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Sympathetic neural regulation in endurance-trained humans: fitness vs. fatness

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Alvarez, Guy E., John R. Halliwill, Tasha P. Ballard, Stacy D. Beske, and Kevin P. Davy. Sympathetic neural regulation in endurance-trained humans: fitness vs. fatness. *J Appl Physiol* 98: 498–502, 2005. First published October 15, 2004; doi:10.1152/japplphysiol.01020.2004.—We tested the hypothesis that muscle sympathetic nerve activity (MSNA) would be higher in endurance-trained (ET) compared with sedentary (Sed) men with similar levels of total body and abdominal adiposity. We further hypothesized that sympathetic baroreflex gain would be augmented in ET compared with Sed men independent of the level of adiposity. To address this, we measured MSNA (via microneurography), sympathetic and vagal baroreflex responses (the modified Oxford technique), body composition (dual-energy X-ray absorptiometry), and waist circumference (Gulick tape) in Sed ($n = 22$) and ET men ($n = 8$). The ET men were also compared with a subgroup of Sed men ($n = 6$) with similar levels of total body and abdominal adiposity. Basal MSNA was greater in the ET compared with Sed men with similar levels of total body and abdominal adiposity (28 ± 2.0 vs. 21 ± 2.0 bursts/min; $P < 0.05$) but similar to the larger group of Sed men ($n = 22$) with higher total body and abdominal adiposity (vs. 26 ± 3 bursts/min; $P > 0.05$). In contrast to our hypothesis, sympathetic baroreflex gain was lower in the ET compared with Sed men (-6.4 ± 0.8 vs. -8.4 ± 0.4 arbitrary integrative units·beat^{-1}·mmHg^{-1}; $P < 0.05$) regardless of the level of adiposity. Taken together, the results of the present study suggest that MSNA is higher in ET compared with Sed men with similar levels of total body and abdominal adiposity. In addition, sympathetic baroreflex gain is lower in ET compared with Sed men. That sympathetic baroreflex gain was lower in ET compared with Sed men regardless of the level of adiposity suggests an influence of the ET state per se.

autonomic nervous system; visceral fat; body fat distribution

THE SYMPATHETIC NERVOUS SYSTEM plays a critical role in the regulation of cardiovascular and metabolic homeostasis. We have previously reported that abdominal visceral fat is an important depot linking obesity with sympathetic neural activation (2). Importantly, the relation between abdominal visceral fat and muscle sympathetic nerve activity (MSNA) is independent of total body fat (2) and evident in nonobese men at levels of abdominal visceral fat below the level typically associated with elevated cardiovascular and metabolic disease risk (1).

Endurance-trained (ET) individuals typically demonstrate lower levels of total and abdominal adiposity compared with their sedentary (Sed) peers, even at the same level of body mass index (24). The results of previous cross-sectional studies suggest that MSNA is similar in young ET and Sed individuals (19, 21), although the potential role of abdominal visceral fat was not considered.

The arterial baroreflex plays a critical role in the beat-to-beat regulation of MSNA and arterial blood pressure. Abrupt decreases and increases in arterial blood pressure produce baroreflex-mediated increases and decreases, respectively, in sympathetic neural activity. In contrast to previous reports (8, 9), we have not observed any reduction in sympathetic baroreflex gain in men with visceral obesity nor any relation between sympathetic baroreflex gain and any measure of total body or regional adiposity (1, 2).

The influence of chronic endurance training on sympathetic baroreflex gain is unclear, in part because of the lack of studies addressing this issue. The results of two longitudinal exercise training interventions have produced discrepant findings. These previous studies were conducted in older adults (20) and in patients with hypertension (7), and the short-term nature of the training stimulus employed in these studies is not consistent with the high volume of endurance training characterizing ET athletes.

Recently, Fadel et al. (6) reported that MSNA was augmented in response to a brief (14 s) hypotensive stimulus produced by unilateral cuff deflation in ET compared with Sed individuals. These observations suggest that sympathetic baroreflex gain may be enhanced in ET compared with Sed humans. However, to our knowledge, this has never been directly tested.

