Sympathetic Neural Adaptation to Hypocaloric Diet With or Without Exercise Training in Obese Metabolic Syndrome Subjects

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OBJECTIVE—Sympathetic nervous system (SNS) overactivity contributes to the pathogenesis and target organ complications of obesity. This study was conducted to examine the effects of lifestyle interventions (weight loss alone or together with exercise) on SNS function.

RESEARCH DESIGN AND METHODS—Untreated men and women (mean age 55 ± 1 year; BMI 32.3 ± 0.5 kg/m²) who fulfilled Adult Treatment Panel III metabolic syndrome criteria were randomly allocated to either dietary weight loss (WL, n = 20), dietary weight loss and moderate-intensity aerobic exercise (WL+EX, n = 20), or no treatment (control, n = 19). Whole-body norepinephrine kinetics, muscle sympathetic nerve activity by microneurography, baroreflex sensitivity, fitness (maximal oxygen consumption), metabolic, and anthropometric measurements were made at baseline and 12 weeks.

RESULTS—Body weight decreased by −7.1 ± 0.6 and −8.4 ± 1.0 kg in the WL and WL+EX groups, respectively (both P < 0.001). Fitness increased by 19 ± 4% (P < 0.001) in the WL+EX group only. Resting SNS activity decreased similarly in the WL and WL+EX groups: norepinephrine spillover by −96 ± 50 and −101 ± 34 ng/min (both P < 0.01) and muscle sympathetic nerve activity by −12 ± 6 and −19 ± 4 bursts/100 heart beats, respectively (both P < 0.01), but remained unchanged in control subjects. Blood pressure, baroreflex sensitivity, and metabolic parameters improved significantly and similarly in the two lifestyle intervention groups.

CONCLUSIONS—The addition of moderate-intensity aerobic exercise to a weight loss program does not confer additional benefits on resting SNS activity. This suggests that weight loss is the prime mover in sympathetic neural adaptation to a hypocaloric diet.

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in middle-aged MetS subjects (5). Because exercise is often added to energy restriction in the treatment of obesity, it is pertinent to clarify its additive benefits. Augmented improvements in metabolic, anthropometric, and cardiovascular parameters have been observed after combined exercise training and dietary weight loss in some (17,20,21), but not other studies (22), and there are limited data regarding their combined effect on sympathetic activity (23). Exercise training may potentially augment weight loss induced sympathoinhibition by promoting a greater loss of fat relative to lean mass (20,21), by further improvement in insulin sensitivity (24) and reduction in plasma leptin concentration (21), and by potentiation of baroreceptor sensitivity (18).

The present study was conducted to (1) test the hypothesis that weight loss by combined hypocaloric diet and aerobic exercise training would be associated with greater sympathoinhibition and improvement in MetS components than hypocaloric diet alone and (2) to examine the interrelationships between reduction in sympathetic tone and concurrent changes in anthropometric, metabolic, insulin sensitivity, plasma leptin concentration, and cardiovascular parameters. A moderate-intensity bicycle riding protocol was chosen as the exercise intervention, based on an earlier study that demonstrated attenuation in whole-body and renal norepinephrine spillover rates with this regimen in healthy men (19).

RESEARCH DESIGN AND METHODS

Men and postmenopausal women, aged 45–65 years, who fulfilled Adult Treatment Panel III criteria for the MetS (25) were recruited through newspaper advertisement. To be eligible, candidates had to have central obesity (waist circumference ≥102 cm in men and ≥88 cm in women) and two or more MetS parameters (5,25). All were nonsmokers; sedentary, defined as physical exercise two or less times per week for <20 min per session (26); with a stable body weight (± 1 kg) in the previous 6 months; and willing to accept random assignment. Exclusion criteria included type 2 diabetes (fasting glucose ≥7 mmol/L); a history of secondary hypertension or cardiovascular, cerebrovascular, renal, liver, or thyroid disease; and use of drugs known to affect measured parameters. Participants treated for hypertension were stratified by sex and hypertensive status in blocks of six and were randomised to allocation in plasma leptin concentration (21), and by potentiation of baroreceptor sensitivity (18).

