Obstructive Sleep Apnea–Dependent and –Independent Adrenergic Activation in Obesity

Guido Grassi, Anna Facchini, Fosca Quarti Trevano, Raffaella Dell’Oro, Francesca Arenare, Francesco Tana, GianBattista Bolla, Anna Monzani, Maria Robuschi, Giuseppe Mancia

Abstract—No agreement exists as to the mechanisms responsible for the sympathetic hyperactivity characterizing human obesity, which has been ascribed recently to a chemoreflex stimulation brought about by obstructive sleep apnea rather than to an increase in body weight, per se. In 86 middle age normotensive subjects classified according to body mass index, waist-to-hip ratio, and apnea/hypopnea index (overnight polysomnographic evaluation) as lean and obese subjects without or with obstructive sleep apnea, we assessed via microneurography muscle sympathetic nerve traffic. The 4 groups were matched for age, gender, and blood pressure values, the 2 obese groups with and without obstructive sleep apnea showing a similar increase in body mass index (32.4 versus 32.0 kg/m², respectively) and waist-to-hip ratio (0.96 versus 0.95, respectively) compared with the 2 lean groups with or without obstructive sleep apnea (body mass index 24.3 versus 23.8 kg/m² and waist-to-hip ratio 0.77 versus 0.76, respectively; $P<0.01$). Compared with the nonobstructive sleep apnea lean group, muscle sympathetic nerve activity showed a similar increase in the obstructive sleep apnea lean group and in the nonobstructive sleep apnea obese group (60.4±2.3 and 59.3±2.0 versus 40.9±1.8 bursts/100 heart beats, respectively; $P<0.01$), a further increase being detected in obstructive sleep apnea subjects (73.1±2.5 bursts/100 heart beats; $P<0.01$). Our data demonstrate that the sympathetic activation of obesity occurs independently in obstructive sleep apnea. They also show that this condition exerts sympathostimulating effects independent of body weight, and that the obstructive sleep apnea–dependent and –independent sympathostimulation contribute to the overall adrenergic activation of the obese state. (Hypertension. 2005;46:321-325.)

Key Words: sleep apnea syndromes ■ sympathetic nervous system ■ chemoreceptors ■ baroreflex

Subjects with obesity are characterized by an increase in urinary norepinephrine (NE), plasma levels of NE, efferent postganglionic muscle sympathetic nerve activity (MSNA), and renal NE spillover rate, thereby displaying a hyperadrenergic state. This has been ascribed primarily to the insulin-resistance state and the subsequent hyperinsulinemia that occurs more frequently with an increase in body weight because in animals and human, insulin has been shown to stimulate the sympathetic nervous system. However, it has also been ascribed to other mechanisms, among which is the chemoreceptor stimulation brought about by obstructive sleep apnea (OSA), a condition that is also common in obese individuals. Indeed, OSA has been reported to be the necessary condition for the obesity-related sympathetic hyperactivity to occur in a study by Narkiewicz et al in which an increased number of sympathetic bursts to skeletal muscle tissues was seen only when obesity and OSA were concomitantly present. The present study was conducted to determine the relative contribution of the increased body weight, per se, versus OSA in producing the sympathetic activation of human obesity. This was obtained by directly assessing via microneurography MSNA in lean subjects without or with OSA and comparing the results with those obtained in age- and gender-matched obese individuals, also without or with OSA.

Methods

Population

The study population consisted of 86 subjects (68 males and 18 females, ranging from 35 to 52 years of age) recruited between 2001 and 2004. Recruitment criteria were based on the presence or absence of: (1) normal body weight (body mass index <25 kg/m² and waist-to-hip ratio <0.85 for females and <0.95 for males) or obesity (body mass index >30 kg/m²; peripheral obesity: waist-to-hip ratio <0.85 for females and <0.95 for males; visceral obesity: waist-to-hip ratio >0.85 for females and >0.95 for males), and (2) OSA newly diagnosed and determined by an apnea/hypopnea index >5 at an overnight polysomnographic study (see below). Subjects were excluded from the study if they had: (1) hypertension, as defined by an office blood pressure elevation (>140 mm Hg systolic or >90 mm Hg diastolic or by use of antihypertensive drugs); (2) congestive heart failure, as determined by symptoms and alterations

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in echocardiographically determined left ventricular diameters and ejection fraction; (3) atrial fibrillation or other major cardiac arrhythmias; (4) history of coronary or cerebrovascular diseases; (5) clinical or laboratory evidence of valvular heart diseases; (6) history of smoking or excessive alcohol consumption; (7) major concomitant diseases, such as renal insufficiency, diabetes mellitus, and other conditions known to affect neuroadrenergic function; and (8) chronic drug treatment of any kind. Subjects were classified as lean subjects without (n=27) or with (n=16) OSA and as obese subjects without (n=18) or with (n=25) OSA. All subjects were studied on an outpatient basis. The study protocol was approved by the ethics committee of our institution. All subjects gave written consent to the study after being informed of its nature and purpose.

