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Weight loss loses neurovascular and muscle metaboreflex control in obesity

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There is accumulated evidence that obesity is positively correlated with the levels of muscle sympathetic nerve activity (MSNA), blood pressure, and forearm vascular resistance and is negatively correlated with the levels of forearm blood flow (22, 24). It seems that part of these hemodynamic changes are mediated by autonomic alterations. Obese individuals have baroreflex dysfunction (8), sleep apnea (17), and chemoreflex hyper-sensitivity during eucapnic conditions (16).

During static exercise, several reflexes are activated, leading to an increase in sympathetic nerve activity. First, central command mediates an immediate increase in sympathetic vasoconstrictor activity. Second, “mechanoreceptors” stimulated by muscle contraction contribute to the reflex increases in the sympathetic nerve activity (12, 28). Third, when ischemic metabolites have accumulated in the exercising muscle bed, chemosensitive afferent nerve fibers called “muscle metaboreceptors” increase sympathetic nerve activity directed to both nonexercising and exercising muscle (15). This “muscle metaboreflex” is the principal reflex system that activates sympathetic nerve activity during static exercise (15, 20). We have recently demonstrated that obese normotensive women have higher MSNA, blood pressure, and forearm vascular resistance levels during central command/mechanoreceptors, and metaboreceptors activation compared with lean normotensive women (18). Also, muscle metaboreflex control of MSNA is blunted in obesity (18). However, the impact of weight loss on the neurovascular control and metaboreflex control is unknown.

Hypocaloric diet and/or exercise training have been recommended as a nonpharmacological treatment to obese individuals (30). Hypocaloric diet has clearly demonstrated that an energy deficit reduces body weight in obese individuals (14). Also, exercise training, given its enhancement in caloric expenditure, is thought to have a synergistic effect on weight loss during a hypocaloric diet in obese individuals. In addition, exercise training provokes beneficial cardiovascular (7) and autonomic (11) adaptations.

The goals of the present investigation were three: 1) to test the hypothesis that weight loss in obese indi-
vials would attenuate MSNA and improve muscle blood flow during mild or moderate exercise, when central command/mechanoreceptors and metaboreceptors are selectively activated; 2) to test the hypothesis that weight loss by a hypocaloric diet associated with exercise training would provoke a greater improvement in neurovascular control at rest and during mild and moderate exercise than hypocaloric diet alone; and 3) to test the hypothesis that weight loss by a hypocaloric diet or a hypocaloric diet associated with exercise training would improve muscle metaboreflex control in obese individuals.

MATERIALS AND METHODS

Study Population

A total of 59 potential normotensive obese women, recruited from the Obesity Ambulatory of the Endocrinology Department, University of São Paulo Medical School, was randomly divided into the hypocaloric diet (n = 29) group and hypocaloric diet associated with exercise training (n = 30) group. Ten of those obese women did not want to adhere to a hypocaloric diet or hypocaloric diet plus exercise training, although they agreed to be studied before and after 4 mo. Thus our final sampling constituted three subgroups: 1) hypocaloric diet (n = 24, age: 32.2 ± 1.4 yr), 2) hypocaloric diet associated with exercise training (n = 25, age: 32.3 ± 1.3 yr), and 3) nonadherent to any of the two interventions (n = 10, age: 34.9 ± 2.1 yr). All individuals were taking no medication and had no evidence of cardiovascular disease at the time of the study. They had normal blood pressure levels according to the Sixth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (10). The study protocol was approved by the Human Subject Protection Committees of the Heart Institute (InCor) and the Clinical Hospital, University of São Paulo Medical School, and written consent was given by each subject that participated in the study.

Measurements and Procedures

Muscle sympathetic nerve activity. MSNA was directly measured from the peroneal nerve by using the technique of microneurography, as previously described (18). MSNA was analyzed in bursts per minute (bursts/min) or bursts per 100 heartbeats (bursts/100 HB).

Forearm blood flow. Forearm blood flow was measured by venous occlusion plethysmography, as previously described (18). Forearm vascular conductance (units) was calculated as (forearm blood flow/mean arterial pressure) × 100 and was expressed in “units” (100 ml (dl of tissue)−1.min−1.mmHg−1).

Miscellaneous measurements. Blood pressure was monitored noninvasively from an automatic blood pressure cuff (Dixtal, DX 2710; Brazil, Manaus). Heart rate was monitored continuously through lead II of ECG.

