Sympathetic Neural Activation in Visceral Obesity

Guy E. Alvarez, MS; Stacy D. Beske, PhD; Tasha P. Ballard, MS; Kevin P. Davy, PhD

Background—Muscle sympathetic nerve activity (MSNA) is elevated in obese humans. However, the potential role of abdominal visceral fat as an important adipose tissue depot linking obesity to elevated MSNA has not been explored. Accordingly, we tested the hypothesis that MSNA would be increased in men (age \( \leq 18 \) to 40 years, body mass index \( \leq 35 \text{ kg/m}^2 \)) with higher abdominal visceral fat (HAVF; \( n = 13 \), abdominal visceral fat \( = 118.1 \pm 15.8 \text{ cm}^2 \)) compared with their age- (28.7 \pm 2.4 versus 25.5 \pm 2.0 years, \( P > 0.05 \)), total fat mass–matched (20.6 \pm 2.1 versus 20.8 \pm 2.4 kg, \( P > 0.05 \)) and abdominal subcutaneous fat–matched (230.6 \pm 24.9 versus 261.4 \pm 34.8 cm\(^2\), \( P > 0.05 \)) peers with lower abdominal visceral fat levels (LAVF; \( n = 13 \), visceral fat = 73.0 \pm 6.0 cm\(^2\)).

Methods and Results—MSNA (microneurography), body composition (dual energy x-ray absorptiometry), and abdominal visceral and subcutaneous fat (computed tomography) were measured in 37 sedentary men across a wide range of adiposity. MSNA was \( \approx 55\% \) higher in men with HAVF compared with men with LAVF (33 \pm 4 versus 21 \pm 2 bursts/min, \( P < 0.05 \)). Furthermore, MSNA was more closely associated with the level of abdominal visceral fat (\( r = 0.65, P < 0.05 \)) than total fat mass (\( r = 0.323, P < 0.05 \)) or abdominal subcutaneous fat (\( r = 0.27, P = 0.05 \)). The relation between MSNA and abdominal visceral fat was independent of total body fat (\( r = 0.61, P < 0.05 \)).

Conclusions—The results of our study indicate that MSNA is elevated in men with visceral obesity. Our observations are consistent with the idea that abdominal visceral fat is an important adipose tissue depot linking obesity with sympathetic neural activation in humans. Furthermore, these findings may have important implications for understanding the increased risk of developing cardiovascular diseases in individuals with visceral obesity. (Circulation. 2002;106:2533-2536.)

Key Words: obesity ■ nervous system, autonomic ■ blood pressure

Excess adipose tissue accumulation is an important risk factor for the development of cardiovascular diseases,\(^1\) and more than 60\% of the US population is considered overweight or obese.\(^2\) The risks associated with obesity depend considerably on the distribution of body fat. The accumulation of adipose tissue in the abdominal visceral region is considered to be the important depot that links obesity with cardiovascular diseases.\(^3\) This association is mediated in part by a cluster of several cardiovascular disease risk factors that frequently has been referred to as the “Metabolic Syndrome.”\(^4\)

Obesity is associated with elevated muscle sympathetic nerve activity (MSNA),\(^5-9\) but there is considerable interindividual variability, even at the same level of adiposity (ie, body mass index). The reason(s) for this variability is (are) unclear. One possibility is that this variability is due, at least in part, to individual differences in the level of abdominal visceral fat. It is presently unknown, however, whether abdominal visceral fat is an important adipose tissue depot linking obesity with elevated MSNA. Accordingly, we hypothesized that MSNA would be increased in men with higher abdominal visceral fat (HAVF, \( n = 13 \)) compared with their age-, total fat mass–, and abdominal subcutaneous fat–matched peers with lower abdominal visceral fat levels (LAVF, \( n = 13 \)).