The present study was designed to test the hypothesis that MSNA would be higher in ET compared with Sed men with similar levels of total body and abdominal adiposity. We further hypothesized that sympathetic baroreflex gain would be augmented in ET compared with Sed men independent of the level of adiposity.

METHODS

Subjects. Twenty-two Sed and eight ET nonobese (body mass index ≤ 25 kg/m^2) men volunteered to participate in the present study. The Sed men had levels of total body and abdominal adiposity consistent with their sedentary behavior. All subjects were normotensive (casual recordings, arterial blood pressure $<140/90$ mmHg) and free from other overt chronic disease as determined from individual health histories. Subjects were further evaluated for the presence of overt cardiopulmonary disease by resting and maximal exercise electrocardiograms. Subjects did not smoke, were nondiabetic (2-h post-glucose load <200 mg/dl), and were not taking any medications. Subjects were classified as Sed if they did not participate in regular physical activity for >20 min >2 days/wk. The ET men were

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involved in a regular endurance training program (duration range = 2–11 yr) and swimming, biking, and/or running endurance competitions. These individuals reported training frequency ranging from 5.6 to 16.3 h/wk at an intensity of 6.0–7.5 on a 10-point scale (10 indicates most difficult of high-intensity training sessions). We also identified a subset of Sed men ($n = 6$) with levels of total body and abdominal adiposity that were similar to the ET men. All of these individuals had a waist circumference of <85 cm (the highest level observed in the ET men). The nature, purpose, risks, and benefits of the study were explained to each subject before informed consent was obtained. The experimental protocols were approved by the University Human Research Committee.

Experimental procedures. A physician's balance scale and a stadiometer were used to measure body mass and height, respectively. Waist and hip circumference were measured using recommended procedures (13), and waist-to-hip ratio was calculated. Body composition was measured by using dual-energy X-ray absorptiometry (DPX-IQ, Lunar Radiation version 4.5c). Maximal oxygen consumption was measured during graded treadmill exercise to exhaustion using open-circuit spirometry (TrueMax 2400, ParvoMedics). Standard criteria for achievement of valid maximal oxygen consumption were met (11). Heart rate was determined from lead II of the electrocardiogram, and beat-by-beat arterial pressure was measured in the finger using photoplethysmography (Finometer, Finapres Medical Systems). Resting finger arterial blood pressures were "adjusted" to brachial arterial blood pressures with an automated device before the injection of vasoactive drugs (see below). Respiration was monitored continuously by using a pneumobelt placed around the upper abdomen. Recordings of multiunit MSNA were obtained from the right peroneal nerve using the microneurographic technique (23). The neural activity was amplified, filtered (700–2,000 Hz), full-wave rectified, and integrated (time constant, 0.1 s) (nerve traffic analyzer, model 662C-3, University of Iowa Bioengineering). Neurograms were considered acceptable as recordings of efferent MSNA according to previously published criteria (23).

Sympathetic and vagal baroreflex responses were measured using the modified Oxford technique (5). Briefly, an antecubital venous catheter was placed in the subject's arm for the injection of vasoactive drugs. After a 20-min rest period and stabilization of baseline arterial blood pressure, heart rate, and respiration, a bolus injection of sodium nitroprusside (100 μg) was given intravenously followed 60 s later by a bolus injection of phenylephrine HCl (150 μg). These pharmacological perturbations decreased and increased, respectively, arterial blood pressure by ~15 mmHg from baseline levels during a 3-min period.

Experimental protocol. All subjects reported to the laboratory between 7:00 AM and 11:00 AM after a 12-h overnight fast. Subjects were instructed to refrain from caffeine and alcohol consumption and to avoid participation in any vigorous activity for 24 h before testing.

Subjects were dressed in light clothing, were instrumented, and rested quietly for 20 min to achieve steady-state levels of all variables before a 10-min recording of basal MSNA, heart rate, arterial blood pressure, and respiration. After baseline recordings, three trials of vasoactive drug injections were performed. A minimum 15 min of quiet rest separated each trial.

