Chronic Sympathetic Attenuation and Energy Metabolism in Autonomic Failure

Cyndya Shibao, Maciej S. Buchowski, Kong Y. Chen, Chang Yu, Italo Biaggioni

Abstract—The sympathetic nervous system regulates thermogenesis and energy homeostasis in humans. When activated it increases energy expenditure, particularly resting energy expenditure. Most human studies used acute infusion of β-blockers as a model to eliminate sympathetic stimulation and to examine the contribution of the sympathetic nervous system to energy metabolism and balance. Clinically, however, it is also important to assess the effect of chronic sympathetic attenuation on energy metabolism. In this context, we hypothesized that resting energy expenditure is decreased in patients with autonomic failure who, by definition, have low sympathetic tone. We measured 24-hour energy expenditure using whole-room indirect calorimeter in 10 adults with chronic autonomic failure (6 women; age, 64.9 ± 9.1 years; body mass index, 25.2 ± 4.4 kg/m²) and 15 sedentary healthy controls of similar age and body composition (8 women; age, 63.1 ± 4.0 years; body mass index, 24.4 ± 3.9 kg/m²). In 4 patients, we eliminated residual sympathetic activity with the ganglionic blocker trimethaphan. We found that, after adjusting for body composition, resting energy expenditure did not differ between patients with autonomic failure and healthy controls. However, resting energy expenditure significantly decreased when residual sympathetic activity was eliminated. Our findings suggest that sympathetic tonic support of resting energy expenditure is preserved, at least in part, in pathophysiological models of chronic sympathetic attenuation. (Hypertension. 2012;59:985-990.)

Key Words: autonomic failure ● energy metabolism ● energy expenditure

Body weight is determined by a balance between energy intake and energy expenditure (EE). Chronic positive energy balance results in accumulation of excessive body fat that may lead to obesity. In this context, the sympathetic nervous system plays an important role in the regulation of EE. Sympathetic β-adrenergic activation increases metabolic rate, which induces thermogenesis under fasting conditions.1–3 This mechanism is largely responsible for the thermic effect of food and provides tonic support to resting EE (REE) in humans.4–6 Furthermore, the sympathetic nervous system modulates substrate oxidation by promoting lipid oxidation through catecholamine-induced lipolysis, which may impact fat mobilization from adipose tissue.7 To date, most studies exploring the regulation of EE by the sympathetic nervous system in humans have used a model of acute administration of β-blockade.4,8 However the effect of chronic sympathetic inhibition on EE and substrate oxidation is not well known. In this context, we postulate that patients with autonomic failure, who, by definition, have very low sympathetic tone, can be used as pathophysiological model of chronic sympathetic attenuation. Therefore, the aim of this study was to determine 24-hour EE, REE, and substrate oxidation in this population and compared them with healthy controls of similar age and body composition. We hypothesized that, when compared with healthy controls, patients with autonomic failure will have decreased EE, REE, and fat oxidation.

Methods

Study Participants
We studied 10 patients with primary forms of autonomic failure, that is, multiple system atrophy or pure autonomic failure (64.9 ± 9.1 years) and 15 healthy controls of similar age (63.1 ± 4.0 years). Autonomic failure patients were recruited from the Autonomic Dysfunction Center at Vanderbilt University. Age-matched controls were recruited from a pool of healthy volunteers from the Vanderbilt community. Eligibility criteria included a sedentary lifestyle defined as no participation in an organized or self-controlled regular exercise program. Exclusion criteria included significant weight change (>5%) in the past 3 months, movement limitations, history of diabetes mellitus (fasting glucose ≥ 126 mg/dL) and history of thyroid disease. Participants who reported use of appetite suppressants, thyroid medications, lithium, antidepressants, 5-dehydroepiandrosterone, and testosterone were also excluded, because they are known to alter energy metabolism. Food containing methylxanthines were excluded from diet for ≥3 days before the metabolic study was conducted at the Clinical Research Center. The study was approved by the Vanderbilt Institutional Review Board, and all of the participants provided informed consent before participating in the study.

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This trial has been registered at www.clinicaltrials.gov (identifier NCT00179023).
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**Screening**

Participants were admitted to the Clinical Research Center at Vanderbilt University, where a health history and physical examination were performed by a study physician (C.S.). In patients with autonomic failure, any medications known to affect blood volume, for example, fludrocortisone, or to stimulate the autonomic nervous system, for example, midodrine, were discontinued for ≥5 half-lives before the study. Autonomic function tests were performed to evaluate the integrity of autonomic reflex arcs, as described previously, and to confirm the diagnosis of autonomic failure following the American Autonomic Society criteria.