The present study was conducted to (1) test the hypothesis that weight loss by combined hypocaloric diet and aerobic exercise training would be associated with greater sympathoinhibition and improvement in MetS components than hypocaloric diet alone and (2) to examine the interrelationships between reduction in sympathetic tone and concurrent changes in anthropometric, metabolic, insulin sensitivity, plasma leptin concentration, and cardiovascular parameters. A moderate-intensity bicycle riding protocol was chosen as the exercise intervention, based on an earlier study that demonstrated attenuation in whole-body and renal norepinephrine spillover rates with this regimen in healthy men (19).

Muscle sympathetic nerve activity. Recordings of multi-unit postganglionic MSNA were made from a tungsten microelectrode (FHC, Bowdoinham, ME) inserted into the right peroneal nerve at the fibular head (5). A subcutaneous reference electrode was positioned 2–3 cm away from the recording site. Standard criteria were used to ascertain an MSNA site. The nerve signal was amplified (×50,000), filtered (bandpass, 700–2,000 Hz), and integrated. Intraarterial blood pressure, electrocardiogram, respiration, and MSNA were digitized with a sampling frequency of 1,000 Hz (PowerLab recording system, model ML 785/88P; ADI Instruments). Resting measurements were recorded over a 15-min period and averaged. Sympathetic bursts were counted manually and expressed as burst frequency (bursts/min) and burst incidence (bursts/s) per cycle.

Statistical methods. Data are presented as means ± SE. Statistical analysis was performed using SigmaStat Version 3.5 (Systat Software, Point Richmond, CA). Comparisons between baseline and post-intervention data were made by two-way repeated-measure ANOVA. The Holm-Sidak test was used for post hoc comparisons. ANCOVA, with adjustment for baseline values, was also performed for the primary outcome variables (norepinephrine spillover and MSNA). Nonparametric data were log-transformed. Subgroup analyses by sex were performed by two-way repeated-measure ANOVA. Areas under the curve were calculated as the trapezoidal rule for glucose and insulin. Associations between changes in selected variables were assessed using Pearson’s and Spearman’s rank correlations. Forward stepwise regressions were carried out with those univariate correlations where P < 0.05. We estimated that a sample size of 20 subjects per
TABLE 1
Anthropometric responses by treatment group

|                     | Control | WL   | WL+EX | Time × group interaction (P) |
|---------------------|---------|------|-------|-----------------------------|
| n                   | 19      | 20   | 20    | —                           |
| Age (years)         | 55 ± 1  | 55 ± 1| 54 ± 1| —                           |
| Sex (male/female)   | 11/8    | 12/8 | 12/8  | —                           |
| BMI (kg/m²)         | 33.0 ± 0.8 | 32.2 ± 0.9| 31.8 ± 0.8| <0.001                      |
| Final               | 33.4 ± 0.8 | 29.8 ± 0.8§| 29.0 ± 0.8§| <0.001                      |
| Change              | 0.4 ± 0.1 | -2.4 ± 0.2§| -2.8 ± 0.3§| <0.001                      |
| Body weight (kg)    | 97.6 ± 3.6 | 94.3 ± 2.3| 92.9 ± 2.9| <0.001                      |
| Final               | 98.6 ± 3.7 | 87.2 ± 2.2§| 84.5 ± 2.5†§| <0.001                      |
| Change              | 1.0 ± 0.3 | -7.1 ± 0.6§| -8.4 ± 1.0§| <0.001                      |
| Waist circumference (cm) | 109.4 ± 2.5 | 106.5 ± 1.9| 105.1 ± 2.2| —                           |
| Final               | 109.3 ± 2.5 | 99.8 ± 2.1†§| 95.3 ± 2.0†§| —                           |
| Change              | -0.1 ± 0.5 | -6.7 ± 0.7§| -9.8 ± 1.2§| <0.001                      |
| Waist-to-hip ratio  | 0.94 ± 0.02 | 0.94 ± 0.02| 0.91 ± 0.02| <0.001                      |
| Final               | 0.94 ± 0.02 | 0.091 ± 0.01†| 0.88 ± 0.02§| <0.001                      |
| Change              | 0.00 ± 0.0 | -0.02 ± 0.01| -0.03 ± 0.01§| 0.012                      |
| Total body fat mass (kg) | 35.5 ± 2.2 | 36.4 ± 1.8| 35.4 ± 1.5| <0.001                      |
| Final               | 35.9 ± 2.3 | 31.2 ± 1.9†| 28.5 ± 1.9†§| <0.001                      |
| Change              | 0.3 ± 0.2 | -5.2 ± 0.7§| -6.9 ± 0.9§| <0.001                      |
| Total body lean mass (kg) | 56.8 ± 2.7 | 53.7 ± 2.2| 53.1 ± 2.8| <0.001                      |
| Final               | 57.6 ± 2.7 | 52.2 ± 2.1†| 52.2 ± 2.7*| <0.001                      |
| Change              | 0.7 ± 0.2 | -1.5 ± 0.5§| -0.9 ± 0.4§| <0.001                      |
| Trunk fat mass (kg) | 21.0 ± 1.2 | 20.6 ± 0.9| 20.1 ± 0.8| <0.001                      |
| Final               | 21.1 ± 1.2 | 17.5 ± 1.0†§| 15.7 ± 0.9†§| <0.001                      |
| Change              | 0.2 ± 0.2 | -3.1 ± 0.5§| -4.4 ± 0.6§| <0.001                      |
| Abdominal fat mass (kg) | 3.3 ± 0.2 | 3.2 ± 0.2| 3.0 ± 0.2| <0.001                      |
| Final               | 3.3 ± 0.2 | 2.6 ± 0.2§| 2.3 ± 0.1†§| <0.001                      |
| Change              | 0.1 ± 0.1 | -0.5 ± 0.1§| -0.8 ± 0.1§| <0.001                      |