Data analysis. MSNA, heart rate, arterial blood pressure, and respiration were recorded continuously and digitized at 500 Hz to a laboratory computer for offline analysis (Windaq, Dataq Instruments). Basal MSNA was quantified as both burst frequency (bursts/min) and burst incidence (bursts/100 beats). MSNA recordings for each subject were normalized by assigning the largest sympathetic burst under resting conditions to an amplitude of 1,000 (arbitrary integrative units). All other bursts from that recording were calibrated against this value. Zero nerve activity level was determined from the mean voltage neurogram during a period of neural silence between sympathetic bursts. Sympathetic baroreflex responses were determined from the relationship between MSNA and diastolic blood pressure during vasoactive drug injections. To perform a linear regression between neural activity and diastolic blood pressure, MSNA was binned over 3-mmHg diastolic blood pressure ranges by using a segregated signal-averaging approach (10). Pairs of MSNA and diastolic blood pressure changes during rising and falling pressure fall on the same relation (18). Therefore, we pooled all pairs during both falling and rising pressures to calculate a single baroreflex sympathetic gain. R-R intervals were binned over 3-mmHg systolic blood pressure. A four-parameter sigmoid was fit to the R-R interval and systolic blood pressure data. Vagal baroreflex gain was calculated from the linear relation after systematically removing bin values in the threshold and saturation regions as described previously (4). Only regressions with r values ≥0.70 were accepted. A minimum of two of the three trials performed for each subject were used to determine average sympathetic and vagal baroreflex gain.

Statistical analysis. Differences in characteristics of the Sed and ET subjects and in the dependent variables were analyzed by independent Student's t-test for each comparison. Bivariate correlation analysis was used to assess relations among variables. Data are expressed as means ± SE. The significance level was set a priori at $P < 0.05$.

RESULTS

Subject characteristics of Sed and ET men. Subject characteristics of Sed and ET men are presented in Table 1. Waist circumference, body fat percent, total fat mass, and resting heart rate (R-R interval was higher) were significantly lower in the ET compared with Sed men ($P < 0.05$). Fat-free mass was greater ($P < 0.05$) in the ET compared with Sed men. There were no significant ($P > 0.05$) differences in age, height, body mass, body mass index, hip circumference, waist-to-hip ratio, or blood pressure (systolic or diastolic). As intended, maximal oxygen consumption (expressed relative to total body mass or FFM) was greater ($P < 0.05$) in the ET compared with Sed.

Basal MSNA and baroreflex responses. There were no differences in basal MSNA burst frequency (28 ± 2 vs. 26 ± 3 bursts/min; $P > 0.05$; Fig. 1, *top*), but burst incidence (54 ± 5 vs. 43 ± 4 bursts/100 beats) tended to be higher ($P = 0.07$) in the ET compared with Sed men. The magnitude of fall in blood pressure with sodium nitroprusside (−13 ± 3 vs. −15 ± 2 mmHg) and rise with phenylephrine HCl (24 ± 2 vs. 21 ± 2

Table 1. *Subject characteristics of sedentary and endurance-trained men*

Variable	Sed ($n = 22$)	ET ($n = 8$)
Age, yr	23.6±1.4	25.1±1.0
Height, cm	180.7±1.8	178.5±2.4
Body mass, kg	77.3±2.1	75.4±2.8
Body mass index, kg/m^2	23.8±0.7	23.6±0.7
Waist circumference, cm	85.2±1.7	80.1±1.4*
Hip circumference, cm	100.5±1.2	96.6±3.3
Waist-to-Hip ratio	0.85±0.01	0.83±0.02
Body fat, %	19.6±1.2	9.2±0.6*
Total fat mass, kg	15.6±1.4	6.9±0.6*
Fat-free mass, kg	58.6±1.0	64.9±2.5*
Systolic blood pressure, mmHg	117.7±1.8	118.9±2.2
Diastolic blood pressure, mmHg	65.2±1.9	67.0±2.9
Heart rate, beats/min	59.6±1.7	51.5±2.8*
R-R interval, s	1.0±0.03	1.3±0.06*
$\dot{V}O_{2\,max}$, ml·kg^{-1}·min^{-1}	49.8±1.8	69.4±2.4*
$\dot{V}O_{2\,max}$, ml·kg FFM^{-1}·min^{-1}	65.1±1.9	80.7±2.8*