**Anthropometric Measurements and Body Composition Analyses**

Body weight was measured to the nearest 0.05 kg with a digital scale. Height was measured to the nearest 1 cm with a mounted stadiometer (Perspective Enterprises, Portage, MI), with subjects wearing socks, undergarments, and a hospital gown. Body composition, including fat mass and fat-free mass (FFM), was measured using dual-energy x-ray absorptiometry using narrow fan-beam technology (Lunar Prodigy, enCore software version 10.5; GE Medical Systems, Madison, WI).

EE and Substrate Oxidation

EE and substrate oxidation were measured using a whole-room indirect calorimeter. This is an airtight room (19,500 L in net volume) equipped with a desk and 2 chairs, an outside window, telephone, a TV/VCR, and an audio system. The research staff and participants can see each other through a glass window connected to an anteroom; communication occurs via an intercom. Oxygen consumption, carbon-dioxide production, air flow rate, temperature (inside and ambient), barometric pressure, and humidity of the air were sampled 60 times per second and integrated at the end of each minute to calculate EE on a minute-by-minute basis. The accuracy of our system is >90% within a minute and allows precise measurement of EE during physical activity and rest. REE (in kilocalories per day) was defined as the average baseline EE during a 30-minute period on supine position after 30 minutes rest in the morning after an overnight fast in the room calorimeter and extrapolated to 24 hours. Respiratory quotient (RQ) was calculated minute-by-minute as a ratio of oxygen consumption and CO₂.

Patients entered the whole-room indirect calorimeter at 8:00 AM, where they remained until 7:00 AM the next morning. Meals were provided at 9:00 AM, 12:30 PM, and 5:00 PM. All of the diets were prepared in a metabolic kitchen and consisted of 50% carbohydrates, 30% fat, and 20% protein. Diet composition was determined by a computerized diet analysis using the Nutrition Data System for Research software. Participants collected 24-hour urine for nitrogen determination. Substrate oxidation rates were calculated using equations of Frayn.

**Physical Activity Monitoring**

Physical activity was monitored during the whole stay in the whole-room indirect calorimeter. Participants followed a protocol that did not include any scheduled activities except for meals and sleep, but they were asked to follow their daily routine as closely as possible. The physical activity was measured using a commercially available Actigraph GT1M accelerometer (Actigraph, Pensacola, FL) placed on the hip at the dominant side of the anterior axillary line. Among commercially used accelerometers, Actigraph provides consistent and high-quality data supported by its feasibility, reliability, and validity. The monitor measures accelerations 30 times per second in the range of 0.05 to 2.00 G and reports counts from the summation of the measured accelerations over a specific epoch. Actigraph data were summed as counts per minute.

**Blood Analyses**

Blood samples were obtained in the fasting state. Plasma glucose concentrations were measured in triplicate by the glucose oxidase method with a glucose analyzer (Beckman, Fullerton, CA). Insulin was measured using standard, double antibody radioimmunoassay (Diagnostic Systems Laboratory, Webster, CT). Catecholamines were determined by high-performance liquid chromatography. Leptin was measured using a standard radioimmunoassay, as described previously.

**Autonomic Blockade Protocol**

Autonomic failure patients were asked to rest quietly in the supine position for 30 minutes before testing at an ambient temperature of 21°C. Blood pressure was measured at 2-minute intervals using an automated sphygmomanometer and continuously by finger plethysmography. ECG and heart rate were monitored throughout the study. REE was assessed by an open-circuit indirect calorimeter with a ventilated canopy (CPX/D System, Medical Graphics Corporation, St Paul, MN). After the baseline REE measurement, continuous infusion of the ganglionic blocker trimethaphan (Cambridge Laboratories) was started at 0.5 mg/min and was increased in a 6-minute interval to one of the following end points: (1) presyncopal symptoms; (2) no additional decrease in blood pressure with increasing infusion rate; or (3) reaching an infusion rate of 4 mg/min. The infusion was continued at the end point rate for 30 minutes. REE was measured continuously during the last 30 minutes of infusion. This sequential design allowed each subject to serve as his/her own control. Complete inhibition of residual sympathetic activity was determined by comparing plasma catecholamine levels at baseline and during the ganglionic blockade. The same investigator (C.S.) conducted all of the studies.

