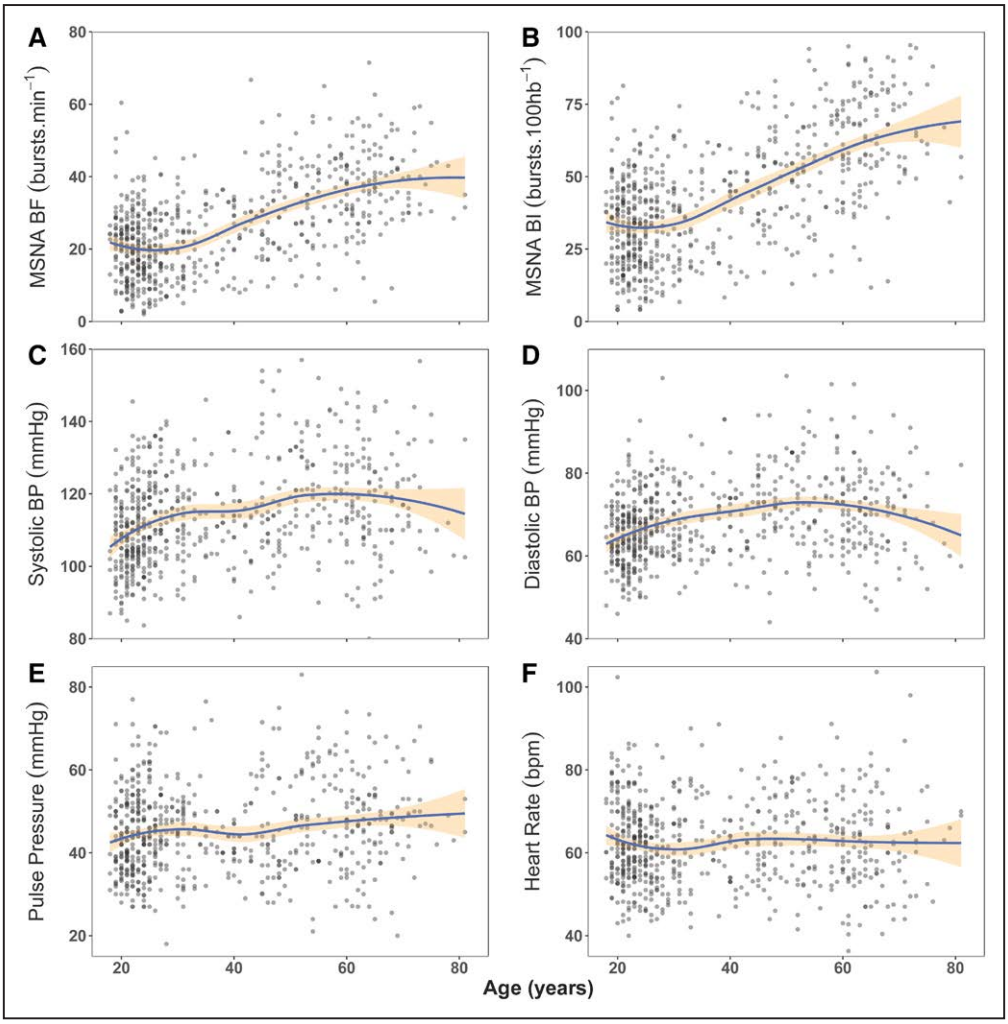

Figure 1. Natural spline models of the age relationships for muscle sympathetic nerve activity (MSNA), blood pressure, and heart rate. The shaded area represents the 95% confidence limits of the best fit linear regression model. Note that both men and women are included together. BF indicates burst frequency; BI, burst incidence; and BP, blood pressure.