Values are means ± SE; n, no. of subjects. $\dot{V}O_{2\,max}$, maximal oxygen consumption per kg body weight; FFM, fat-free mass; Sed, sedentary; ET, endurance trained. *$P < 0.05$ vs. Sed.

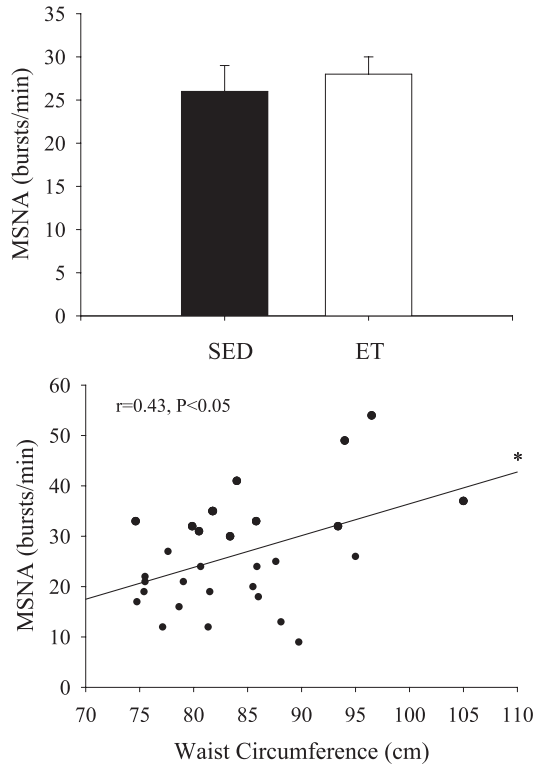

Fig. 1. *Top*: muscle sympathetic nerve activity (MSNA) in sedentary (Sed; $n = 22$) and endurance-trained (ET; $n = 8$) men. Values are means ± SE. *Bottom*: relation between waist circumference and MSNA in pooled sample ($n = 30$).

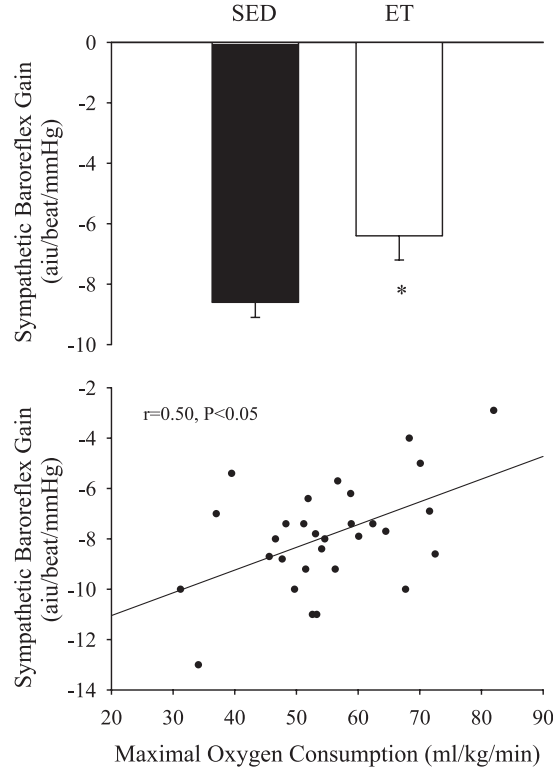

Fig. 2. *Top*: sympathetic baroreflex gain in Sed ($n = 22$) and ET ($n = 8$) men. Values are means ± SE. *$P < 0.05$. *Bottom*: relation between maximal oxygen consumption and sympathetic baroreflex gain in the pooled sample ($n = 30$). Aiu, Arbitrary integrative units.