**Statistical Analysis**

Summary statistics are reported separately for autonomic failure patients and the controls. Continuous variables are reported as mean ± SEM unless otherwise specified and categorical variables as counts and percentages. Simple linear regression was performed in autonomic failure patients and healthy controls to determine the association between REE and FFM. An ANCOVA, adjusting for FFM and sex, was used to compare REE between groups. Patient characteristics and data on substrate oxidation were compared using Student’s t test or Mann-Whitney U test depending on the normality of the data. A 2-tailed P < 0.05 was considered significant. The analyses were performed using SPSS for Windows (version 19.0; SPSS).

**Results**

**Study Population**

Standardized autonomic function tests confirmed the diagnosis of autonomic failure in all of the study patients. These tests proved parasympathetic and sympathetic impairment with severe orthostatic hypotension (65.0 ± 9.1 mm Hg fall in SBP on standing), marked attenuation of the respiratory sinus arrhythmia (1.1 ± 0.02, normal > 1.2), and profound decrease in systolic blood pressure during phase II of the Valsalva maneuver (−64.7 ± 9.3 mm Hg, normal ≥ 20 mm Hg) with absence of blood pressure overshoot during phase IV. The pressor response to cold pressor test and handgrip test were also attenuated (11.0 ± 3.3 mm Hg, normal ≥20 mm Hg; 7.1 ± 4.3 mm Hg, normal ≥20 mm Hg, respectively). Supine plasma norepinephrine was low 179.7 ± 58.4 pg/mL and increased to 497.0 ± 154.6 pg/mL in the upright posture.

Demographic characteristics of the autonomic failure patients and healthy controls are presented in Table 1. There were no significant differences in age, body mass index, fat mass, FFM, and bone mineral density. Serum concentrations of fasting glucose, free fatty acids, insulin, and leptin did not differ between patients with autonomic failure and healthy controls.
Total 24-hour EE and physical activity were significantly lower in patients with autonomic failure compared with healthy controls (Figure 1A and 1B). REE was similar (P=0.05) in both groups (Figure 2). The association of REE and FFM for patients with autonomic failure and healthy controls is shown in Figure 3A and 3B. In a generalized linear model adjusted for FFM and sex, the autonomic failure status did not affect REE (P=0.57), and most of the variability of REE was explained by differences in FFM.

The 24-hour RQ and nonprotein RQ did not differ between patients with autonomic failure and healthy controls (Table 2). Carbohydrate and protein oxidation rates (grams per kilogram of FFM per day) were similar, whereas fat oxidation was significantly lower in the autonomic failure group.

### Table 1. Demographic Characteristics of the Study Subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>AF Patients (n=10)</th>
<th>Healthy Controls (n=15)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female</td>
<td>4/6</td>
<td>7/8</td>
<td>0.56</td>
</tr>
<tr>
<td>Age, y</td>
<td>64.9±9.1</td>
<td>63.1±4.0</td>
<td>0.58</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170.1±6.8</td>
<td>168.3±7.6</td>
<td>0.58</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72.9±13.8</td>
<td>69.5±13.9</td>
<td>0.56</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.2±4.4</td>
<td>24.4±3.9</td>
<td>0.66</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>36.6±8.8</td>
<td>30.6±11.2</td>
<td>0.17</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>25.5±8.6</td>
<td>21.2±10.4</td>
<td>0.29</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>45.9±9.7</td>
<td>48.7±10.3</td>
<td>0.51</td>
</tr>
<tr>
<td>Bone mineral density, g/cm²</td>
<td>1.1±0.1</td>
<td>1.2±0.2</td>
<td>0.19</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>97.6±11.4</td>
<td>101.4±9.1</td>
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<td>Free fatty acids, μmol/L</td>
<td>306.5±77.46</td>
<td>418.9±248.7</td>
<td>0.25</td>
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<tr>
<td>Insulin, μU/mL</td>
<td>11.1±6.9</td>
<td>8.1±4.6</td>
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<tr>
<td>Leptin, ng/mL</td>
<td>15.7±15.2</td>
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Values are mean±SD. AF indicates autonomic failure; BMI, body mass index.

### EE and Substrate Oxidation in Autonomic Failure

Total 24-hour EE and physical activity were significantly lower in patients with autonomic failure compared with healthy controls (Figure 1A and 1B). REE was similar (P=0.05) in both groups (Figure 2). The association of REE and FFM for patients with autonomic failure and healthy controls is shown in Figure 3A and 3B. In a generalized linear model adjusted for FFM and sex, the autonomic failure status did not affect REE (P=0.57), and most of the variability of REE was explained by differences in FFM.

The 24-hour RQ and nonprotein RQ did not differ between patients with autonomic failure and healthy controls (Table 2). Carbohydrate and protein oxidation rates (grams per kilogram of FFM per day) were similar, whereas fat oxidation was significantly lower in the autonomic failure group.