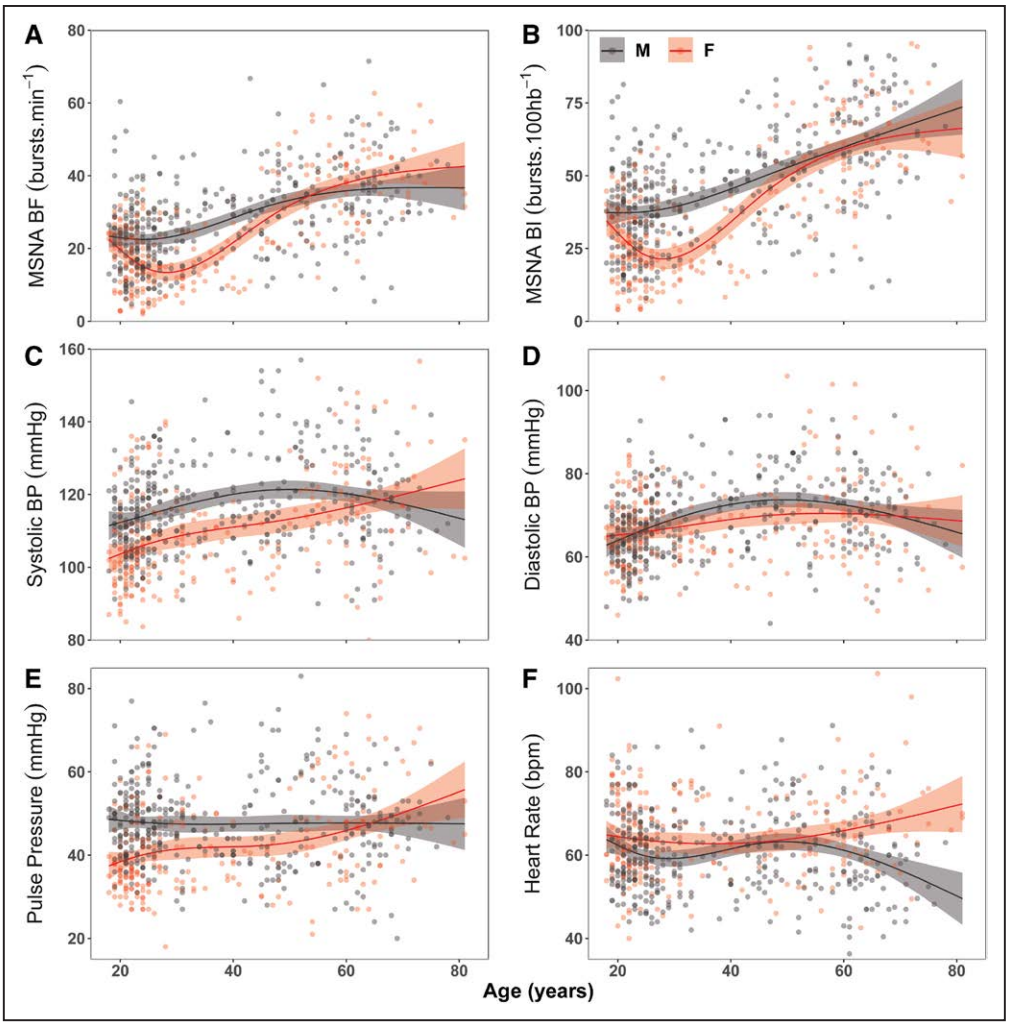

Figure 2. Natural spline models of the age relationships for muscle sympathetic nerve activity (MSNA), blood pressure, and heart rate for men (black) and women (red). The shaded area represents the 95% confidence limits of the best fit linear regression model. BF indicates burst frequency; BI, burst incidence; and BP, blood pressure.

years) to zenith (≈70 years) was much greater for females (+27 bursts·min^{-1}; +42 bursts·100 heartbeats^{-1}) than for males (+13 bursts·min^{-1}; +32 bursts·100 heartbeats^{-1}; P<0.0001, P=0.003, respectively). Figure 3 presents for both men and women the best-fit models for these cross-sectional data, with estimated fifth, 20th, 50th, 80th, and 95th percentiles of the MSNA burst frequency or burst incidence at each age.

As evident from Figure 2, mean MSNA of women and men converged by age 50. Participant characteristics were, therefore, evaluated separately for females and males <50 (younger) and ≥50 years of age (older). These comparisons are presented in Table 2. Mean MSNA burst frequency (17±9 versus 25±10 bursts·min^{-1}; P<0.0001) and blood pressure (106±11/66±8 versus 116±11/68±9 mm Hg; P<0.001/P=0.008) were significantly lower in the younger females than in younger males, but equivalent in the older women and men (38±11 versus 35±12 bursts·min^{-1}; P=0.11; 119±15/71±13 versus 121±13/72±9 mm Hg; P=0.50/P=0.56).