mmHg) below and above baseline blood pressure, respectively, was similar in the two groups (both $P > 0.05$). Cardiovagal baroreflex gain was not significantly different between groups regardless of whether R-R interval (18.7 ± 2.9 vs. 15.4 ± 1.5 ms/mmHg) or heart rate (−0.98 ± 0.12 vs. −1.11 ± 0.09 beats/mmHg) was used as the efferent response variable (both $P > 0.05$). In contrast to our hypothesis, however, sympathetic baroreflex gain (−6.4 ± 0.8 vs. −8.4 ± 0.4 arbitrary integrative units $\cdot beat^{-1} \cdot mmHg^{-1}$; $P < 0.05$; Fig. 2, *top*) was significantly lower in the ET compared with Sed.

Subject characteristics of Sed and ET men with similar total body and abdominal adiposity. Subject characteristics of Sed and ET men with similar levels of total and abdominal adiposity are presented in Table 2. Subject age, body mass, body mass index, fat-free mass, R-R interval, and maximal oxygen consumption were all significantly greater, whereas percent body fat was significantly lower, in the ET compared with Sed men ($P < 0.05$). Height, hip circumference, waist-to-hip ratio, systolic blood pressure, diastolic blood pressure, and resting heart rate were not significantly different in the ET compared with Sed men ($P > 0.05$). As intended, waist circumference and total fat mass were similar ($P > 0.05$) in the ET and Sed men.

Basal MSNA and baroreflex responses in Sed and ET men with similar total body and abdominal adiposity. Basal MSNA burst frequency (28 ± 2 vs. 21 ± 2 bursts/min; Fig. 3) and incidence (54 ± 5 vs. 37 ± 4 bursts/100 beats) were significantly greater in the ET compared with Sed with similar total body and abdominal adiposity. The magnitude of fall in blood pressure with sodium nitroprusside and rise with phenylephrine HCl below and above baseline blood pressure, respectively, was similar in the two groups (data not shown; both $P > 0.05$). Cardiovagal baroreflex gain (18.7 ± 2.9 vs. 15.0 ± 2.5 ms/mmHg; $P > 0.05$) was not different in the two groups. However, sympathetic baroreflex gain (−6.4 ± 0.8 vs. −8.6 ± 0.5 arbitrary integrative units $\cdot beat^{-1} \cdot mmHg^{-1}$; $P < 0.05$) was lower in the ET compared with Sed men with similar total body and abdominal adiposity.

Table 2. *Subject characteristics of Sed and ET men with similar levels of total body and abdominal adiposity*

Variable	Sed ($n = 6$)	ET ($n = 8$)
Age, yr	20.5±1.0	25.1±1.0*
Height, cm	180.7±2.5	178.5±2.4
Body mass, kg	68.5±1.3	75.4±2.8*
Body mass index, kg/m^2	21.0±0.5	23.6±0.7*
Waist circumference, cm	77.2±1.0	80.1±1.4
Hip circumference, cm	94.5±1.1	96.6±3.3
Waist-to-hip ratio	0.82±0.02	0.83±0.02
Body fat, %	12.8±1.6	9.2±0.6*
Total fat mass, kg	8.7±1.1	6.9±0.6
Fat-free mass, kg	56.3±1.7	64.9±2.5*
Systolic blood pressure, mmHg	120.3±3.6	118.9±2.2
Diastolic blood pressure, mmHg	64.2±1.5	67.0±2.9
Heart rate, beats/min	57.7±3.2	51.5±2.8
R-R interval, s	0.95±0.03	1.3±0.06*
$\dot{V}O_{2\,max}$, ml$\cdot$kg$^{-1}\cdot$min^{-1}	52.0±1.9	69.4±2.4*
$\dot{V}O_{2\,max}$, ml$\cdot$kg FFM$^{-1}\cdot$min^{-1}	63.2±1.6	80.7±2.8*

Values are mean ± SE. *n,* no. of subjects. *$P < 0.05$ vs. Sed.