Handgrip exercise. After the maximal voluntary contraction (MVC, average of three trials) was obtained, handgrip isometric exercise was performed with the dominant arm with the use of a handgrip dynamometer.

Leptin and insulin resistance. Plasmatic leptin levels were determined by immunofluorimetric assay. Plasmatic insulin levels were determined by radioimmunoassay. Insulin resistance was estimated by homeostasis model assessment (HOMA score) and calculated with the formula: fasting serum insulin (µU/ml) × fasting plasma glucose (mmol/l)/22.5 (13). In addition, insulin resistance was estimated by a mathematical model for the determination of total insulin (AUC

Body composition determination. Whole body dual-energy X-ray absorptiometry measurements were made with a HOLOGIC QDR-2000 densitometer (3). 

Dietary protocol. The basal energy requirements were estimated using the Food and Agriculture Organization/World Health Organization/United Nations University (FAO/WHO/UNU) (31) equation multiplied by a factor of 1.3. During 16 wk, energy intake was reduced 600 kcal/day. The hypocaloric diet consisted of 50–70% carbohydrates, 10–15% protein, and 15–30% fat. On alternate weeks every patient visited the clinical nutritionist for a regular checkup. On each visit, the subjects were weighed and encouraged to record their intake to ensure adherence to the dietary protocol. The expected weight loss was about 5–10% of the initial weight.

Exercise training. Exercise training consisted of three 60-min exercise sessions per week during 4 mo. Each exercise session consisted of 30–40 min of aerobic cycling exercise and 20 min of exercise resistance and flexibility. The exercise intensity was established by heart rate levels that corresponded to an anaerobic threshold up to 10% below the respiratory compensation point obtained in a progressive cardiopulmonary exercise test. The anaerobic threshold was determined to occur at the point where there was a loss of linearity between oxygen uptake and carbon dioxide production or at the point where the ventilatory equivalent for oxygen or end-tidal oxygen partial pressure curves reached their respective minimum values and began to rise during the progressive exercise test. The respiratory compensation point was determined as the point where the ventilatory equivalent for carbon dioxide was lowest before a systematic increase or where end-tidal carbon dioxide partial pressure reached a maximum value and began to decrease. The peak oxygen uptake was considered at the end of the bicycle cardiopulmonary exercise test (ramp protocol with 10- to 15-W increments every minute up to exhaustion) when the subject no longer maintained the bicycle velocity at 60 rpm.

Experimental Protocol

Protocol 1: Mild static handgrip exercise (10% MVC).

The purpose of this study was to determine the impact of weight loss by a hypocaloric diet or a hypocaloric diet associated with exercise training on the magnitude of change in MSNA, mean blood pressure, forearm blood flow, forearm vascular conductance, and heart rate at rest and during mild handgrip exercise (10% MVC), with activation of central command and mechanoreceptors in obese women. Initially, the arm was positioned for venous occlusion plethysmography. After the leg was positioned for microneurography, an adequate nerve recording site was obtained. Baseline MSNA, forearm blood flow, mean blood pressure, and heart rate were recorded for 3 min. Handgrip isometric exercise was performed for 3 min at 10% of MVC. MSNA and heart rate were recorded continuously during the handgrip exercise. Mean blood pressure was measured every minute, and forearm blood flow was measured each 15 s.

Protocol 2: Moderate static handgrip exercise (30% MVC).

The purpose of this study was to determine the impact of weight loss by the hypocaloric diet or hypocaloric diet associated with exercise training on the magnitude of change in MSNA, mean blood pressure, forearm blood flow, forearm vascular conductance, and heart rate during moderate handgrip exercise (30% of MVC) with activation of central command, mechanoreceptors, and metaboreceptors in obese
physical measurements, vascular measurements, systemic measurements, neural measurements, 0.05.

mean blood pressure; HR, heart rate; FBF, forearm blood flow.

or moderate exercise. When significance was found, Scheffe’s post hoc comparison was performed. Probability values of \( \leq 0.05 \) were considered statistically significant.

RESULTS

Baseline Measurements

Before interventions, there was no difference in physical characteristics among the three groups studied (Table 1). In addition, the three groups showed similar neural, systemic, and vascular levels (Table 1).

Hypocaloric diet and hypocaloric diet associated with exercise training significantly reduced body weight and body mass index (Table 1). Hypocaloric diet associated with exercise training significantly decreased fat body mass but caused no change in lean body mass (Table 1). However, hypocaloric diet alone caused both a significant decrease in fat body mass and a significant reduction in lean body mass (Table 1). In the nonadherent group, physical characteristics were unchanged after 4 mo of followup (Table 1).