Overall, in either sex, MSNA burst frequency (and burst incidence) related only weakly to systolic blood pressure, with R^2 values ranging from 1.5% to 4.4% and all P>0.15. In both men and women, systolic blood pressure rose by ≈10 mm Hg between the ages of 20 and 50 years (Figure 2D). From 50 to ≈80 years, systolic blood pressure increased on average by an additional 12 mm Hg in females but fell, by 5 mm Hg, in this cohort of males (Figure 2D). By contrast, there were no sex differences with respect to diastolic blood pressure-age relationships (Figure 2C). Heart rate was similar between males and females up to ≈50 years. Thereafter, heart rate rose in women and fell in men, by 10 beats per minute (Figure 2E).

Compared with age 30, MSNA burst frequency at age 70 was 57% higher in males but 3-fold greater in females; corresponding increases in systolic blood pressure were 1 (95% CI, –4 to 5) and 12 (95% CI, 6–16) mm Hg. This apparent sex difference with respect to age-related changes in the MSNA (input) versus blood pressure (output) relationship was represented as a 3-way interaction (between age, sex, and burst frequency) in regression models with blood pressure as the outcome. For both systolic (P=0.10) and diastolic blood pressure (P=0.15), there was some evidence for this interaction. These findings are represented graphically in the conditioning plots[24] of Figure 4, where the relationship of MSNA burst frequency to systolic blood pressure is shown in 8 subsets of the data formed by sex and rolling age groups. In males, the MSNA