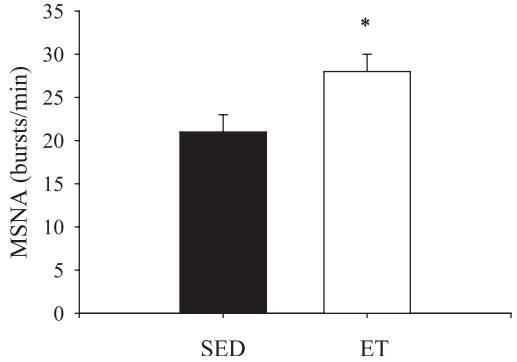

Fig. 3. MSNA in Sed ($n = 6$) and ET ($n = 8$) men with similar levels of total body and abdominal adiposity. Values are means ± SE. *$P < 0.05$.

Correlations in ET and Sed men. Waist circumference was the only significant body composition or abdominal fat distribution-related correlate of basal MSNA ($r = 0.43$; $P < 0.05$; Fig. 1, *bottom*) in the pooled sample ($n = 30$). Sympathetic baroreflex gain was significantly correlated with maximal oxygen consumption ($r = 0.50$, $P < 0.05$; Fig. 2, *bottom*). However, there were no significant correlates of vagal baroreflex gain in these men. There were no significant correlates of basal MSNA or cardiovagal baroreflex gain in the ET and Sed men ($n = 14$) with similar total body and abdominal adiposity. As observed in the larger sample, sympathetic baroreflex gain was significantly correlated with maximal oxygen consumption ($r = 0.55$, $P < 0.05$) in ET and Sed men with similar total body and abdominal adiposity.

DISCUSSION

There are two new and important findings from the present study. First, MSNA was higher in ET compared with Sed men with similar levels of total body and abdominal adiposity. Second, sympathetic baroreflex gain was reduced in ET compared with Sed men independent of the level of adiposity. Furthermore, the lower sympathetic baroreflex gain observed in ET men was associated with their higher maximal oxygen consumption. Cardiovagal baroreflex gain was not significantly different in the two groups.

We have previously reported that abdominal visceral fat is an important adipose tissue depot linking obesity and sympathetic neural activation in humans (2). Abdominal visceral fat is more closely associated with MSNA than total adiposity, even among nonobese individuals (1). In the present study, waist circumference, a surrogate measure of visceral fat, was the only correlate of MSNA in the pooled sample. The observation that MSNA is similar in ET and Sed in previous cross-sectional studies (19, 21) may be confounded by higher levels of abdominal visceral fat in the Sed individuals. That MSNA is higher in ET individuals compared with adiposity-matched Sed peers is consistent with this idea.

Consistent with our observations, higher levels of MSNA have been reported in middle-aged and older master athletes compared with Sed age-matched individuals (15). The mechanism responsible for the higher level of MSNA in habitually exercising older adults is not entirely clear. Unfortunately, abdominal adiposity was not measured in this previous study. However, a state of higher energy flux (i.e., a relatively higher level of energy intake and energy expenditure under conditions of energy balance) may contribute to the higher levels of MSNA observed in habitually exercising older adults. Recently, Bell et al. (3) reported that an experimental reduction in energy flux in habitually exercising older adults was associated with a corresponding reduction in MSNA and resting energy expenditure (3). Therefore, it is possible that a high energy flux and low level of abdominal adiposity may exert opposite influences on MSNA in ET athletes. As such, the higher MSNA observed in the young ET compared with Sed individuals with similar total body and abdominal adiposity in the present study may be the result of a higher energy flux in the former group. Importantly, this effect may only be revealed when abdominal adiposity is considered.

