Influences of Gender on the Interaction between Sympathetic Nerve Traffic and Central Adiposity

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Context: Sympathetic activation promotes insulin resistance and arterial hypertension with increasing adiposity. A difference in the relationship between adiposity and sympathetic activity between women and men could contribute to the known gender difference in cardiovascular disease risk.

Objective: We tested whether muscle sympathetic nerve activity (MSNA) is correlated differently with waist circumference, waist to hip ratio (WHR), and body mass index (BMI) in women and men.

Design and Setting: We pooled data from two microneurography centers (Berlin, Germany; Gdansk, Poland) for a cross-sectional study.

Participants: We studied 111 normotensive, healthy Caucasian subjects (70 males and 41 females). Age ranged between 19 and 62 yr and BMI ranged between 18 and 40 kg/m².

Intervention: No intervention was applied during the study.

Measurements: Supine heart rate, blood pressure, and MSNA were recorded after at least 30 min rest.

Results: MSNA in bursts per minute was age dependent in both sexes \( r \) (male) \( = 0.56, r \) (female) \( = 0.34, P < 0.01 \). Controlling for waist and hip circumferences, age dependence remained highly significant in men \( r = 0.43 \) and women \( r = 0.43 \). Adjusting for age, in men, waist circumference \( r = 0.29 \), WHR \( r = 0.39 \), and BMI \( r = 0.31 \) were predictive for MSNA and directly correlated \( P < 0.01 \) but not in women. Adjusting for BMI, in men, only WHR \( r = 0.40 \) remained predictive for MSNA.

Conclusion: These data support the hypothesis of a gender difference in the regulation of the sympathetic nervous system, in which MSNA mainly relates to WHR in men but not women. The phenomenon may contribute to the sexual dimorphism in cardiovascular disease risk. (J Clin Endocrinol Metab 93: 4974–4978, 2008)

Studies in patients fulfilling metabolic syndrome criteria suggest that sympathetic activation promotes insulin resistance and arterial hypertension with increasing adiposity (1). Muscle sympathetic nerve activity (MSNA) is positively correlated with increased body weight (2). Yet some obese patients are normotensive and feature normal sympathetic nerve activity (3, 4). The observation may be explained in part by the fact that sympathetic activity is more closely correlated with abdominal than with sc fat mass (5–8). Indeed, sympathetic activity is similar in sc obese and nonobese men (5, 6). Another possible explanation for the variable expression of MSNA is that genetic or non-genetic factors affect the interaction between fat tissue and sympathetic nerve activity. Female gender may be such a factor. Even though percent body fat is higher in women than men (9), MSNA tends to be reduced at least before menopause (10, 11). Previous studies in smaller numbers of subjects suggested that gen-

Abbreviations: BMI, Body mass index; MSNA, muscle sympathetic nerve activity; WHR, waist to hip ratio.
nder differences in adipose tissue distribution had an impact on MSNA (12). Possibly fat distribution affects sympathetic responses differently in men and women. However, direct measurements of sympathetic nerve activity addressing this issue in a sufficient number of patients are rare. The issue is clinically relevant, given the known gender difference in cardiovascular disease risk that abates at an older age (13, 14). Therefore, we tested the hypothesis that the relationship between sympathetic nerve activity and waist circumference as a marker of central adiposity may be different between men and women. We analyzed the relationship between adiposity and MSNA in a relatively large cohort of healthy men and women with various degrees of adiposity. We focused our analysis on waist circumference, which closely correlates with visceral fat mass (15).

Subjects and Methods

We studied 111 Caucasian subjects, 70 men and 41 women. Body mass index (BMI) ranged between 18 and 40 kg/m². Subjects were recruited in Berlin (n = 43) and Gdansk (n = 68). All subjects were normotensive with blood pressure less than 140/90 mm Hg and healthy as judged by a history, physical examination, and routine blood testing. Subjects received no medication or hormone replacement therapies. The Institutional Review Board Committee approved the study and informed consent was obtained from all subjects.

Subjects were weighed with light clothes after they had emptied the bladder. We measured waist circumference at a level midway between the lower rib margin and iliac crest with the tape all around the body in horizontal position and hip circumference at the level trochanter major while the subject was standing to calculate the waist to hip ratio (WHR).

Cardiovascular and sympathetic measurements were conducted with the subjects supine. Electrocardiogram and beat-by-beat blood pressure (Finapres; Ohmeda, Englewood, CO) were measured continuously (Carotidmate Pro +; Critikon, Tampa, FL) as described previously (16). Nerve activity was amplified with a total gain of 100,000, bandpass filtered (0.7–2 kHz), full-wave rectified, and integrated. After instrumentation, subjects rested for at least 20 min to achieve a stable baseline. Then resting heart rate, blood pressure, and MSNA were recorded.