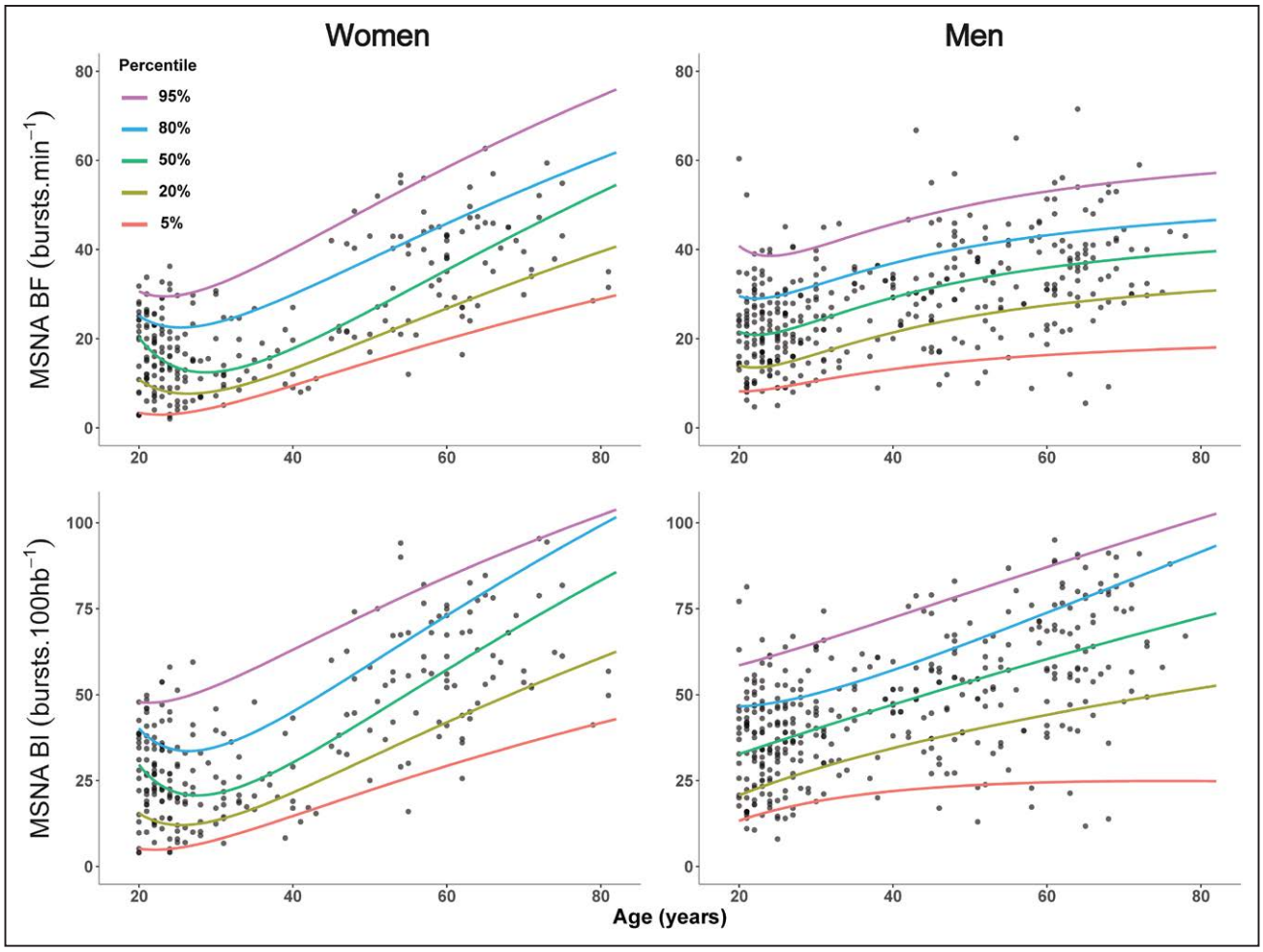

Figure 3. Muscle sympathetic nerve activity (MSNA) burst frequency and incidence percentiles for men and women from age 18 to 80 y. BF indicates burst frequency; and BI, burst incidence.

burst frequency-blood pressure slopes were weakly positive or flat and varied only slightly across age groups, whereas in females, slopes became more positive as age increased and were strongly positive with respect to systolic blood pressure beyond age 40, and diastolic blood pressure beyond age 30.

Discussion

The present cross-sectional study of a cohort of healthy normotensive males and females, 3-fold larger than any previously reported, adds to the existing literature by demonstrating first, that population changes in MSNA burst frequency with advancing age are sigmoidal rather than linear (Figure 1), and second, that the time course, direction and magnitude of age-related changes in MSNA differ between the sexes.

The influence of sex on MSNA burst frequency and incidence was age dependent. At age 20, MSNA was similar in males and females, but decreased thereafter in women, reaching a nadir at age 30. In both sexes, MSNA began to increase at age 30. From 30 years of age onward, MSNA increased 3-fold in females but only by ≈50% in males. Consequently, MSNA remained significantly lower in women than men until age 50; thereafter the trajectories of women and men converged. Such changes were not a simple consequence of higher heart rate, which did not increase with age overall and which was, after age 60, significantly lower in men than in women (Figure 2). For both sexes, rate-independent MSNA burst incidence also displayed nonlinear ascension, with similar between-sex discordance within the fourth decade (Figure 2).

These nonobese females and males differed with respect to the relative influence of age and BMI on sympathetic vasoconstrictor discharge. In women, age accounted for 41% and BMI for 11% of the variance in MSNA, whereas in men the respective proportions were 23% and 1%, respectively. Why age plays a greater role in determining MSNA in females than in males is unclear. The initial upward inflection in burst frequency was evident in both sexes at age 30. Since the average onset of natural menopause is ≈51 years,[25] such timing excludes diminished endogenous estrogen concentrations as the principal responsible mechanism. Narkiewicz et al,[9] who specifically documented menopausal history, also concluded that the age-related increase in MSNA is independent of menopausal status. However, a central sympatho-inhibitory effect of estrogen, as observed experimentally, could account both for the marked differences, within the third and fourth decades, between MSNA of men and women, and attenuation of such action for the steeper upward course of female burst

Table 2. Participant Characteristics Below and Above Age 50

Variable	<50 y		≥50 y	
	Women	Men	Women	Men
n	184	282	76	116
Age, y	26±7	29±9	62±8*	61±7*
Height, cm	165±8	178±6†	163±7	175±7
Mass, kg	62±11	79±11†	75±16*	82±13*†
BMI, kg·m^2	23±4	25±3†	28±6*	27±4*
Heart rate, beats·min^{-1}	64±10	61±9	66±11	60±11†
Systolic blood pressure, mm Hg	106±11	116±11†	119±15*	121±13*
Diastolic blood pressure, mm Hg	66±8	68±9	71±13*	72±9*
Mean blood pressure, mm Hg	79±8	84±9†	87±13*	88±9*
Pulse pressure, mm Hg	40±9	48±9†	48±12*	48±11
MSNA burst frequency, bursts·min^{-1}	17±9	25±10†	38±11*	35±12*
MSNA burst incidence, bursts·100 heartbeats^{-1}	27±14	41±15†	59±17*	60±19*

Group mean data are displayed as mean±SD. BMI indicates body mass index; and MSNA, muscle sympathetic nerve activity.
*Different from <50 y (P<0.05).
†Different from women (P<0.05).

frequency after age 30.[26] An additional potential mechanism for these differing MSNA distributions by sex is age-related weight gain. Importantly, study participants, on average, were not overweight (Table 1) but when comparing individuals aged ≥50 years to those aged <50 years, mean BMI was 2 kg·m^2 higher in males, but 6 kg·m^2 greater in females (Table 2).