Data are means ± SE. Baseline values did not differ between groups for any parameter. *P < 0.05 and †P < 0.001 vs. baseline; ‡P ≤ 0.01 vs. WL group; §P < 0.01 vs. control group. WL, weight loss by caloric restriction; WL+EX, weight loss by caloric restriction and aerobic exercise.

RESULTS

Out of 123 subjects screened for eligibility, 64 were enrolled since they met inclusion criteria. Five dropped out after baseline testing; therefore, 59 subjects completed the study. At baseline, treatment groups were well matched for age, sex, anthropometric, metabolic, blood pressure, and fitness measurements (Tables 1–3) and also for habitual dietary intake (data not shown).

Dietary and fitness parameters. Daily energy intake decreased by 600 ± 100 and 560 ± 90 calories in the WL and WL+EX groups, respectively (P both <0.001). Macronutrient changes from baseline included reductions in fat (by 3 ± 1 and 5 ± 1% of total energy, respectively, P both <0.05) and saturated fat (by 4 ± 1% in both groups, P both <0.001) and an increase in relative protein consumption (by 4 ± 1 and 3 ± 1%, respectively, P both <0.001). There were no significant dietary changes in the control group. Mean urinary sodium excretion decreased by 22 to 37 mmol/day across the three groups (Table 3, group effect, P = 0.12; group by time interaction, P = 0.62). Potassium excretion did not change. Aerobic capacity increased by 19 ± 4% in the WL+EX group only, as did maximum workload by 38 ± 4 W (P both <0.001, Table 2).

Body weight and composition. Body weight decreased by 7.6 ± 0.7 and 8.8 ± 0.9% in the WL and WL+EX groups, respectively (P = 0.20 between groups) and there were concomitant reductions in fat mass (Table 1). The reduction in waist circumference was significantly greater in the WL+EX compared with the WL group (P = 0.01), and this was also reflected in the change in trunk fat mass, which tended to decrease more in the former group (P = 0.06). Lean body mass declined significantly in both lifestyle intervention groups. Change in lean body mass correlated with absolute change in dietary protein intake (g/day, r = 0.47, P = 0.002), indicating that reduction in protein consumption during weight loss was associated with loss of lean mass. Subgroup analysis by sex showed that men lost more weight (8.8 ± 0.8 vs. 6.2 ± 0.8 kg), total body fat (7.2 ± 0.8 vs. 4.3 ± 0.6 kg), and trunk fat (4.7 ± 0.5 vs. 2.3 ± 0.4 kg) than women (P all <0.05). Women in the WL+EX group maintained their lean body mass (mean change was −0.5 ± 0.5 kg, P = 0.26), whereas the men in the WL+EX group tended to lose lean mass (mean change was −1.1 ± 0.6 kg, P = 0.07).
3) High-sensitivity CRP decreased significantly only in WL and by similar magnitude in both lifestyle groups (Table 2). Triglycerides and plasma leptin levels decreased significantly both in WL and WL+EX (Table 2). Spontaneous cardiac baroreflex sensitivity increased by 50% in the WL group and 45% in the WL+EX group (Table 2). Resting metabolic rate tended to decrease (time effect, \( P = 0.08 \)) but when normalized to fat-free mass, there were no significant group effects or interactions.