Data sets from both centers were analog-to-digital converted at 500 Hz using the WinDAQ pro+ software (Dataq Instruments Inc., Akron, OH). R-R intervals, diastolic blood pressure, systolic blood pressure values, and sympathetic bursts were defined off-line for the complete records using a program written by one of the authors (A.D.) that is based on PV-wave software (Visual Numerics Inc., Houston, TX). The number of bursts per minute (burst frequency), the number of bursts per 100 heart beats (burst incidence), and the mean area under the MSNA bursts per minute were quantified using an automated detection algorithm (17).

All data are expressed as mean ± SEM. Interindividual differences were compared by the unpaired t-test. Relationships between measurements were assessed by single and multiple linear regressions. In both genders, the estimated slopes of regression lines were calculated. The interaction between parameters was assessed by comparing regression slopes and intercepts in male and female subjects before and after correction for aging (SPSS software, version 14.0 for Windows, SPSS Inc., Chicago, IL). Results of single parameters are reported with nominal p values, and sympathetic bursts were defined off-line for the complete records using a program written by one of the authors (A.D.) that is based on PV-wave software (Visual Numerics Inc., Houston, TX). The number of bursts per minute (burst frequency), the number of bursts per 100 heart beats (burst incidence), and the mean area under the MSNA bursts per minute were quantified using an automated detection algorithm (17).

Results

Demographic data of the study population is given in Table 1. Mean age and BMI were similar in women and in men. Systolic blood pressure, diastolic blood pressure, BMI, waist circumference, and WHR were directly correlated with age in both women and men. Sympathetic activity in bursts per minute was also age dependent in both groups. However, in men a larger proportion of the variability in sympathetic activity was explained by an age effect. To test for independent influences of age and body composition on MSNA, we calculated partial correlations for either age or waist and hip circumferences as well as WHR. Controlling for waist and hip circumferences, age dependence remained highly significant in men (r = 0.43) and women (r = 0.43). When we adjusted for age, waist circumference (r = 0.29), WHR (r = 0.39), and BMI (r = 0.31) predicted MSNA in men (P < 0.01). However, after adjustment for age, the relationship between waist circumference or BMI and MSNA was reversed in women. BMI and waist circumference were highly correlated in our study population (women r = 0.95, men r = 0.92). Adjusting for BMI in men, only WHR (r = 0.40) remained predictive for MSNA. The

### Table 1. Baseline characteristics

| Parameter          | Men      | Statistic       | Women     |
|--------------------|----------|-----------------|-----------|
| n                  | 70       | 41              |
| Age (yr)           | 39 ± 1.4 | 39 ± 1.7        |
| Weight (kg)        | 82.6 ± 2.0 | 75.3 ± 2.8     |
| Height (cm)        | 177.5 ± 0.8 | 165.7 ± 0.9     |
| BMI (kg/m²)        | 26.5 ± 0.6 | 27.4 ± 0.9      |
| Waist circumference (cm) | 92.0 ± 1.7 | 84.8 ± 2.5      |
| Hip circumference (cm) | 100.2 ± 1.2 | 104.2 ± 2.0     |
| WHR                | 0.91 ± 0.01 | 0.81 ± 0.01     |
| Heart rate (beats/min) | 64 ± 1.1  | 65 ± 1.2        |
| RR interval (msec) | 954 ± 15 | 944 ± 18        |
| Systolic blood pressure (mm Hg) | 124 ± 2 | 116 ± 2 |
| Diastolic blood pressure (mm Hg) | 74 ± 1 | 70 ± 1 |
| MSNA frequency (bursts/min) | 31 ± 2 | 28 ± 2 |
| MSNA incidence (bursts per 100 beats) | 49 ± 3 | 43 ± 3 |
| MSNA (normal burst area) | 13.1 ± 0.7 | 11.2 ± 0.8     |

### Table 2. Regression analysis

| Parameter          | r (men)       | r (women)      |
|--------------------|---------------|---------------|
| BMI vs.            |               |               |
| Age (yr)           | 0.305<sup>a</sup> | 0.452<sup>b</sup> |
| MSNA age corrected (bursts/min) | 0.307<sup>a</sup> | -0.296 |
| Waist circumference vs. |               |               |
| Age (yr)           | 0.305<sup>a</sup> | 0.427<sup>b</sup> |
| MSNA age corrected (bursts/min) | 0.287<sup>a</sup> | -0.317<sup>a</sup> |
| MSNA BMI corrected (bursts/min) | 0.033 | -0.080 |
| WHR vs.            |               |               |
| Age (yr)           | 0.429<sup>b</sup> | 0.379<sup>a</sup> |
| MSNA age corrected (bursts/min) | 0.390<sup>a</sup> | 0.114 |
| MSNA BMI corrected (bursts/min) | 0.399<sup>a</sup> | 0.165 |

Relationship of BMI (kilograms per square meter), waist circumference, and WHR vs. age and MSNA (bursts per minute) in men and women after correction for the influences of age and BMI.