Age-related impairment of cardiovascular autonomic modulation, whether originating at mechano-receptor afferent sites, centrally, or within sympathetic efferents, will alter tonic and reflex regulation of MSNA. For example, structural or functional attenuation of conduit artery distensibility at carotid and aortic sites housing baroreceptor nerve endings, elevating their discharge threshold, will disinhibit reflexively sympathetic outflow. A study of 88 participants (42 women) ranging in age from 19 to 73 years documented an inverse relationship between carotid compliance and MSNA before, but not after, age-adjustment.[27] Centrally, age-related pathologies, such as inflammation, increased oxidative stress and diminished bioavailable nitric oxide, induce upward resetting of central sympathetic outflow by altering cortical or brain stem autonomic function.[28–30] Our recent discovery of a significant relationship between nocturnal micro-arousals from sleep (an age-related phenomenon[31]) and MSNA during wakefulness[32] adds further insight into why resting sympathetic discharge can vary so greatly amongst individuals of similar age, sex, blood pressure and BMI, and hence why the confidence limits surrounding normative data are so broad (Figure 3).

The Framingham investigators attributed age-related increases in blood pressure in their community to a progressive rise in peripheral resistance.[1] With fibular sympathetic nerve discharge correlating directly with calf vascular resistance,[33,34] a modest relationship between age-related changes in MSNA and blood pressure, as reported previously,[8,9] could be anticipated. However, overall, MSNA related only weakly to systolic blood pressure. In men, there was no systematic change with age in the relationship between resting burst frequency and concurrently measured blood pressure. In contrast, women had a positive slope after age 40 for systolic blood pressure and after age 30 for diastolic blood pressure. This female-specific age-effect is concordant with previous findings by other investigators. For example, positive correlations between resting MSNA and total peripheral resistance have been documented in young men and in postmenopausal women, but not in young women, in whom a relationship was revealed only when β_2-mediated vasodilation was blocked by propranolol[35]; after ganglionic blockade, blood pressure has been observed to fall less in young women than in older males and females.[7,36] In premenopausal women, sympathetic activation coincident with the surge in endogenous estradiol during the mid-luteal phase of the menstrual cycle is not accompanied by parallel increases in mean arterial pressure, a finding consistent with the concept that, despite sex differences in receptor sensitivity and arterial calibre, in young women augmentation of endothelium-mediated vasodilatation by endogenous estrogen can counter any increase in tonic neurogenic vasoconstrictor input.[37]

Vianna et al[38] observed that the rise in mean arterial pressure induced by a single sympathetic burst was attenuated in older men (+1.7 mm Hg), relative to young men (+2.6 mm Hg) and women (+2.6 mm Hg), and lowest in older women (+1.2 mm Hg). In the present cohort, MSNA burst frequency at age 70 compared with age 30 was 57% higher in males but 3-fold greater in females; corresponding increases in systolic blood pressure were 1 (95% CI, −4 to 5) and 12 (95% CI, 6–16) mm Hg. Those observations and Figures 1, 2, and 4 suggest that with aging, transduction of MSNA into blood pressure, although attenuated, may be functionally more consequential in females than in males, whether due to relatively greater increases in burst frequency and hence neural norepinephrine release or augmented arterial or venous constriction in response to the similar noradrenergic input[39] resulting from