MSNA burst frequency (bursts/min) and pulse synchronous sympathetic activity (bursts/100 HB) were significantly reduced after the hypocaloric diet and hypocaloric diet associated with exercise training (Table 1). Further analysis showed that the absolute

Table 1. Physical, neural, systemic, and vascular measurements in obese women submitted to hypocaloric diet or hypocaloric diet associated with exercise training and in obese women with nonadherence to any of these two interventions

<table>
<thead>
<tr>
<th>Physical measurements</th>
<th>Diet Pre</th>
<th>Diet Post</th>
<th>Diet and Training Pre</th>
<th>Diet and Training Post</th>
<th>Nonadherent Pre</th>
<th>Nonadherent Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>87.8 ± 1.9</td>
<td>78.9 ± 1.8*</td>
<td>86.0 ± 2.0</td>
<td>76.9 ± 1.8*</td>
<td>86.0 ± 2.8</td>
<td>84.6 ± 3.0</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>34.7 ± 0.5</td>
<td>31.2 ± 0.6*</td>
<td>32.9 ± 0.4</td>
<td>29.5 ± 0.5*</td>
<td>33.1 ± 0.8</td>
<td>32.5 ± 0.8</td>
</tr>
<tr>
<td>Fat body mass, kg</td>
<td>36.5 ± 2.2</td>
<td>31.8 ± 1.8*</td>
<td>38.2 ± 1.7</td>
<td>31.4 ± 1.3*</td>
<td>37.2 ± 1.7</td>
<td>34.0 ± 0.8</td>
</tr>
<tr>
<td>Lean body mass, kg</td>
<td>44.6 ± 1.5</td>
<td>40.4 ± 1.2*</td>
<td>41.8 ± 1.4</td>
<td>40.6 ± 1.4</td>
<td>42.7 ± 1.3</td>
<td>43.2 ± 1.8</td>
</tr>
<tr>
<td>Maximal voluntary contraction, kg</td>
<td>27.4 ± 1.1</td>
<td>29.3 ± 1.3</td>
<td>29.6 ± 1.2</td>
<td>29.4 ± 1.2</td>
<td>28.1 ± 1.7</td>
<td>30.3 ± 1.5</td>
</tr>
</tbody>
</table>

Values are means ± SE. Pre, preintervention; Post, postintervention; MSNA, muscle sympathetic nerve activity; HB, heartbeats; MBP, mean blood pressure; HR, heart rate; FBF, forearm blood flow; FVC, forearm vascular conductance. *Different from preintervention, \( P < 0.05 \).

Fig. 1. Absolute changes in resting muscle sympathetic nerve activity (MSNA) in obese women submitted to hypocaloric diet or hypocaloric diet associated with exercise training and in obese women with nonadherence to any of these two interventions. Reduction in MSNA burst frequency was significantly greater in the hypocaloric diet or hypocaloric diet associated with exercise training groups than in the nonadherent group (A). Reduction in pulse synchronous sympathetic activity tended to be greater in the hypocaloric diet or hypocaloric diet associated with exercise training groups than in the nonadherent group (B). HB, heartbeats. *Different from nonadherent group, \( P < 0.05 \).
change in MSNA burst frequency (bursts/min, Fig. 1A) or pulse synchronous sympathetic activity (bursts/100 HB, Fig. 1B) after the two interventions were greater compared with the obese nonadherent group. Mean blood pressure and heart rate tended to reduce in the groups submitted to the hypocaloric diet or hypocaloric diet associated with exercise training (Table 1). Forearm blood flow had a tendency to increase in the hypocaloric diet associated with the exercise training group. In the hypocaloric diet and nonadherent groups, however, forearm blood flow was unchanged (Table 1). Of interest was the fact that forearm vascular conductance (calculated by values of forearm blood flow and mean arterial pressure from Table 1) was significantly increased by the hypocaloric diet associated with exercise training (Table 1). The analysis of the absolute changes showed that, in fact, the increase in forearm vascular conductance in the exercise training group was greater than in the hypocaloric diet group and nonadherent group (Fig. 2).