**Metabolic variables.** Fasting plasma glucose and insulin levels were reduced and by similar magnitude in both lifestyle groups (\( P \leq 0.001 \)), whereas glucose tolerance (glucose AUC0–120 and 2-h glucose concentration) did not change. Whole-body insulin sensitivity index increased by 49% in the WL group and 45% in the WL+EX group (\( P \leq 0.001 \)). Fasting triglycerides, HDL cholesterol, and plasma leptin levels decreased significantly and by similar magnitude in both lifestyle groups (Table 3). High-sensitivity CRP decreased significantly only in the WL+EX group. Resting metabolic rate tended to decrease (time effect, \( P = 0.08 \)) but when normalized to fat-free mass, there were no significant group effects or interactions.

**Cardiovascular parameters.** Resting blood pressure decreased by similar magnitude in both lifestyle groups (Table 2). Spontaneous cardiac baroreflex sensitivity increased by 50% in the WL group and 45% in the WL+EX group (\( P \leq 0.001 \)). The increase in baroreflex sensitivity was greater in men than women (6.3 ± 1.6 vs. 1.3 ± 1.2 ms/mmHg, \( P = 0.02 \)).

**Sympathetic activity.** Because of difficulties with arterial line placement in four subjects, paired norepinephrine kinetics data were available for 55 participants (17 control, 20 WL, and 18 WL+EX). Arterial norepinephrine concentration and calculated norepinephrine spillover rates were significantly reduced after both WL and WL+EX treatment, whereas no changes were noted in norepinephrine plasma clearance (Fig. 1). The percentage change in norepinephrine spillover rate averaged −22 ± 6% for the WL group and −22 ± 7% for the WL+EX group (\( P \leq 0.01 \)). After adjustment for baseline values by ANCOVA, between-group differences in the final value were significant for the WL and WL+EX groups versus the control group (\( P \leq 0.01 \)). Acceptable paired MSNA recordings were obtained in 46 subjects (15 control, 15 WL, and 16 WL+EX). Both the WL and WL+EX interventions were associated with reductions in MSNA (Fig. 2): burst frequency decreased by 25 ± 2 and 29 ± 7% (\( P \leq 0.001 \)), respectively, and burst incidence by 16 ± 12% and 27 ± 5%, respectively (\( P \leq 0.01 \)). After adjustment for baseline values by ANCOVA, between-group differences in the final value were significant for the WL and WL+EX groups versus the control group (\( P \leq 0.05 \)), whereas differences between the WL and WL+EX group were not significant.

No significant sex effects were observed for the change in sympathetic activity after lifestyle interventions.

**Correlation and regression analysis.** Change in waist-to-hip ratio was the strongest correlate of change in whole-body norepinephrine spillover rate after lifestyle interventions for the whole group (\( r = 0.31, P = 0.06 \)). This was also the case in men (\( r = 0.36, P = 0.08 \)), whereas in women, change in total body fat mass (\( r = 0.52, P = 0.06 \)), trunk fat mass (\( r = 0.55, P = 0.04 \)), abdominal fat mass (\( r = 0.60, P = 0.02 \)), and HDL cholesterol levels (\( r = −0.60, P = 0.02 \)) were the strongest correlates. The reduction in MSNA burst incidence after lifestyle interventions correlated significantly with anthropometric changes in the whole-group and in both sexes (Table 4). Improvement in individual MetS components (fasting glucose, insulin sensitivity, and HDL cholesterol) were also associated with the reduction in MSNA in men. Increases in baroreflex sensitivity and fitness level were not associated with change in either whole-body norepinephrine spillover rate or MSNA. Stepwise linear regression analysis of the whole-group showed that change in total body fat mass (\( P = 0.03 \)) and plasma leptin concentration (\( P = 0.01 \)) were the strongest independent predictors of change in MSNA burst incidence, explaining 33 and 21% of the variance, respectively. Change in whole-body norepinephrine spillover was predicted by change in abdominal fat