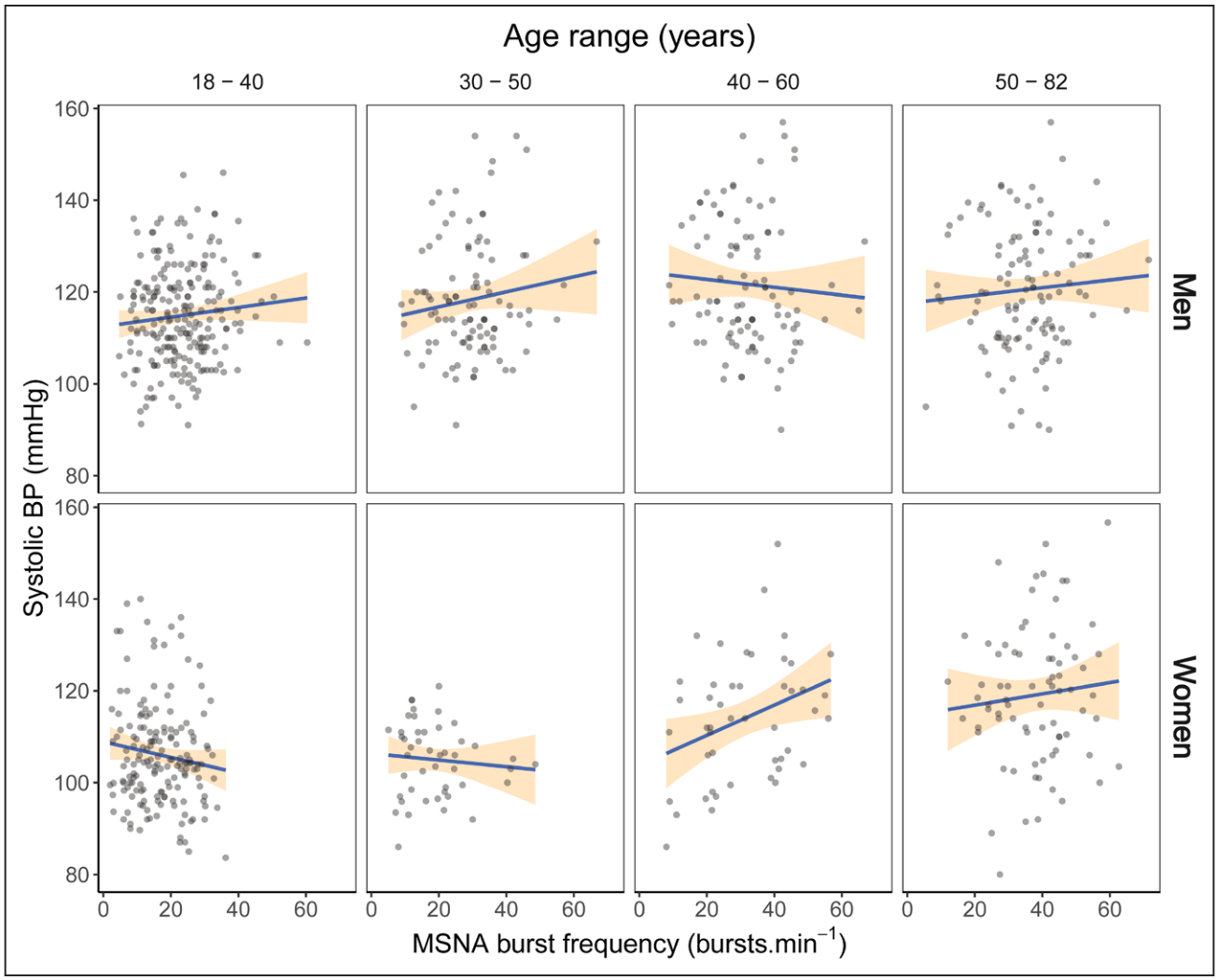

Figure 4. Systolic blood pressure vs muscle sympathetic nerve activity (MSNA) burst frequency relationships by sex and age grouped as a rolling average. BP indicates blood pressure.

heightened α_1-adrenoceptor responsiveness,[40] or smaller calibre vessels.[2,41] After trimethaphan, older and young men were shown to exhibit similar reductions in systemic vascular resistance,[36] whereas total peripheral resistance fell twice as far in older, postmenopausal than in young women.[7]

Microneurography has been an insightful method to characterize the presence or contribution of heightened central sympathetic drive to skeletal muscle vasculature across a range of conditions and disease states. However, distribution of that which is considered normal across the lifespan (ie, the range of MSNA values from the fifth to 95th percentiles) in this cross-sectional survey cautions that if too few participants are recruited, such investigations may be underpowered to detect true differences. Between-subject standard deviations for any particular age are ≈0.3× the difference between the upper and lower percentile and can be used as input to power calculations for future comparative studies (see Table 3 and Table S2).