Before interventions, there was no difference in leptin, glucose, and insulin levels among the three groups studied (Table 2). Both the hypocaloric diet and hypocaloric diet associated with exercise training significantly decreased the leptin levels (Table 2). After interventions, glucose levels were unchanged in the hypocaloric diet and hypocaloric diet associated with exercise training groups. Insulin levels were lower in the hypocaloric diet group but not in the hypocaloric diet associated with exercise training, in which these levels remained unchanged. The hypocaloric diet significantly decreased insulin resistance estimated by the HOMA score and AUC_{glucose}. In addition, the hypocaloric diet caused no change in AUC_{insulin} and in the AUC_{glucose-to-AUC_{insulin}} ratio (Table 2). In contrast, the hypocaloric diet associated with exercise training significantly decreased insulin resistance estimated by the HOMA score, AUC_{insulin}, and AUC_{glucose-to-AUC_{insulin}} ratio (Table 2). In the nonadherent group, no changes in leptin levels, glucose levels, and insulin resistance were found.

The hypocaloric diet caused no change in peak oxygen uptake in obese women, whereas the hypocaloric diet associated with exercise training significantly increased peak oxygen uptake in obese women (Table 2).

**Mild Handgrip Exercise**

The data of MSNA, mean blood pressure, heart rate, and forearm blood flow are shown in Table 3. MSNA slightly increased during mild exercise in all three groups studied. In the groups submitted to the hypocaloric diet or hypocaloric diet associated with exercise training, the absolute levels of MSNA burst frequency were significantly lower throughout mild exercise compared with the levels achieved before interventions. The magnitude of responses of MSNA burst frequency throughout mild exercise, analyzed by the interaction of phase effect (pre vs. post) and time effect (minutes of exercise), showed no significant difference between pre- and posthypocaloric diet or pre- and posthypocaloric diet associated with exercise training.

Similar results were found in the pulse synchronous sympathetic activity. The absolute levels of pulse synchronous sympathetic activity throughout mild exercise were lower after the hypocaloric diet or hypocaloric diet associated with exercise training than before the hypocaloric diet or hypocaloric diet associated with exercise training (Fig. 3A), although no change in the magnitude of response of pulse syncro-

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**Table 2. Metabolic measurements and insulin resistance estimated by HOMA and total area under the curve of insulin and glucose levels during oral glucose tolerance test in obese women submitted to hypocaloric diet or hypocaloric diet associated with exercise training and in obese women with nonadherence to any of these two interventions**

<table>
<thead>
<tr>
<th></th>
<th>Diet</th>
<th>Diet and Training</th>
<th>Nonadherent</th>
<th>Diet</th>
<th>Diet and Training</th>
<th>Nonadherent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin, ng/ml</td>
<td>48.5 ± 2.5</td>
<td>35.0 ± 2.2*</td>
<td>40.5 ± 5.0</td>
<td>33.8 ± 4.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>87.3 ± 2.4</td>
<td>81.2 ± 1.8</td>
<td>83.5 ± 3.6</td>
<td>80.4 ± 1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin, μU/ml</td>
<td>16.5 ± 2.2</td>
<td>10.5 ± 1.0*</td>
<td>12.6 ± 1.9</td>
<td>8.8 ± 1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA score</td>
<td>3.7 ± 0.5</td>
<td>2.2 ± 0.2*</td>
<td>2.5 ± 0.3</td>
<td>1.7 ± 0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC_{glucose}, mg dl⁻¹·120 min⁻¹</td>
<td>17,364 ± 619</td>
<td>15,158 ± 575*</td>
<td>15,948 ± 1,046</td>
<td>13,663 ± 872</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC_{insulin}, μU·ml⁻¹·120 min⁻¹</td>
<td>11,211 ± 1,450</td>
<td>7,833 ± 1,000</td>
<td>9,788 ± 2,538</td>
<td>6,494 ± 1,401</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC_{glucose}/AUC_{insulin}</td>
<td>1.99 ± 0.25</td>
<td>2.44 ± 0.29</td>
<td>2.36 ± 0.51</td>
<td>2.57 ± 0.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V_{O2} peak, ml·kg⁻¹·min⁻¹</td>
<td>18.0 ± 0.7</td>
<td>18.7 ± 0.6</td>
<td>18.3 ± 1.0</td>
<td>18.8 ± 1.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. HOMA, homeostasis model assessment; TAUC, total area under the curve (AUC); V_{O2} peak, peak oxygen uptake.