**Measurements**

The methodological details of the measurements made in the present study have been reported previously. Briefly, measurements included body mass index, waist-to-hip ratio, sphygmomanometric and beat-to-beat finger (Finapres 2300; Ohmeda) systolic and diastolic blood pressure, heart rate (electrocardiogram), respiration rate (pneumotacograph), oxygen saturation (pulse oximeter; Nellcor), and multiunit recording of efferent postganglionic MSNA (microneurography), which provides a direct and highly reproducible quantification of sympathetic activity. They also included plasma NE (high-performance liquid chromatography), plasma renin activity (radioimmunoassay), plasma leptin (radioimmunoassay), fasting plasma glucose (radioenzymatic method), and insulin (radioimmunoassay) levels, which were determined from a blood sample taken from an antecubital vein. From the formula plasma insulin × fasting plasma glucose/22.5, calculation was made of the homeostasis model assessment of insulin resistance (HOMA-IR), which was used as an estimate of insulin resistance. With the exception of sphygmomanometric systolic and diastolic blood pressure, as well as of the hormonal and metabolic parameters, measurements were displayed on thermic paper of an ink polygraph (Gould 3800). MSNA was quantified as burst frequency over time (bursts per minute) and as burst frequency corrected for heart rate values (bursts per 100 heartbeats). Before or after the study proper (see below), all subjects underwent an overnight polysomnographic recording that included an electromyogram, a thoracic and an abdominal impedance for determining respiratory effort and thus the obstructive nature of the apneic episodes, and an oxygen saturation as well as a nasal and an oral airflow determination (thermists). The presence, absence, and severity of OSA was defined by the number of episodes of apnea and hypopnea per hour of sleep according to the formula: total n° of apneas + hypopneas/total sleep time (minutes) × 60. Apnea/hypopnea index <5 was regarded as normal, whereas values of 5 to 15, 15 to 30, and >30 were considered indices of mild, moderate, and severe apnea, respectively. Apnea was defined as a complete cessation of nasal and oral airflow lasting ≥10 s, whereas hypopnea was defined as a reduction in airflow of <50% of control values accompanied by an arousal or by a decrease in oxygen saturation >3%. Determination of OSA presence by a single overnight polysomnographic recording has been shown to be highly reproducible and adequate to make diagnosis. This is confirmed by the evidence that in a group of patients followed by the Division of Pulmonary Care of our hospital, the apnea/hypopnea index differed by no ≤5.0% when assessed in 2 different sessions spaced from each other by a 3- to 4-week interval.

**Protocol and Data Analysis**

All subjects came to the laboratory in the morning. They were put in the supine position and fitted with the intravenous cannula, microelectrodes for MSNA recording, and other measuring devices. Blood samples for the assay of hormonal and metabolic variables were then taken, and blood pressure was measured 3× with a mercury sphygmomanometer. After a 30-minute time interval, systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, oxygen saturation, and MSNA were measured continuously during a 30-minute basal state, with the subjects awake and in absence of any apnea, hypopnea, or oxygen desaturation episodes. In about half of the subjects (n=40), the microneurographic session preceded the polysomnographic examination by 2 to 3 days, whereas in the remaining half (n=46), it followed the polysomnographic examination by a comparable time interval. Data were collected in a quiet room at a constant temperature of 20°C to 21°C and analyzed by a single investigator (A.F.) unaware of the belonging of the subjects to the 4 different groups. For all variables, baseline values from individual subjects were averaged for each group and expressed as mean±SEM. Comparisons between groups were made by 2-way ANOVA. The 2-tailed t test for unpaired observations was used to locate between-group differences. The Bonferroni correction was used for multiple comparisons. A multivariate analysis was also performed with age, gender, blood pressure, body mass index, waist-to-hip ratio, leptin, HOMA index, and apnea/hypopnea index as the independent variables and MSNA as the dependent one. A value of P<0.05 was considered statistically significant.