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Values are mean±SD. AF indicates autonomic failure; BMI, body mass index.

**Figure 1.** Total energy expenditure (EE) and physical activity (PA) in autonomic failure and healthy controls during the 24-hour stay in the whole-room indirect calorimeter. Total EE was significantly lower in patients with autonomic failure (AF) vs controls (A). Furthermore, patients with autonomic failure have decreased physical activity vs controls (B).

**Figure 2.** Resting energy expenditure (REE) measured using whole-room indirect calorimeter was similar between patients with autonomic failure vs controls (P=0.42).

**Figure 3.** Simple linear regression between resting energy expenditure (REE) and fat-free mass (FFM) in patients with autonomic failure (AF), REE=459.8±21(95% CI, 11–32)FFM (A) and healthy controls, REE=426.2±21(95% CI, 15–30)FFM (B). Differences in FFM explained 76% of REE variability.
Table 2. Substrate Oxidation

<table>
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<th>AF Patients (n=10)</th>
<th>Healthy Control (n=15)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total daily RQ</td>
<td>0.89±0.01</td>
<td>0.87±0.01</td>
<td>0.18</td>
</tr>
<tr>
<td>Total daily nonprotein RQ</td>
<td>0.91±0.01</td>
<td>0.89±0.01</td>
<td>0.26</td>
</tr>
<tr>
<td>Total daily carbohydrate oxidation, g/kg · d</td>
<td>5.40±0.37</td>
<td>6.00±0.42</td>
<td>0.32</td>
</tr>
<tr>
<td>Total daily fat oxidation, g/kg FFM · d</td>
<td>1.11±0.13</td>
<td>1.68±0.20</td>
<td>0.03*</td>
</tr>
<tr>
<td>Total daily protein oxidation, g/kg FFM · d</td>
<td>1.49±0.18</td>
<td>1.79±0.12</td>
<td>0.16</td>
</tr>
<tr>
<td>Sleep RO</td>
<td>0.85±0.02</td>
<td>0.84±0.01</td>
<td>0.51</td>
</tr>
<tr>
<td>Sleep carbohydrate oxidation, g/kg FFM · sleep</td>
<td>0.62±0.14</td>
<td>0.48±0.06</td>
<td>0.30</td>
</tr>
<tr>
<td>Sleep fat oxidation, g/kg FFM · sleep</td>
<td>0.23±0.06</td>
<td>0.22±0.03</td>
<td>0.87</td>
</tr>
<tr>
<td>Sleep protein oxidation, g/kg FFM · sleep</td>
<td>0.25±0.02</td>
<td>0.31±0.02</td>
<td>0.11</td>
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</table>

Data are mean±SEM. Total daily RQ is the average respiratory quotient during 24-h stay in the room calorimeter. Sleep RO is the respiratory quotient measured during sleep between midnight and 4:00 AM. Total substrate oxidation data are expressed in grams per kilogram of fat-free mass per day. Sleep substrate oxidation is expressed in grams per kilogram of fat-free mass per 4 h of sleep.

(P<0.05). RQ during sleep in autonomic failure patients was similar compared with healthy controls (P=0.51); there were no differences in sleep substrate oxidation (Table 2).

Contribution of Residual Sympathetic Tone to REE in AF

Four patients with autonomic failure (3 men and 1 woman diagnosed with pure autonomic failure) agreed to participate in this protocol. Maximum autonomic attenuation was determined by the reduction in plasma norepinephrine from 55.0±12.8 at baseline to 25.0±2.7 pg/mL at the end of residual autonomic blockade. REE decreased by 117.9±35.2 kcal/d (8%) during autonomic blockade compared with baseline (Figure 4).

Discussion

The major finding of our study is that REE was similar in autonomic failure patients compared with healthy controls of similar age and body composition. The sympathetic nervous system plays a role in energy balance through the regulation of REE, which accounts for 60% to 80% of total EE in humans. This system regulates REE mostly through stimulation of β-adrenoreceptors. During intravenous administration of the nonselective β-adrenergic antagonist propanolol, REE decreases.8 Therefore, it is unexpected that REE was preserved in autonomic failure patients who are characterized by low sympathetic activity. A possible explanation for our findings is that even patients with severe autonomic failure have some degree of residual sympathetic activity.9 Our patients had low supine plasma norepinephrine levels (179.7±58.40 pg/mL) compared with normal values reported for their age (359±30 pg/mL).20 The fact that their low plasma norepinephrine decreased with further autonomic blockade is evidence of their residual sympathetic tone. More importantly, REE decreased by 8% in autonomic failure patients during autonomic blockade, indicating that REE was tonically maintained by this residual sympathetic activity. Furthermore, it is possible that chronic sympathetic attenuation induced a compensatory β-adrenoreceptor upregulation, which could contribute to the preserved tonic sympathetic contribution to REE. This phenomenon has been documented previously in the literature in autonomic failure patients in the vascular system.21–23 Similarly, a recent report by Newsom et al24 showed that reduction in sympathetic activity with 6-day treatment with transdermal clonidine administration (0.2 mg/d) produced a compensatory upregulation of β-adrenoreceptor stimulation of REE.