*Different from preintervention, P < 0.05.
Table 3. Neural, systemic, and vascular measurements at rest and during mild or moderate handgrip exercise in obese women submitted to hypocaloric diet or hypocaloric diet associated with exercise training and in obese women with nonadherence to any of these two interventions

<table>
<thead>
<tr>
<th></th>
<th>Mild Handgrip Exercise (10% of MVC)</th>
<th>Moderate Handgrip Exercise (30% of MVC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest 1 min 2 min 3 min</td>
<td>Rest 1 min 2 min 3 min</td>
</tr>
<tr>
<td><strong>Neural measurements</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSNA, bursts/min D</td>
<td>** 37 ± 1** 39 ± 1** 40 ± 1** 40 ± 1**</td>
<td>** 38 ± 1** 45 ± 1** 47 ± 2** 50 ± 2**</td>
</tr>
<tr>
<td></td>
<td>** 29 ± 1†** 30 ± 1† 30 ± 1† 30 ± 1†</td>
<td>** 29 ± 1†** 34 ± 1†† 36 ± 1†† 38 ± 1††</td>
</tr>
<tr>
<td>D + T Pre</td>
<td>** 37 ± 1** 39 ± 1 40 ± 1 41 ± 1*</td>
<td>** 36 ± 1** 42 ± 1* 44 ± 1* 46 ± 1*</td>
</tr>
<tr>
<td></td>
<td>** 29 ± 1†** 30 ± 1†† 31 ± 1†† 31 ± 1††</td>
<td>** 30 ± 1** 35 ± 1†† 37 ± 1†† 39 ± 1††</td>
</tr>
<tr>
<td>NA Pre</td>
<td>** 39 ± 2** 40 ± 1 40 ± 2 39 ± 1</td>
<td>** 37 ± 1** 43 ± 1 50 ± 3* 50 ± 3*</td>
</tr>
<tr>
<td>Post</td>
<td>** 36 ± 1** 38 ± 1 38 ± 1 40 ± 2</td>
<td>** 36 ± 1** 42 ± 1 45 ± 3* 47 ± 3*</td>
</tr>
<tr>
<td><strong>Systemic measurements</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBP, mmHg D</td>
<td>** 97 ± 2** 101 ± 2 102 ± 2* 104 ± 3**</td>
<td>** 98 ± 2** 102 ± 3 111 ± 3* 118 ± 3*</td>
</tr>
<tr>
<td></td>
<td>** 93 ± 1** 92 ± 1† 93 ± 2† 93 ± 1†</td>
<td>** 93 ± 1** 94 ± 1† 101 ± 1†† 106 ± 2††</td>
</tr>
<tr>
<td>D + T Pre</td>
<td>** 99 ± 2** 98 ± 2 101 ± 2 100 ± 2</td>
<td>** 96 ± 2** 102 ± 2 108 ± 3* 117 ± 4*</td>
</tr>
<tr>
<td></td>
<td>** 93 ± 2†** 94 ± 2 95 ± 2* 98 ± 2*</td>
<td>** 94 ± 2** 99 ± 2 105 ± 2* 111 ± 3*</td>
</tr>
<tr>
<td>NA Pre</td>
<td>** 98 ± 2** 100 ± 2 99 ± 2 101 ± 3</td>
<td>** 100 ± 2** 105 ± 2 110 ± 2 121 ± 4*</td>
</tr>
<tr>
<td>Post</td>
<td>** 97 ± 4** 99 ± 3 100 ± 3 103 ± 4*</td>
<td>** 98 ± 3** 106 ± 3 112 ± 5* 116 ± 5*</td>
</tr>
<tr>
<td>HR, beats/min D</td>
<td>** 71 ± 2** 73 ± 2 74 ± 2 75 ± 2</td>
<td>** 73 ± 2** 80 ± 2* 83 ± 2* 86 ± 3*</td>
</tr>
<tr>
<td></td>
<td>** 66 ± 2†** 68 ± 2† 68 ± 2† 69 ± 2†</td>
<td>** 67 ± 2†** 71 ± 2† 74 ± 2†† 78 ± 3††</td>
</tr>
<tr>
<td>D + T Pre</td>
<td>** 69 ± 1** 72 ± 2* 72 ± 2* 72 ± 2*</td>
<td>** 70 ± 2** 76 ± 2* 80 ± 3* 82 ± 3*</td>
</tr>
<tr>
<td></td>
<td>** 65 ± 2†** 67 ± 2† 67 ± 2† 68 ± 2††</td>
<td>** 66 ± 2** 72 ± 2* 77 ± 2* 79 ± 3*</td>
</tr>
<tr>
<td>NA Pre</td>
<td>** 68 ± 3** 69 ± 3 69 ± 3 69 ± 3</td>
<td>** 68 ± 4** 72 ± 3 75 ± 3 77 ± 3*</td>
</tr>
<tr>
<td>Post</td>
<td>** 67 ± 2** 67 ± 3 67 ± 2 70 ± 2</td>
<td>** 67 ± 3** 72 ± 3 77 ± 3* 78 ± 3*</td>
</tr>
<tr>
<td><strong>Vascular measurements</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBF, ml·min⁻¹·100 g⁻¹ D</td>
<td>** 1.99 ± 0.2** 2.11 ± 0.2 2.28 ± 0.2* 2.34 ± 0.2*</td>
<td>** 2.17 ± 0.2** 2.43 ± 0.2 2.63 ± 0.3 2.82 ± 0.3*</td>
</tr>
<tr>
<td></td>
<td>** 1.97 ± 0.1** 2.10 ± 0.2 2.23 ± 0.2* 2.31 ± 0.2*</td>
<td>** 2.05 ± 0.1** 2.29 ± 0.2 2.44 ± 0.2 2.50 ± 0.2*</td>
</tr>
<tr>
<td>D + T Pre</td>
<td>** 1.74 ± 0.1†** 1.86 ± 0.1 1.96 ± 0.1 2.02 ± 0.1*</td>
<td>** 1.85 ± 0.1** 2.06 ± 0.1 2.46 ± 0.2* 2.70 ± 0.2*</td>
</tr>
<tr>
<td></td>
<td>** 2.20 ± 0.1††** 2.41 ± 0.1† 2.44 ± 0.1* 2.60 ± 0.1††</td>
<td>** 2.21 ± 0.1** 2.96 ± 0.2†† 3.08 ± 0.2†† 3.32 ± 0.2††</td>
</tr>
<tr>
<td>NA Pre</td>
<td>** 1.72 ± 0.2** 1.75 ± 0.2 1.83 ± 0.2 1.93 ± 0.2</td>
<td>** 1.91 ± 0.2** 2.11 ± 0.2 1.95 ± 0.2 2.15 ± 0.3</td>
</tr>
<tr>
<td>Post</td>
<td>** 1.66 ± 0.2** 1.59 ± 0.1 1.74 ± 0.2 1.75 ± 0.2</td>
<td>** 1.76 ± 0.1** 1.93 ± 0.2 1.89 ± 0.2 2.05 ± 0.3</td>
</tr>
</tbody>
</table>