Methods

Subjects

Thirty-seven men (body mass index \( \leq 35 \text{ kg/m}^2 \)) volunteered to participate in the present study; 31 were white, 3 were Asian, 2 were Hispanic, and 1 was black. The individuals from the minority ethnic/racial groups did not differ in the variables studied in any obvious way from their white counterparts. Twenty-six of the 37 individuals were pair-matched on the basis of their similar total fat mass and abdominal subcutaneous fat levels but disparate levels of abdominal visceral fat; a fourteenth pair meeting these criteria could not be identified. All subjects were normotensive, nonobabetic, and free from other overt chronic diseases, and had normal resting and maximal exercise electrocardiograms. The subjects were sedentary, did not smoke, and were not taking medications. The nature, purpose, risks, and benefits were explained to each subject before obtaining informed consent. The Colorado State University Human Subjects Committee approved all experimental protocols.

Received August 26, 2002; revision received September 23, 2002; accepted September 23, 2002.

From the Departments of Physiology and Biophysics and Medicine (K.P.D.), University of Mississippi Medical Center, Jackson; Departments of Health and Exercise Science and Physiology (G.E.A., T.P.B.), Colorado State University, Fort Collins; and Hebrew Research Center for the Aged (S.D.B.), Research and Training Institute, Boston, Mass.

Correspondence to Kevin P. Davy, PhD, University of Mississippi Medical Center, Department of Physiology and Biophysics, 2500 North State St, Jackson, MS 39216. E-mail kdavy@physiology.umsmed.edu

© 2002 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org

DOI: 10.1161/01.CIR.0000041244.79165.25

2533
Experimental Procedures

Body mass and height were measured with a balance scale and a stadiometer, respectively. Waist-to-hip ratio was calculated from the respective circumferences. Body composition was measured using dual energy x-ray absorptiometry (DPX-IQ, Lunar Radiation Corp) using software version 4.5c. Computed tomography scans (HiSpeed Ct, GE Medical) were performed to quantify abdominal visceral and subcutaneous fat levels. Maximal oxygen consumption was measured during graded treadmill exercise to exhaustion using open circuit spirometry (TrueMax 2400, ParvoMedics). Heart rate was determined from an ECG, beat-by-beat arterial pressure was measured by finger photoplethysmography (TNO Biomedical Instrumentation), and respiration was monitored using a pneumobelt. Resting arterial blood pressures were adjusted to brachial arterial blood pressures with an automated device (Dinamap, Critikon Co) before the injection of vasoactive drugs (see below). Recordings of multiunit MSNA were obtained from the right peroneal nerve using the microneurographic technique as described previously and were considered acceptable according to previously published criteria.

We have previously reported that men with higher levels of abdominal visceral fat have reduced vagal baroreflex gain. Therefore, a secondary aim was to determine whether sympathetic baroreflex gain was similarly reduced. As such, vagal and sympathetic baroreflex responses were measured using the modified Oxford technique.

Experimental Protocol

All subjects were studied in the morning between 7:00 AM and 11:00 AM after a 12-hour overnight fast. Subjects were instructed to refrain from caffeine, alcohol, and vigorous activity 24 hours before all testing sessions.

After steady state levels of all variables were achieved, a 10-minute recording of basal MSNA was obtained. Subsequently, a bolus injection of sodium nitroprusside (100 µg) was given intravenously, followed 60 seconds later by a bolus injection of phenylephrine HCl (150 µg). These pharmacological perturbations decreased and increased arterial blood pressure ~15 mm Hg from baseline levels during a 3-minute period. Three trials were completed, and they were separated by a minimum of 15 minutes quiet rest.

Data Analysis

Abdominal visceral and subcutaneous fat regions were determined using commercially available medical imaging software (SliceOmatic ver. 4.2, Tomovision) as described previously.

MSNA, heart rate, arterial blood pressure, and respiration were recorded continuously and digitized at 500 Hz to a laboratory computer for later analysis using signal processing software (Windaq, Dataq Instruments). Basal MSNA was quantified as both burst frequency (bursts/min) and burst incidence (bursts/100 beats). Vagal and sympathetic baroreflex responses were determined from the relationships between R-R interval and systolic blood pressure and MSNA and diastolic blood pressure, respectively, during vasodepressor drug injections.

Statistical Analysis

Differences in subject characteristics and dependent variables between groups were assessed with independent Student’s t tests. Relations among variables for all 37 subjects were assessed using bivariate and partial correlation analysis. The magnitude and significance of the relations were similar when the analyses were restricted to the 13 pairs of subjects. Data are expressed as mean±SEM. The significance level was set a priori at P<0.05.