**Results**

As shown in the Table, the 4 groups of subjects were matched for age and gender. Compared with OSA and non-OSA lean individuals, body mass index and waist-to-hip ratio were elevated similarly in obese subjects with and without OSA. Sphygmomanometric blood pressure, finger blood pressure, respiration rate, and plasma glucose were superimposable in the 4 groups, whereas heart rate was greater in the obese group with OSA than in the other 3 groups, the difference achieving statistical significance, however, only when comparison was made with lean OSA individuals. Oxygen saturation showed a progressive decrease from the lean to the obese group, a further reduction being detected in obese subjects with OSA. Compared with the 2 lean groups, plasma insulin, HOMA index, plasma leptin, and plasma renin activity were all increased in the obese group without OSA, a further increase being observed in the group in which obesity and OSA were concomitantly present. The Figure shows the polysomnographic, plasma NE, and MSNA data. The apnea/hypopnea index was similar in the lean and obese groups with OSA, in either group being markedly greater than that characterizing the corresponding group without OSA. Compared with lean individuals without OSA, MSNA, expressed as burst frequency over time or corrected for heart rate, showed an increase in lean individuals with OSA. The increase was similar to that of obese individuals without OSA but less than that of obese individuals with OSA, in which MSNA reached the maximal between-group value. This was the case in male and female subjects. In the multivariate analysis performed on the whole studies sample, MSNA was positively related to waist-to-hip ratio, apnea/hypopnea index, and HOMA index (β coefficient 0.73±0.09, 0.66±0.11, and 0.64±0.12, respectively; P<0.01 for all), while showing no significant relationship with the other hemodynamic and metabolic variables. Plasma NE was greater in the 2 obese than in the 2 lean groups, however, with no significant difference being detected between OSA and non-OSA individuals.

**Discussion**

In the present study, sympathetic nerve activity was: (1) greater in obese subjects without OSA than in lean subjects without OSA, (2) greater in obese subjects with OSA than in lean subjects with OSA, and (3) greater in subjects with than in those without OSA, regardless the presence or absence of
obesity. This allows the following conclusions to be drawn. (1) The sympathetic activation seen in human obesity occurs independently on OSA; (2) OSA has a sympathostimulating effect that is independent of body weight but additive to that displayed by the overweight state; and (3) the OSA-dependent and OSA-independent sympathostimulating effects contribute to the overall sympathetic hyperactivity of obesity.

Our data confirm the conclusion reached by Narkiewicz et al.\(^1\) that OSA has a sympathostimulating effect and additionally show that this is the case regardless of any body weight abnormality. They are also in line with the evidence provided by the same authors that the OSA-dependent sympathetic stimulation plays a role in the hyperadrenergic state characterizing obesity. However, they disagree with the conclusion they draw that obesity is associated with no hyperadrenergic state if there is no OSA because under this circumstance, our obese individuals exhibited a clear-cut increase in MSNA compared with the non-OSA lean controls. We can speculate that the underestimation by Narkiewicz et al.\(^1\) of the non-OSA–related sympathostimulating factors was attributable to the high prevalence in their study of females, in whom

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lean Subjects Without OSA (n=27)</th>
<th>Lean Subjects With OSA (n=16)</th>
<th>Obese Subjects Without OSA (n=18)</th>
<th>Obese Subjects With OSA (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>21/6</td>
<td>13/3</td>
<td>14/4</td>
<td>20/5</td>
</tr>
<tr>
<td>Age (y)</td>
<td>47.6±1.6</td>
<td>47.4±1.8</td>
<td>49.1±2.1</td>
<td>48.7±1.5</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>23.9±0.4</td>
<td>24.3±0.7</td>
<td>32.2±0.6†</td>
<td>32.6±0.6†</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.76±0.01</td>
<td>0.77±0.01</td>
<td>0.95±0.01†</td>
<td>0.96±0.01†</td>
</tr>
<tr>
<td>Sphygmo BP (S/D, mm Hg)</td>
<td>131.3±1.9/82.9±2.2</td>
<td>133.1±2.3/84.4±1.1</td>
<td>133.8±2.1/84.0±1.3</td>
<td>133.5±2.0/84.7±1.3</td>
</tr>
<tr>
<td>Finger BP (S/D, mm Hg)</td>
<td>129.5±1.8/81.2±1.3</td>
<td>130.8±2.4/82.3±1.4</td>
<td>131.1±2.0/82.7±1.3</td>
<td>131.9±2.2/83.5±1.5</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>69.4±1.3</td>
<td>70.2±1.4</td>
<td>72.7±1.4</td>
<td>74.1±1.3‡</td>
</tr>
<tr>
<td>Respiration rate (breaths/min)</td>
<td>19.4±0.4</td>
<td>19.7±0.4</td>
<td>19.9±0.5</td>
<td>19.3±0.5</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>98.9±0.2</td>
<td>97.8±0.3</td>
<td>98.1±0.4</td>
<td>97.3±0.4</td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>4.15±0.3</td>
<td>4.31±0.4</td>
<td>4.51±0.4</td>
<td>4.67±0.4</td>
</tr>
<tr>
<td>Plasma insulin (µU/mL)</td>
<td>8.2±0.4</td>
<td>9.4±0.4</td>
<td>13.5±0.7**</td>
<td>15.8±0.8§†</td>
</tr>
<tr>
<td>HOMA index (a.u.)</td>
<td>1.54±0.06</td>
<td>1.79±0.08‡</td>
<td>2.76±0.13†</td>
<td>3.32±0.11§†</td>
</tr>
<tr>
<td>Plasma leptin (mg/mL)</td>
<td>5.2±1.3</td>
<td>7.7±1.5</td>
<td>10.4±1.3†</td>
<td>13.8±1.5§†</td>
</tr>
<tr>
<td>Plasma renin activity (mg/mL/h)</td>
<td>0.8±0.2</td>
<td>1.1±0.3</td>
<td>1.9±0.4**</td>
<td>2.3±0.4**</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Sphygmo BP indicates sphygmomanometric blood pressure (average of 3 measurements); S, systolic; D, diastolic; a.u., arbitrary units. *P<0.01 vs lean subjects without OSA; †P<0.01 vs lean subjects with OSA; ‡P<0.05 vs lean subjects with OSA; §P<0.05 vs obese subjects without OSA.