Values are means ± SE. D, hypocaloric diet group; D + T, hypocaloric diet associated with exercise training group; NA, nonadherent group. *Different from rest, $P < 0.05$; † different from preintervention, $P < 0.05$. 

Nonsymptomatic activity during exercise was found between pre- and postinterventions. In the nonadherent group, no change in MSNA burst frequency and pulse synchronous sympathetic activity throughout exercise was found between pre- and postinvestigation phases.

Mean blood pressure and heart rate slightly increased during mild exercise in all three groups studied. In the hypocaloric diet group or hypocaloric diet associated with exercise training group, the absolute levels of mean blood pressure and heart rate were significantly lower throughout mild exercise compared with the levels achieved before interventions. The magnitude of responses of mean blood pressure and heart rate during exercise was similar between the pre- and posthypocaloric diet or the pre- and posthypocaloric diet associated with exercise training. In the nonadherent group, no change in mean blood pressure and heart rate was found between the pre- and postinvestigation phases.

Forearm blood flow increased during mild exercise in all three groups studied. In the hypocaloric diet associated with the exercise training group, the absolute levels of forearm blood flow throughout mild exercise were significantly higher compared with the levels before interventions. In contrast, in the hypocaloric...
diet group, the absolute levels of forearm blood flow were unchanged during mild exercise. The hypocaloric diet associated with exercise training or hypocaloric diet alone had no effect on the magnitude of response of forearm blood flow during mild exercise. Similarly, after the hypocaloric diet associated with exercise training, the absolute levels of forearm vascular conductance (calculated by values of forearm blood flow and mean arterial pressure from Table 3) throughout mild exercise were significantly higher compared with the levels before interventions (Fig. 4A). The absolute levels of forearm vascular conductance during mild exercise were unchanged by the hypocaloric diet alone (Fig. 4A). Both the hypocaloric diet associated with exercise training or the hypocaloric diet alone had no effect on the magnitude of response of forearm vascular conductance during mild exercise. In the nonadherent group, no change in forearm blood flow and forearm vascular conductance during mild exercise was found between pre- and postinvestigation phases.