<sup>a</sup> P < 0.05.<br>
<sup>b</sup> P < 0.01.
results of the regression analysis of BMI, waist circumference, and WHR vs. age and MSNA in bursts per minute after correction for age and BMI are shown in Table 2. BMI, waist circumference, and WHR did not correlate with blood pressure after correction for the influences of age. Figure 1 illustrates the correlation between MSNA and waist circumference (top panel) and between MSNA and BMI (bottom panel) in women and men. Waist circumference, WHR, and BMI were correlated with sympathetic activity in men but not women. Finally, backward regression analysis with WHR and waist and hip circumference as starting variables revealed independent influences of waist circumference on nerve activity in men only.

Discussion

We observed a gender difference in the relationship between sympathetic vasomotor tone and measures of central adiposity. With increasing age, central adiposity and MSNA increased in women and men. In men, MSNA was correlated with BMI, waist circumference, and WHR after we adjusted for age. In contrast, with age adjustment, the correlation between BMI, waist circumference, and WHR with sympathetic activity in women was reversed. In men but not women, WHR was correlated with MSNA, even after adjustment for BMI. An increase in BMI, waist circumference, WHR, blood pressure, and MSNA with aging has been described in numerous studies. With increasing age, women may accumulate fat more rapidly than men (9). The phenomenon has been attributed to a more pronounced decline in physical activity and peak oxygen consumption in women compared with men. Indeed, adjustment for these variables reduced the age-related increase in waist circumference from 2 to 1% per decade in men and from 4 to 1% per decade in women (9).

Adipose tissue generates signals regulating sympathetic activity. The leptinergic system appears to be particularly important in this regard (18, 19). Gender and adiposity may affect brain leptin release (20). In animals, leptin applied into the brain increases sympathetic nerve traffic to peripheral tissues (21). Circulating leptin concentrations are correlated with sympathetic activity in some but not all studies (22). Yet MSNA was not...
related to BMI in hypertensive women, despite higher leptin levels (23). Sympathetic activity may be more closely correlated with leptin that is bound to a truncated leptin receptor than to free leptin concentrations (18). Our study suggests that the increase in sympathetic activity with age (10, 11) may not be fully explained by increased adiposity.

In any event, total and central body fat was associated with raised catecholamine levels in older men (24). In another study, central obesity was characterized by greater sympathetic activation compared with peripheral obesity. The authors suggested that metabolic factors rather than gender or baroreflex mechanisms explained the sympathetic activation (2). Furthermore, adiposity was associated with sympathetic vasomotor tone in women and men. The regression line may be shifted downward such that at a given degree of adiposity, sympathetic activity is lower in young women (12). Earlier studies suggested that such differences exist only in younger subjects. The mean age of our subjects was 39 yr, which might explain the failure to observe gender differences in MSNA. Waist to thigh ratio was the primary factor related to sympathetic activity in this study. However, a smaller study showed that the correlation between waist to thigh ratio and sympathetic activity was significant only in men (12). Our study confirms and extends the observation. Central fat distribution (WHR) was correlated with sympathetic activity in men, even after adjustment for age and BMI. The observation suggests that fat distribution is an important variable affecting MSNA in men. The relationship was absent in women.

Our study suggests that female gender may be a factor rendering the sympathetic nervous system less sensitive to increased adiposity and central fat distribution. The findings that leptin is associated with the risk of coronary heart disease in men but not older women supports the hypothesis (25). It is tempting to speculate that gender may affect the response of central sympathetic pathways to adipose tissue derived leptinergic signals. The response may also be affected by genetic factors. For example, in Pima Indians, circulating leptin levels and resting energy expenditure increase appropriately with increasing adipose tissue mass (26). Yet sympathetic vasomotor tone and blood pressure fail to increase with increasing obesity (26).

One limitation of our study is that we did not measure visceral adipose tissue directly using imaging techniques. We cannot completely exclude the possibility that our findings result from a gender difference in the relationship between visceral adipose tissue mass and waist circumference. However, several studies showed a good correlation between visceral adipose tissue mass and waist circumference over a wide age range (15, 27). Another possible limitation is that we measured only sympathetic nerve traffic to skeletal muscle in the leg. We cannot exclude a gender difference in the regional distribution of sympathetic activity to target organs that are not accessible to nerve recordings in human subjects (28). Preferential cardiac sympathetic activation in patients with heart failure, coronary artery disease, arterial hypertension, or ventricular arrhythmias are an example for regionalization of sympathetic activity (29).

Despite these issues, we suggest that abdominal fat is an important adipose tissue depot regulating MSNA in men. However, our study also suggests that women may be protected from sympathetic activation through a hitherto unknown mechanism. Thus, sympathetic activation is influenced by the amount of adipose tissue, which is highly correlated with circulating leptin levels and the sensitivity of the central nervous system to adipose tissue derived signals. The sensitivity of the central nervous system to adipose tissue derived signals appears to be modulated by fat distribution and gender. From a metabolic point of view, lower sympathetic activity in women may be a disadvantage as low resting sympathetic activity may predispose to further weight gain (30). On the other hand, raised sympathetic activity contributes to obesity-associated arterial hypertension (31), which may provide a cardiovascular benefit for women.

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