Values of apnea/hypopnea index (AHI), plasma NE, and MSNA, expressed as bursts per minute (bs/min) and as bursts corrected for heart rate (bs/100 hb) in lean subjects without (L−) or with (L+) OSA and in obese subjects without (O−) or with (O+) OSA. Data are shown as means±SEM. Asterisks (∗P<0.05; †P<0.01) refer to the statistical significance between groups.
peripheral obesity is common at variance from visceral obesity, which is more typical of the male gender. However, visceral obesity is the condition that leads to a particularly marked increase in plasma insulin, plasma leptin, and sympathetic activity, thus making the contribution of factors related to obesity, per se, rather than OSA more clear. In our study, 79% of the obese subjects were males, in contrast with the 58% of the study by Narkiewicz et al.19

Several other results of our study deserve to be discussed. First, as mentioned above, our data provide the first evidence that OSA is associated with a marked MSNA increase not only in obese but also in lean individuals. It is likely that in both conditions, this increase originates from the stimulation of peripheral chemoreceptors brought about by the anoxia induced by the hypopneic–apneic episodes.17–19 However, it should be emphasized that other mechanisms are probably involved. For example, we and others have shown that in OSA subjects, there is an impairment of the arterial baroreflex and thus of the ability of this mechanism to provide a continuous restraint on sympathetic tone.30,31 Furthermore, in the lean subjects of the present study, OSA was associated with greater values of insulin resistance (HOMA index) as well as of leptin and plasma renin activity, similar to what was seen in obese subjects with OSA versus those without OSA.32–34 Because insulin resistance (through hyperinsulinemia, leptin, and plasma renin activity (through angiotensin II) stimulate sympathetic activity,11–15,29,35,36 the possibility exists that the OSA-dependent sympathetic activation is attributable not only to reflex but also to metabolic factors, the same multiple mechanisms operating in lean and obese individuals with OSA. However, because sympathetic stimulation increases insulin resistance and directly or indirectly stimulates renin secretion from juxtaglomerular cells,36,37 it is of course also possible that the sequence of events is the opposite. That is, the greater insulin resistance and plasma renin activity values associated with OSA do not cause but result from a metabolically independent sympathetic activation, possibly only originating from reflex mechanisms. Second, for a similar body mass index value, the presence or absence of OSA made a large difference in the degree of sympathetic overactivity. This suggests that studies aimed at comparing sympathetic activity in obese and lean subjects (as well as in obese states of different severity) require the assessment of OSA presence, which should be matched for prevalence and severity between groups. Finally, our data show that the assessment of sympathetic activity via plasma NE assay is capable to detect the increase in adrenergic drive associated with obesity but not that linked to OSA. This confirms the limitations of the approach that measures circulating levels of the adrenergic neurotransmitter as marker of sympathetic tone shown in previous studies.2,5,10,20,21,38

Perspectives

The results of our study have a limitation and a clinical implication. The limitation refers to the fact that we investigated obese subjects of mild to moderate degree, and thus, our data cannot be extrapolated safely to more severe obese individuals in whom the relative contribution of OSA-dependent versus OSA-independent sympathostimulating mechanisms remain to be determined. The clinical implication is that not only obese but also lean subjects with OSA may be exposed to the adverse effects of an increased sympathetic drive on cardiac and vascular function.18,39 They may additionally be exposed to the adverse effect of insulin resistance, which is the best predictor of the risk of developing diabetes mellitus.40 In practical terms, this means that the therapeutic approaches, such as continuous positive airway pressure,41,42 used in obese subjects with OSA to eliminate the apneic episodes and to improve insulin sensitivity might also be helpful when this condition occurs in lean individuals.

References


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