It is noteworthy that acute autonomic withdrawal with trimethaphan reduces REE by approximately the same magnitude, 5% to 7%, in all of the groups that we have studied, including healthy young subjects, obese young subjects,25 and also autonomic failure patients. In obesity, the additional increase in REE is not attributed to the greater sympathetic tone seen in that condition but to an increase in FFM. In contrast, in autonomic failure, REE is likely maintained by residual sympathetic tone acting on a compensatory upregulation of β-adrenoreceptor responses, as discussed previously.

To our knowledge, this is the first study to examine REE in autonomic failure. Patients with spinal cord injury, particularly those who have lesions in higher levels (T6 and above)
and, in particular, anaerobic exercise increase fat oxidation. It is well established that increased physical activity level observed in patients with autonomic failure have decreased fat oxidation. Sympathetic tone is implicated in the regulation of lipolysis, therefore, it is possible that residual sympathetic tone was still modulating REE regulation but not lipolysis. However, a more plausible explanation of decreased fat oxidation was the low habitual physical activity during the day. That lowered physical activity during the day may be responsible for the decrease in daytime fat oxidation in autonomic failure patients.

In this study, we also found that patients with autonomic failure have decreased fat oxidation. Sympathetic tone is involved in the regulation of lipolysis, and it is possible that residual sympathetic tone was still modulating REE regulation but not lipolysis. However, a more plausible explanation of decreased fat oxidation was the low habitual physical activity level observed in patients with autonomic failure. It is well established that increased physical activity and, in particular, anaerobic exercise increase fat oxidation, compared with inactive sedentary behavior. Our observation that fat oxidation was similar between autonomic failure patients and healthy controls during sleep supports the notion that lowered physical activity during the day may be responsible for the decrease in daytime fat oxidation in autonomic failure patients.

Patients with autonomic failure have lower level of physical activity, reduced EE, and decreased rate of fat oxidation compared with healthy controls, all important risk factors for obesity. Nonetheless, empirical observations from our clinic are that obesity is very rare in patients with autonomic failure (Figure 5). Thus, our findings imply that patients with autonomic failure would have to decrease their energy intake to maintain energy balance and avoid weight gain.

In this context, the parasympathetic nervous system that regulates feeding behavior by transmitting satiety or hunger signals to the brain may play a role. These signals travel to the brain via vagal afferents transmitting their stimuli to the nucleus of the solitary tract and from there to efferent in different centers involved in appetite control, including the hypothalamus. There are multiple peptides and hormones that exert their feeding behavior actions through this pathway; among them are peptide YY, cholecystokinin, glucagon-like peptide 1, and ghrelin. Whether these molecules are increased or decreased in autonomic failure patients in response to food intake requires further investigation. Insight into the mechanisms responsible for this putative decrease in food intake will be of importance not only to our understanding of the pathophysiology of this disorder, but may be relevant to general mechanisms of appetite control.

Our study has some limitations. First, because of the relatively small number of patients with autonomic failure, we did not have the power to detect the effect of confounding factors, such as personal characteristics (eg, sex, age, body size, and composition) and comorbidities. Second, direct measurement of other physiological variables, such as heart rate and cardiac output, could be helpful to delineate the relative contribution of central versus peripheral factors to the variability in the REE and RQ results. Finally, we did not measure maximal oxygen consumption, considered a good predictor of physical activity capacity in adults. However, the use of this assessment is very limited in patients with autonomic failure because of neuromechanical impairments that leads to exercise-induced hypotension.

The study has several strengths. For the first time we measured continuously EE, substrate oxidation, and physical activity in patients with autonomic failure. The study was conducted using a reference standard whole-room indirect calorimetry to measure oxygen uptake, substrate oxidation, and EE. We consider this study as a necessary first step to understanding the mechanism of the effect of chronic sympathetic attenuation on EE and substrate oxidation.

**References**


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