Results

Subject Characteristics

Subject characteristics for men with LAVF and HAVF are shown in the Table. No differences in age, height, body mass, body mass index, waist and hip circumferences, body fat percentage, total fat mass, abdominal subcutaneous fat, total abdominal fat, systolic blood pressure, diastolic blood pressure, heart rate, or maximal oxygen consumption were observed in the LAVF and HAVF groups (all P>0.05). As intended, abdominal visceral fat and the waist-to-hip ratio were higher in the HAVF group (both P<0.05).

Subject Characteristics in Men With LAVF and HAVF Levels

<table>
<thead>
<tr>
<th>Variable</th>
<th>LAVF (n=13)</th>
<th>HAVF (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>25.5±2.0</td>
<td>28.7±2.4</td>
</tr>
<tr>
<td>Height, cm</td>
<td>181.8±2.8</td>
<td>179.4±2.0</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>86.8±4.3</td>
<td>86.4±4.0</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.3±1.3</td>
<td>27.0±1.4</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>92.1±3.0</td>
<td>96.6±4.3</td>
</tr>
<tr>
<td>Hip circumference, cm</td>
<td>106.3±2.4</td>
<td>104.4±2.1</td>
</tr>
<tr>
<td>Waist-to-hip ratio, units</td>
<td>0.87±0.01</td>
<td>0.92±0.03*</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>23.3±2.0</td>
<td>23.1±1.7</td>
</tr>
<tr>
<td>Total fat mass, kg</td>
<td>20.8±2.4</td>
<td>20.6±2.1</td>
</tr>
<tr>
<td>Lean body mass, kg</td>
<td>62.8±2.5</td>
<td>62.6±2.1</td>
</tr>
<tr>
<td>Abdominal subcutaneous fat, cm²</td>
<td>261.4±34.8</td>
<td>230.6±24.9</td>
</tr>
<tr>
<td>Abdominal visceral fat, cm²</td>
<td>73.0±6.0</td>
<td>118.1±15.8*</td>
</tr>
<tr>
<td>Total abdominal fat, cm²</td>
<td>334.4±39.9</td>
<td>348.8±39.1</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>116±2</td>
<td>119±2</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>65±2</td>
<td>69±3</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>60±3±3</td>
<td>65±2</td>
</tr>
<tr>
<td>VO₂max, mL · kg⁻¹ · min⁻¹</td>
<td>44.8±2.1</td>
<td>44.7±2.2</td>
</tr>
</tbody>
</table>

All values are mean±SEM. VO₂max indicates maximal oxygen consumption. *P<0.05 vs. LAVF.

Figure 1. Basal muscle sympathetic nerve activity expressed in bursts/min (A) and bursts/100 beats (B) in men with LAVF and HAVF. Values are mean±SEM. *P<0.05 versus LAVF.
Alvarez et al. Sympathetic Activation in Visceral Obesity

2535

Figure 2. Relations between basal muscle sympathetic nerve activity and abdominal visceral fat (A), abdominal subcutaneous fat (B), and total fat mass (C).

**Basal MSNA and Baroreflex Responses in LAVF and HAVF**

Basal MSNA burst frequency (32±4 versus 21±2 bursts/min) and burst incidence (51±6 versus 38±4 burst/100 bts, Figure 1) were significantly higher in HAVF men compared with LAVF men. Sympathetic baroreflex gain was similar in the 2 groups (−9.1±0.7 versus −8.9±0.6 arbitrary integration units · beat⁻¹ · mm Hg⁻¹, P<0.05), but vagal baroreflex gain was lower in HAVF compared with LAVF men (13.8±1.7 versus 20.0±2.4, ms/mm Hg, P<0.05).