**Table 2**

|                                   | Control | WL     | WL+EX  | Time × group interaction (\( P \)) |
|-----------------------------------|---------|--------|--------|----------------------------------|
| \( \text{VO}_{2\max} \) (ml • FFM\(^{-1}\) • min\(^{-1}\)) |          |        |        |                                  |
| Baseline                          | 29.3 ± 1.4 | 27.1 ± 1.3 | 29.1 ± 1.4 |                                  |
| Final                             | 27.6 ± 1.5 | 26.8 ± 1.6 | 34.2 ± 1.4§||                                  |
| Change                            | −1.8 ± 1.0 | −0.3 ± 1.0 | 5.1 ± 1.1§|| <0.001 |
| Maximum workload (W)              |          |        |        |                                  |
| Baseline                          | 169 ± 9  | 155 ± 9 | 163 ± 10 |                                  |
| Final                             | 161 ± 10 | 148 ± 9 | 201 ± 12‡||                                  |
| Change                            | −7 ± 4   | −7 ± 5  | 38 ± 4§|| <0.001 |
| Heart rate (bpm)                  |          |        |        |                                  |
| Baseline                          | 62 ± 2   | 63 ± 2  | 61 ± 2  |                                  |
| Final                             | 63 ± 2   | 61 ± 3* | 57 ± 2‡ |                                  |
| Change                            | 1 ± 1    | −2 ± 2  | −5 ± 1† |                                  |
| Systolic blood pressure (mmHg)    |          |        |        |                                  |
| Baseline                          | 136 ± 4  | 134 ± 4 | 131 ± 3 |                                  |
| Final                             | 133 ± 4  | 124 ± 4‡ | 121 ± 4‡ |                                  |
| Change                            | −2 ± 3   | −10 ± 2 | −10 ± 2 | 0.035                            |
| Diastolic blood pressure (mmHg)   |          |        |        |                                  |
| Baseline                          | 75 ± 2   | 76 ± 2  | 76 ± 2  |                                  |
| Final                             | 75 ± 2   | 73 ± 2* | 72 ± 2‡ |                                  |
| Change                            | 0 ± 1    | −3 ± 1  | −4 ± 1  | 0.222                            |

Data are means ± SE. Baseline values did not differ between groups for any parameter. \(* P < 0.05\), \(† P < 0.01\), and \(‡ P < 0.001\) vs. baseline; \(§ P < 0.05\) vs. WL group; \(|| P < 0.01\) vs. control group. Blood pressure and heart rate represent the average of five supine readings measured by Dinamap monitor. WL, weight loss by caloric restriction; WL+EX, weight loss by caloric restriction and aerobic exercise.
mass ($P = 0.02$) in women, which explained 36% of the variance.

**DISCUSSION**

The main finding of this study is that incorporation of regular, moderate-intensity aerobic exercise training during a dietary weight loss program does not confer additional benefits on resting sympathetic neural activity, compared with weight loss alone, in middle-aged subjects with MetS obesity. Body weight reduction of 8–9% was accompanied by a 22% reduction in whole-body norepinephrine spillover and comparable attenuation of MSNA in both lifestyle groups. Similarly, we identified no further enhancement of exercise training on MetS components (blood pressure, fasting plasma glucose, triglyceride, and HDL cholesterol levels or insulin sensitivity), despite a 19% increase in fitness and a significantly greater reduction in central adiposity in the WL+EX group. However, com-