The influence of endurance exercise training on MSNA remains unclear (17); both no change in normotensive middle-aged and older adults (20) and a decrease in young hypertensive adults (7) have been reported. The reason(s) for this discrepancy is unclear but may be related to age, hypertensive status, or the degree to which abdominal adiposity was reduced with exercise training. Unfortunately, abdominal adiposity was not measured in these previous studies. As such, future studies are needed to determine whether exercise training-induced reductions in abdominal visceral fat are associated with corresponding reductions in MSNA.

Sympathetic baroreflex gain was significantly lower in ET compared with Sed men regardless of whether the two groups demonstated similar levels of total body and abdominal adiposity. These observations suggest that the lower sympathetic baroreflex gain was an effect of the ET state per se and not an indirect influence of total body or abdominal adiposity. The mechanism(s) responsible for the lower sympathetic baroreflex gain in the ET individuals in the present study is unclear. However, one mechanism may involve a neural component because young ET individuals typically demonstrate similar (22) or higher, not lower, arterial compliance compared with Sed age-matched individuals, and a more compliant aorta and carotid arteries should translate into superior not reduced sympathetic baroreflex gain.

Our present findings are inconsistent with the recent report by Fadel et al. (6) that endurance training was associated with an augmented MSNA response to a brief hypotensive stimulus produced by unilateral leg cuff deflation. The reasons for this discrepancy are unclear but may be related in part to the methodology employed. For example, we used the modified Oxford technique to estimate sympathetic baroreflex gain. In contrast, Fadel et al. calculated "baroreflex responsiveness" as the quotient of the change in MSNA per unit change in diastolic blood pressure from baseline to 14 s after cuff release. In addition, the arterial blood pressure stimulus was larger in the ET athletes studies by Fadel et al. However, the arterial blood pressure stimulus was similar in the ET compared with Sed men in the present study. Finally, it is possible that the volume of endurance training performed by the subjects or other factors may have contributed to the different outcome in our study and the study by Fadel et al. Future studies will be necessary to clarify this issue.

Our observation that the ET athletes demonstrate reduced sympathetic baroreflex gain may have important implications for understanding the occurrence of orthostatic intolerance in some ET athletes (16). In addition, the elevated MSNA observed in the ET athletes in the present study may subserve

both a metabolic and cardiovascular function. The higher level of MSNA observed in some ET athletes may contribute to a greater sympathetic adrenergic support of resting metabolic rate (3) as well as act to restrain the tremendous vasodilatory reserve observed in ET individuals (14).

There are some limitations of the present study that should be discussed. First, the sample size of the study was small. Therefore, the inclusion of a larger number of subjects (particularly ET subjects and the comparison group of Sed men with similar total and abdominal adiposity) may yield a different outcome. For example, a larger sample size may have provided the additional statistical power needed to detect differences in basal MSNA burst incidence between the ET and larger group of Sed individuals ($n = 22$). However, it is important to emphasize that we have relied on the basal MSNA burst frequency for interpreting our observations for two important reasons. First, basal MSNA burst frequency is the most commonly used expression of basal MSNA because it is the most physiologically meaningful. Second, there is significant fixed and proportional bias in the reproducibility of basal MSNA burst incidence (12).

Second, the athletes included in the present study were engaged in moderate- to high-intensity endurance training for an average of almost 6 yr (range 2–11 yr). In addition, the Sed subjects had levels of maximal oxygen consumption that were above average for young Sed men. Therefore, the results of the present study should not be generalized to the type of exercise training recommended to the general public for improving cardiovascular and metabolic health.

Third, only young men were included in the present study. Thus the interaction of age or gender with endurance training is unclear.

Finally, the present study was cross sectional in design. Thus it is possible that genetic or other factors (i.e., mode and/or length of training) could contribute to our present findings. Future intervention studies will be necessary to confirm or refute our observations.

In summary, the results of the present study suggest that sympathetic baroreflex gain is lower in ET compared with Sed men. The mechanism(s) responsible for the lower sympathetic baroreflex gain observed in the ET men is unclear. MSNA is higher in ET compared with Sed men when the level of total and abdominal adiposity is similar. Thus total body and abdominal adiposity should be considered when studying the influence of endurance training on sympathetic nervous system activity in humans.

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