**Body Composition and Anthropometric Correlates**

Basal MSNA was more closely associated with abdominal visceral fat (r=0.65, P<0.05; Figure 2A) than it was with total fat mass (r=0.35, P=0.05, Figure 2B) or abdominal subcutaneous fat (r=0.27, P=0.05, Figure 2C). The relation between MSNA and abdominal visceral fat was independent of total fat mass (r=0.61, P<0.05). Basal MSNA was also correlated with body mass index (r=0.32, P=0.05), waist circumference (r=0.32, P=0.05), waist-to-hip ratio (r=0.38, P<0.05), body fat percentage (r=0.35, P<0.05), and total abdominal fat (r=0.42, P<0.05). Neither vagal nor sympathetic baroreflex gains were correlated with any body composition or anthropometric variables.

**Discussion**

The major new finding was that basal MSNA was ~55% higher in men with elevated abdominal visceral fat compared with their age-, total fat mass-, and abdominal subcutaneous fat-matched peers with lower levels. In addition, basal MSNA was more closely associated with abdominal visceral fat than it was with total fat mass or abdominal subcutaneous fat. Importantly, the relation between basal MSNA and abdominal visceral was independent of total fat mass. Thus, our observations are consistent with the idea that abdominal visceral fat is an important adipose tissue depot that links obesity with sympathetic neural activation.

Consistent with our previous finding, vagal baroreflex gain was reduced in men with elevated abdominal visceral fat in the present study. Contrary to our hypothesis, however, sympathetic baroreflex gain was similar in these men compared with their age-, total fat mass-, and subcutaneous fat-matched peers with lower levels of abdominal visceral fat. In contrast to the report by Grassi et al., sympathetic baroreflex gain was not related to any measure of adiposity in the present study. The reason(s) for this discrepancy may include the degree of obesity studied and methodology used.

Visceral obesity has been hypothesized to be the result of a neuroendocrine disorder associated with hypothalamic-pituitary axis dysregulation and sympathetic nervous system activation. Grassi et al. have reported that dysregulation of the hypothalamic-pituitary axis may contribute to the elevated basal MSNA observed in obese subjects. Thus, it is possible that hypothalamic-pituitary dysregulation could contribute to the elevated basal MSNA observed in visceral obesity. Future studies will be necessary to determine whether this or other mechanisms are responsible.

We have previously reported that waist circumference (ie, abdominal adiposity) is an important determinant of the age-related increase in basal MSNA in humans. Taken together with the results of the present study, these findings suggest that elevated abdominal visceral fat is an important determinant of basal MSNA in male humans. Future studies will be necessary to confirm the results of earlier studies implicating abdominal visceral fat as a contributing factor to age-related differences in basal MSNA.

The accumulation of fat in the abdominal visceral region is a critical correlate of the metabolic syndrome. Sympathetic neural activation is considered to be an important feature of the metabolic syndrome, and is also important in the pathogenesis of cardiovascular disease. Therefore, elevated MSNA may be associated with or serve as a marker for the elevated risk of cardiovascular disease in visceral obesity. Future studies will be necessary to determine whether the reduction in abdominal visceral fat with weight loss is an important determinant of the corresponding reduction in basal MSNA.

The subjects in the present study were young overweight and mildly obese men with average aerobic fitness and no
evidence of overt chronic disease. It is possible that the presence of obesity-associated co-morbidities would amplify the group differences reported herein. Similarly, it is possible that a higher prevalence of obstructive sleep apnea in individuals with higher abdominal visceral fat in the present study could account for their increased MSNA levels.20 Future studies will be necessary to confirm or refute these possibilities.

In summary, the results of the present study suggest abdominal visceral fat is an important adipose tissue depot that links obesity with elevated basal MSNA. The mechanisms responsible for these observations remain unclear. Importantly, these findings may have implications for understanding the elevated risk of developing cardiovascular diseases in men with visceral obesity.

Acknowledgments
This work was supported by National Institutes of Health awards HL62283 and HL67227 (Dr Davy). The authors thank John Halliwill, PhD, for sharing his baroreflex analysis software (see reference 14).

References
Sympathetic Neural Activation in Visceral Obesity
Guy E. Alvarez, Stacy D. Beske, Tasha P. Ballard and Kevin P. Davy

Circulation. 2002;106:2533-2536; originally published online October 28, 2002;
doi: 10.1161/01.CIR.0000041244.79165.25

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/106/20/2533

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/