| TABLE 3 | Metabolic responses by treatment group |
|---------|--------------------------------------|
|         | Control | WL   | WL+EX | Time × group interaction (P) |
| n       | 19      | 20   | 20    |                          |
| Fasting glucose (mmol/l) |          |      |       |                          |
| Baseline | 5.5 ± 0.1 | 5.7 ± 0.2 | 5.6 ± 0.1 |                          |
| Final   | 5.3 ± 0.1 | 5.1 ± 0.1† | 5.0 ± 0.1‡ |                          |
| Change  | -0.2 ± 0.1 | -0.6 ± 0.2§ | -0.6 ± 0.1§ | 0.022 |
| Fasting insulin (mU/l) |          |      |       |                          |
| Baseline | 15.8 ± 1.0 | 18.3 ± 1.1 | 15.8 ± 1.3 |                          |
| Final   | 17.8 ± 2.0 | 12.9 ± 1.0‡§ | 12.8 ± 1.2‡§ |                          |
| Change  | 2.1 ± 1.3 | -5.4 ± 1.2§ | -2.9 ± 0.8§ | <0.001 |
| HOMA-IR |          |      |       |                          |
| Baseline | 4.10 ± 0.31 | 4.91 ± 0.31 | 4.09 ± 0.38 |                          |
| Final   | 4.60 ± 0.56 | 3.25 ± 0.29‡§ | 3.20 ± 0.32‡§ |                          |
| Change  | 0.50 ± 0.34 | -1.66 ± 0.32§ | -0.89 ± 0.23§ | <0.001 |
| Insulin AUC0-120 (mU · 1⁻¹ · min⁻¹) |          |      |       |                          |
| Baseline | 9,541 ± 807 | 10,250 ± 1,038 | 9,382 ± 940 |                          |
| Final   | 9,640 ± 603 | 7,851 ± 902‡ | 7,343 ± 870‡ |                          |
| Change  | 99 ± 444 | -2,340 ± 819§ | -2,030 ± 606§ | 0.024 |
| ISI     |          |      |       |                          |
| Baseline | 2.36 ± 0.17 | 2.13 ± 0.15 | 2.74 ± 0.29 |                          |
| Final   | 2.33 ± 0.18 | 3.13 ± 0.33‡ | 3.85 ± 0.59‡§ |                          |
| Change  | -0.04 ± 0.13 | 1.00 ± 0.27§ | 1.10 ± 0.42§ | 0.001 |
| HDL cholesterol (mmol/l) |          |      |       |                          |
| Baseline | 1.21 ± 0.06 | 1.19 ± 0.05 | 1.23 ± 0.07 |                          |
| Final   | 1.18 ± 0.06 | 1.12 ± 0.05* | 1.19 ± 0.06* |                          |
| Change  | -0.02 ± 0.03 | -0.07 ± 0.03 | -0.09 ± 0.04 | 0.394 |
| Triglycerides (mmol/l) |          |      |       |                          |
| Baseline | 2.1 ± 0.3 | 1.8 ± 0.3 | 2.0 ± 0.2 |                          |
| Final   | 2.0 ± 0.3 | 1.3 ± 0.2‡§ | 1.4 ± 0.2‡§ |                          |
| Change  | -0.1 ± 0.2 | -0.5 ± 0.2§ | -0.7 ± 0.2§ | 0.048 |
| Fasting leptin (ng/ml) |          |      |       |                          |
| Baseline | 13.3 ± 1.8 | 17.8 ± 3.7 | 15.3 ± 3.2 |                          |
| Final   | 15.3 ± 2.7 | 10.3 ± 2.4‡ | 9.5 ± 2.3‡§ |                          |
| Change  | 2.0 ± 1.2 | -7.5 ± 1.8§ | -5.8 ± 1.5§ | <0.001 |
| hs-CRP (mg/l) |          |      |       |                          |
| Baseline | 3.2 ± 0.5 | 2.4 ± 0.4 | 2.7 ± 0.4 |                          |
| Final   | 3.2 ± 0.5 | 2.3 ± 0.4 | 1.8 ± 0.3†§ |                          |
| Change  | 0.0 ± 0.4 | -0.2 ± 0.2 | -0.9 ± 0.3§ | 0.035 |
| Urinary sodium (mmol/day) |          |      |       |                          |
| Baseline | 189 ± 21 | 145 ± 16 | 147 ± 16 |                          |
| Final   | 143 ± 10 | 108 ± 10* | 125 ± 11 |                          |
| Change  | -37 ± 18 | -37 ± 10 | -22 ± 16 | 0.622 |
| RMR (cal/24 h) |          |      |       |                          |
| Baseline | 1,704 ± 92 | 1,651 ± 106 | 1,585 ± 130 |                          |
| Final   | 1,646 ± 98 | 1,515 ± 76 | 1,528 ± 89 |                          |
| Change  | -57 ± 86 | -136 ± 78 | -57 ± 75 | 0.719 |
| RMR (cal · 24 h⁻¹ · FFM⁻¹) |          |      |       |                          |
| Baseline | 28.1 ± 1.0 | 29.3 ± 1.5 | 27.8 ± 1.1 |                          |
| Final   | 27.2 ± 1.0 | 27.9 ± 1.3 | 27.9 ± 1.3 |                          |
| Change  | -0.9 ± 1.3 | -1.4 ± 1.5 | 0.1 ± 1.2 | 0.674 |

Data are means ± SE. Baseline values did not differ between groups for any parameter. *P < 0.05, †P < 0.01, and ‡P < 0.001 vs. baseline; §P < 0.05 vs. control group. HOMA-IR, homeostasis model assessment insulin resistance index; ISI, whole-body Matsuda (32) insulin sensitivity index; RMR, resting metabolic rate.
bined exercise and weight loss was associated with a reduction of plasma hs-CRP concentrations that was not observed in the WL group.