Moderate Handgrip Exercise

The data of MSNA, mean blood pressure, heart rate, and forearm blood flow during moderate exercise are shown in Table 3.

MSNA progressively and significantly increased during moderate exercise in all three groups studied. In the hypocaloric diet group or hypocaloric diet associated with exercise training group, the absolute levels of MSNA burst frequency were significantly lower throughout moderate exercise compared with the levels achieved before interventions. The magnitude of responses, analyzed by the interaction of phase effect and time effect, showed no significant difference between the pre- and posthypocaloric diet or the pre- and posthypocaloric diet associated with exercise training. Similar results were found in pulse synchronous sympathetic activity. The absolute levels of pulse synchronous sympathetic activity were lower throughout moderate exercise after the hypocaloric diet or hypocaloric diet associated with exercise training (Fig. 3B), although these interventions caused no change in the magnitude of response of pulse synchronous sympathetic activity. In the nonadherent group, no change in MSNA was found between pre- and postinvestigation phases.

Mean blood pressure progressively and significantly increased during moderate exercise in all three groups studied, consistent with moderate static handgrip exercise. In the hypocaloric diet group or hypocaloric diet associated with exercise training group, the absolute...
levels of mean blood pressure were lower throughout moderate exercise compared with the levels achieved before interventions. The magnitude of responses of mean blood pressure was similar between the pre- and posthypocaloric diet or pre- and posthypocaloric diet associated with exercise training. In the adherent group, no change in mean blood pressure was found between the pre- and postinvestigation phases.

Heart rate significantly increased during moderate exercise in all three groups studied. In the hypocaloric diet group or hypocaloric diet associated with exercise training group, the absolute levels of heart rate were lower throughout moderate exercise compared with the levels achieved before interventions. The magnitude of responses showed no significant difference between pre- and posthypocaloric diet or pre- and posthypocaloric diet associated with exercise training. In the obese nonadherent group, no change in heart rate was found between the pre- and postinvestigation phases.

Forearm blood flow increased during moderate exercise in all three groups studied. Of interest, in the hypocaloric diet associated with exercise training group, the magnitude of responses of forearm blood flow throughout exercise was significantly increased after the hypocaloric diet associated with exercise training. In contrast, the hypocaloric diet alone had no effect on the magnitude of responses of forearm blood flow throughout moderate exercise. Similar results were found in forearm vascular conductance. In the hypocaloric diet associated with the exercise training group, the magnitude of responses of forearm vascular conductance (calculated by values of forearm blood flow and mean arterial pressure from Table 3) throughout the exercise was significantly increased (Fig. 4B). In the hypocaloric diet group, however, the magnitude of response of the forearm vascular conductance throughout moderate exercise was similar between the pre- and postintervention. In the nonadherent group, forearm blood flow and forearm vascular conductance were unchanged when the pre- and postinvestigation phases were compared.

Posthandgrip Circulatory Arrest

Figure 5 depicts the individual data of MSNA during circulatory arrest in the hypocaloric diet group, the hypocaloric diet associated with exercise training group, and the obese nonadherent group. The levels of MSNA were maintained above baseline during posthandgrip circulatory arrest when the metaboreflex is isolated. Hypocaloric diet or hypocaloric diet associated with exercise training provoked a significant and similar increase in MSNA during posthandgrip circulatory arrest. These findings suggest an improvement in muscle metaboreflex control after weight loss. In the obese nonadherent group, no change in MSNA during circulatory arrest was found between the pre- and postinvestigation phases.

DISCUSSION

The novelty of the present study is the fact that weight loss by a hypocaloric diet or hypocaloric diet associated with exercise training improves muscle metaboreflex control of MSNA in obese women. In addition, MSNA levels during mild and moderate exercise are lower after body weight loss, despite the unchanged MSNA response. Exercise training associated with a hypocaloric diet remarkably increases forearm vascular conductance responses during moderate handgrip exercise in obese women.