The principal strengths of the present investigation are the female and male cohort sizes and age distributions, the absence of hypertension and of known confounding co-morbidities and medications that might alter MSNA or its impact on blood pressure or heart rate, and agnosticism concerning data linearity. In particular, the cohort studied was one of normotensive nonsmokers, free from obesity, diabetes mellitus, dyslipidemia, chronic vascular inflammatory diseases or other conditions that might compromise vascular health or influence neurovascular transduction. Derived from a healthy normotensive cohort, these data should not be construed as representative of the general adult population, and in particular, the average older man or women, as the elderly are proportionately less likely to be nonmedicated and untouched by chronic disease. The principal limitations are incomplete data concerning subjects' background (primarily white), physical conditioning, oral contraceptive use, parity, menopausal status, and sleep architecture. For example, obstructive sleep apnea increases muscle sympathetic burst frequency during wakefulness.[42] The prevalence of obstructive sleep apnea increases with age and BMI and is more common in men than in women across the lifespan.[43] Not all participants in this database were screened for this with formal polysomnography, but, if a significant bias toward increased daytime resting MSNA as a central neural after-effect of longstanding obstructive sleep apnea pertained in these participants, a greater BMI-attributable

Table 3. Approximate SDs of Sex- and Age-Specific MSNA Burst Frequency and Incidence

	Women		Men	
Age, y	MSNA BF, bursts·min^{-1}	MSNA BI, bursts·100 hb^{-1}	MSNA BF, bursts·min^{-1}	MSNA BI, bursts·100 hb^{-1}
20	8	13	10	14
30	8	14	9	14
40	9	15	10	15
50	11	16	11	17
60	12	17	11	19
70	13	18	12	21
80	14	18	12	23

Data are calculated from quantile analyses. BF indicates burst frequency; BI, burst incidence; hb, heartbeats; and MSNA, muscle sympathetic nerve activity.

variance in MSNA would have been anticipated for males than for females. The present analysis is exclusively cross-sectional. Of interest, longitudinal data acquired from a female volunteer on 6 occasions (from age 39 to 63, with only the first included in the present analysis) over 24 years (Figure S1) are concordant: MSNA rose but blood pressure remained relatively constant over the quarter century. Finally, fibular nerve data may not be representative of age-related changes in sympathetic discharge directed at other hemodynamically important vascular beds.

Perspectives

The present cross-sectional data, derived from healthy nonobese normotensive adults, demonstrate qualitative as well as quantitative age-associated differences between males and females with respect to the magnitude of sympathetic vasoconstrictor discharge. Compared with age 20, at age 30 years, MSNA is lower in women, but not in men. MSNA, thereafter, increases nonlinearly in both sexes, after age 30, with a slope that is steeper in females than in males. Women enrolled in community-dwelling longitudinal cohort studies exhibit an earlier (from the third decade onward) and steeper nonlinear rise in systolic, diastolic, mean, and pulse pressure than men.[2] In the present analysis, the MSNA burst frequency-blood pressure slopes of males were weakly positive or flat and varied only slightly across age groups, whereas in females, slopes became more positive as age increased and were strongly positive with respect to systolic blood pressure beyond age 40, and diastolic blood pressure beyond age 30, paralleling this epidemiological observation.[2] However, despite the 27 bursts·min^{-1}, or 3-fold, increase in mean MSNA burst frequency in women from nadir (≈30 years) to zenith (≈70 years) and the +13 bursts·min^{-1} or 57% mean increase in men across the same span, concurrently measured systolic blood pressure was not elevated, indicating that through one or more mechanisms, healthy older men and women are shielded from this increased vasoconstrictor burden, and as a consequence, do not develop uniformly neurogenic hypertension.[3,28,29] Since important population health benefits could accrue, elucidating such defences should be an important focus for future research. Finally, by establishing age- and sex-related 95% confidence limits, the MSNA percentile curves derived from this large data set may help inform the design and sample size of comparisons of burst frequency or incidence in disease states, referenced to healthy controls.

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Disclosures

None.

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Novelty and Significance

What Is New?

- These normative cross-sectional data from healthy adults demonstrate nonlinear, sex-specific increases in muscle sympathetic nerve activity (MSNA) after age 30, greater in women than men.
- Positive relationships between MSNA and systolic blood pressure are evident only in women >40.

What Is Relevant?

- Sex-specific nonlinear age-related changes in MSNA parallel those of systolic blood pressure.
- Despite having 3-fold higher sympathetic vasoconstrictor discharge than those aged 30, women at 70 remained normotensive.

Summary

In healthy nonobese normotensive adults, changes in MSNA with age are nonlinear and differ by sex. Unlike men, after age 20 women's MSNA falls to a nadir at 30. Thereafter, MSNA ascension is steeper in females. Age-specific correlations between MSNA and systolic blood pressure are absent in men but evident in women >40.