Our findings are in agreement with those of Trombetta et al. (23), who conducted the only other comparable study in premenopausal obese women (albeit using non-adherent participants as control subjects) and observed similar reductions in resting MSNA after 4 months hypocaloric diet or hypocaloric diet and exercise training. Our metabolic results also concur with those of the CALERIE study, which identified no incremental benefit of weight loss through increased energy expenditure via exercise as opposed to weight loss by hypocaloric diet alone, on insulin action and coronary heart disease risk factors, when caloric deficit was matched in the two treatment groups (33,34). On the other hand, the Oslo Diet and Heart Study showed that 1-year intervention with combined diet and exercise was more effective than diet alone in the treatment of the MetS (17). It is likely that a combination of factors, including weight loss, negative energy balance, dietary composition, metabolic changes, and increased fitness in the WL + EX group, contributed to the observed sympathoinhibition after lifestyle intervention in the present study.

Considerable evidence exists that dietary-induced reductions in body weight are sympathoinhibitory: reductions in whole-body norepinephrine spillover (5), MSNA (5,23,35), and an increase in the parasympathetic indexes of heart rate variability (36) have previously been reported. Similarly, exercise intervention alone, using the same bicycle riding protocol as in the present study, has been shown to lower whole-body norepinephrine spillover.
by 24% and renal norepinephrine spillover by 41% in healthy young men independent of changes in body weight (19). It has been hypothesized that changes in central sympathetic outflow associated with body weight modification or increased fitness may have a reflex origin (35). The cardiac baroreflex is a compound reflex, where ~70% of both vagal and sympathetic components of heart rate range are mediated by the arterial baroreceptors and ~30% by cardiopulmonary baroreceptors. Both weight loss (5,35,37) and exercise training (38) are known to potentiate cardiovagal baroreflex sensitivity and the baroreceptor-sympathetic reflex (18,35); however, the present study is the first to examine their combined effects. Our results show no additive effect of exercise and hypocaloric diet, beyond that attained by hypocaloric diet alone. The results do, however, emphasize that weight loss is a highly effective strategy to improve baroreflex function, as spontaneous cardiac baroreflex sensitivity increased by ~50% in both lifestyle groups. Potential contributing mechanisms include increased arterial distensibility or improved neural transduction of barosensory vessel stretch into vagal outflow (39).

Sympathoinhibition after lifestyle intervention correlated positively with change in anthropometric variables in the present study. Change in waist-to-hip ratio and abdominal fat mass were most strongly associated with reduction in whole-body norepinephrine spillover, whereas changes in body weight, total body, and trunk fat masses and plasma leptin concentration were the strongest predictors of change in MSNA. The subcutaneous fat depot is the major source of leptin in humans, owing to the combination of a mass effect and a higher secretion rate in the subcutaneous than visceral adipose region (40). Experimental evidence in obese rodents supports the notion of selective leptin resistance in obesity, with preservation of leptin-dependent sympathoexcitation, but resistance to its anorexigenic effects (41). Although no definitive leptin administration studies have been performed in humans to characterize its effect on SNS activity, both the present study and an earlier weight loss trial performed by our group (5) suggest that reduction in plasma leptin is a significant independent predictor of sympathoinhibition after lifestyle intervention. Improvement in insulin resistance as indicated by decreased fasting insulin concentration and increased whole-body insulin sensitivity index also correlated with change in MSNA and support the notion that hyperinsulinemia enhances central sympathetic outflow (42). Changes in electrolyte status that coincide with energy restriction can modulate the response of the SNS. In particular, sodium depletion to ≤80 mmol/day has been shown to override the suppressive effect of energy restriction and instead trigger sympathetic activation and baroreflex impairment (43). In the present study, we chose not to supplement with sodium, as we felt this was more representative of weight loss in the community at large. Average 24-h urinary sodium excretion decreased modestly to levels commensurate (at week 12) with intermediate sodium intake in the DASH-Sodium trial (44). SNS activation would not be expected at this level of sodium intake; however, some contribution to sympathoinhibition versus baseline intake cannot be ruled out. Consumption of the DASH dietary pattern, which is rich in potassium and magnesium and reduced in total and saturated fat, may have also contributed to the observed reductions in blood pressure in the present study. Overall, however, absolute potassium intake did not change in our study, because of relatively high baseline consumption and use of the DASH diet at hypocaloric levels.