We have previously demonstrated that muscle metaboreflex control of MSNA is blunted in normotensive obese women (18). The present study extends our knowledge to the fact that weight loss improves muscle metaboreflex control of MSNA in obesity, because MSNA levels during circulatory arrest were increased after body weight reduction by caloric restriction or caloric restriction associated with exercise training. Nevertheless, it could be argued that the greater response in muscle sympathetic nerve discharge during circulatory arrest was due to a decrease in MSNA levels after weight loss rather than an actual improvement in muscle metaboreflex control. There are, at least, two potential evidences against this argument. First, during a cold pressor test, when the sympathetic discharge is greatly increased, there was no difference in MSNA response between lean women and obese women (data not shown). Second, we have previously found that the response (delta change) in MSNA during handgrip exercise at 30% of MVC in obese women is preserved compared with lean women (18). Nevertheless, the actual mechanisms implicated in the im-

![Fig. 5. Individual responses of MSNA during circulatory arrest in obese women submitted to a hypocaloric diet or hypocaloric diet associated with exercise training and in obese women with nonadherence to any of these two interventions. During posthandgrip circulatory arrest, MSNA remained above baseline. Note that both hypocaloric diet or hypocaloric diet associated with exercise training significantly increased the responses of MSNA during posthandgrip circulatory arrest. In contrast, there was no change in MSNA in the nonadherent group.](https://ajpheart.physiology.org)
provement of muscle metaboreflex after weight loss is an open area for future investigations.

As hypothesized, body weight loss decreased MSNA levels during mild or moderate exercise in obese individuals. In addition, this decrease in MSNA seems to be centrally mediated. The pulse synchronous sympathetic activity (bursts/100 HB) was decreased after weight loss, which demonstrates that this sympathoinhibition is independent of the change in heart rate provoked by hypocaloric diet or hypocaloric diet associated with exercise training. It is possible that an improvement in baroreflex function may have something to do with the sympathoinhibition after weight loss. Previous studies (8, 23) have demonstrated that a hypocaloric diet increased the baroreflex control of MSNA in obese individuals.

A previous study (18) has demonstrated that forearm blood flow is decreased in obese women at rest and during mild and moderate exercise. In the present study, we found that weight loss by caloric restriction associated with exercise training, in contrast to weight loss by caloric restriction alone, improves the response of muscle vascular conductance during exercise in obese individuals. In humans, muscle vasodilatory response during exercise depends on the equilibrium between vasoconstrictor force mediated by α₁-adrenergic receptors (5, 21) and vasodilator force mediated by β₂-adrenergic receptors (5, 21) and local nitric oxide release (4). The similarity in MSNA reduction after caloric restriction diet and caloric restriction associated with the exercise training groups is consistent with the idea that the vasoconstrictor force is not implicated in the enhancement of forearm vascular conductance in the exercise-trained group. It seems more reasonable that exercise training has improved the nitric oxide release in obese individuals, in whom the endothelial dysfunction has been reported (9, 25). Alternatively, exercise training may have improved the vasodilatory response via β₂-adrenergic receptors, even though the actual role of these receptors in mediating the reflex vasodilatory response during exercise in obese individuals is unknown.

Another interesting finding is the attenuation in the tachycardia response during exercise after weight loss. In the present study, we did not assess directly cardiac sympathetic activity, but MSNA is highly correlated to cardiac norepinephrine spillover at rest. In addition, changes in MSNA and cardiac norepinephrine spillover during physiological maneuvers are similar (29). Thus we can suggest that the sympathoinhibition explains the lowered heart rate response during exercise after weight loss.

Despite the similar reduction in body weight, energy expenditure via exercise training associated with caloric restriction in contrast to caloric restriction alone, preserves lean body mass in obese individuals. In addition, exercise training and caloric restriction provoke greater reduction in body fatness (−17 vs. −12%) and, in consequence, greater reduction in leptin levels (−37 vs. −27%) than caloric restriction alone. This linkage between body fatness and leptin levels is demonstrated in the present study (r = 0.6, P < 0.05) as in another study (27). These results are consistent with the importance of the exercise training in the nonpharmacological treatment of human obesity.

Confirming previous findings (19), our results demonstrate that body weight loss in obese individuals improves insulin resistance. In addition, our findings suggest that exercise training exacerbates the improvement in insulin sensitivity during oral glucose tolerance test.

Limitations

Although the hypocaloric diet was well controlled on alternate weeks when every patient visited the clinical nutritionist to ensure adherence to the dietary protocol, it is possible that some patients did not precisely follow the established dietary protocol. Because our sampling included only women, we avoided confounding by gender, but at the same time, we reduced the generalization of our findings.

In summary, the present findings demonstrate that weight loss improves muscle metaboreflex control in obese women. The sympathoinhibition during exercise after weight loss is centrally mediated. Finally, in contrast to caloric restriction alone, exercise training associated with caloric restriction in obesity women increases the reflex-mediated muscle vascular conductance during moderate exercise.

DISCLOSURES

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REFERENCES