In our study, both WL and WL+EX produced comparable changes in metabolic risk factors, which were in the direction associated with reduced coronary heart disease risk. One exception was the change in plasma HDL cholesterol, which decreased significantly and by similar magnitude in both lifestyle groups. The impact of weight loss on lipids depends on a number of factors including energy balance, dietary composition, and concomitant exercise level (45). Using the same moderate-intensity exercise protocol, Reid et al. (46) demonstrated a significant increase in HDL cholesterol; however, this was diminished when exercise was prescribed together with weight loss. The relative reduction in total and saturated fat intake from baseline may have contributed to the decline in HDL cholesterol in our study (45). Change in HDL cholesterol correlated inversely with change in sympathetic activity, which likely reflects favorable alterations in HDL metabolism with loss of visceral fat mass, since change in HDL also related inversely to change in abdominal fat. It is also possible that reduction in central sympathetic outflow per se may have increased levels of HDL by increasing blood flow to peripheral vascular beds, thereby enhancing lipoprotein lipase activity (47). In our study, hs-CRP improved only in the WL+EX group, which was unexpected in light of previous work, including our own, which consistently shows that levels of this acute-phase reactant decrease after dietary weight loss (48).

The strengths of the present study are its randomized controlled design, which accounted for the effects of familiarization on sympathetic measurements; the use of both norepinephrine kinetics methodology and direct measurement of postganglionic MSNA to quantify sympathetic neural drive; and the close individualized supervision of each participant. Our study also has some limitations. First, only a subset of subjects had paired MSNA data and hence the sample size precludes demonstration of differences smaller than 30% between groups. Second, exercise training has many different facets, including frequency,

### TABLE 4

| Univariate correlates with change in muscle sympathetic nervous activity burst incidence (bursts/100 heart beats) | Whole group (n = 31) | Men (n = 18) | Women (n = 13) |
|----------------------------------------------------------|----------------------|-------------|--------------|
| ΔWeight (kg)                                              | 0.38 0.04            | 0.51 0.03   | 0.37 0.21    |
| ΔBMI (kg/m²)                                              | 0.39 0.03            | 0.51 0.03   | 0.34 0.26    |
| ΔTotal body fat mass (kg)                                 | 0.40 0.03            | 0.49 0.04   | 0.52 0.07    |
| ΔAbdominal fat L1–L4 (kg)                                 | 0.43 0.08            |             |              |
| ΔTrunk fat mass (kg)                                      | 0.33 0.07            | 0.48 0.04   |              |
| ΔFasting insulin (mU/l)                                   | 0.39 0.03            | 0.41 0.09   |              |
| ΔFasting glucose (mmol/l)                                 | 0.56 0.02            |             |              |
| ΔLog ISI                                                 | −0.31 0.097          | −0.50 0.04  |              |
| ΔHOMA-IR                                                 | 0.44 0.07            |             |              |
| ΔHDL cholesterol (mmol/l)                                 | −0.54 0.02           |             |              |
| Log Δleptin (ng/ml)                                       | 0.46 0.01            | 0.62 0.02   |              |

Whole-group data represent pooled correlates of WL and WL+EX groups.
duration, intensity, and exercise type. Our exercise protocol was based on moderate-intensity aerobic training on alternate days over a 12-week period, and thus further studies are required to examine whether higher intensity or frequency training or the inclusion of resistance exercise has additional benefits on neuroendocrine function. For instance moderate-intensity exercise training 7 days per week has been associated with greater reduction in norepinephrine spillover than the same protocol 3 days per week (49,19). Resistance exercise training improves postexercise heart rate recovery and heart rate variability, reflecting improved cardiac vagal activity (50), but there is a paucity of data to date using robust measurements of sympathetic activity in this setting.

In conclusion, this study provides evidence that both hypocaloric diet and hypocaloric diet with exercise training elicit significant improvements in resting sympathetic neural drive and MetS components. The results suggest that weight loss, and in particular abdominal fat loss, is the prime mover in sympathetic neural adaptation to a hypocaloric diet. These findings support the adoption of lifestyle changes for the prevention of cardiovascular sequelae of obesity.

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