Sympathetic Activity in Obese Subjects With and Without Obstructive Sleep Apnea

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Background—Obese humans are reported to have increased muscle sympathetic nerve activity (MSNA). Obstructive sleep apnea (OSA) may also be accompanied by increased MSNA. Because there is a high prevalence of OSA in obese humans, it is possible that high MSNA reported in obese subjects may in fact reflect the presence of OSA in these subjects. We tested the hypothesis that obesity, per se, in the absence of OSA, is not accompanied by increased MSNA.

Methods and Results—We measured MSNA in 25 healthy normal-weight subjects and 30 healthy sedentary obese subjects. All subjects were screened by history and examination to exclude subjects with OSA or hypertension. OSA was further excluded by overnight polysomnographic studies. Despite careful screening, polysomnography revealed that 1 of 25 normal-weight subjects and 9 of 30 obese subjects had occult OSA (P=0.015). MSNA was similar in normal-weight subjects (41±3 bursts per 100 heartbeats) and obese subjects without sleep apnea (42±3 bursts per 100 heartbeats, P=0.99). MSNA in the 9 obese subjects with occult OSA was 61±8 bursts per 100 heartbeats, which was higher than MSNA in normal-weight subjects without sleep apnea (P=0.02) and higher than MSNA in obese subjects without sleep apnea (P=0.02).

Conclusions—Obesity alone, in the absence of OSA, is not accompanied by increased sympathetic activity to muscle blood vessels. (Circulation. 1998;98:772-776.)

Key Words: obesity ■ sleep ■ nervous system, autonomic ■ nervous system, sympathetic

The link between obesity and cardiovascular disease is well recognized.1–3 The sympathetic nervous system, as an important contributor to the regulation of both the cardiovascular system and energy expenditure, is widely assumed to play a major role in the pathophysiology of obesity.4–7 Numerous studies over the past 2 decades have compared sympathetic nervous system activity in normal-weight and obese individuals. Studies based on catecholamine levels produced conflicting results,8–10 but the consensus favors increased norepinephrine levels in obese humans.9 Using studies of whole-body and regional norepinephrine kinetics in humans, Vaz et al10 found an increase in renal norepinephrine spillover but a reduction in sympathetic activity in the heart. Arterial plasma norepinephrine and whole-body plasma norepinephrine spillover were unrelated to body mass index (BMI). In humans, direct intraneural measurements of sympathetic nerve activity using microneurography have confirmed increased sympathetic neural drive in conditions such as heart failure,11 pregnancy-induced hypertension,12 and aging.13 Studies using microneurography have consistently shown increased muscle sympathetic nerve activity (MSNA) in obese Caucasian subjects.16–20 These observations suggest that obesity in humans is associated with increased sympathetic outflow and that body fat is a major determinant of sympathetic neural discharge.

In striking contrast, there is decreased activation of the sympathetic nervous system in animal models of obesity.21,22 Increased sympathetic activation is accompanied by increased resting metabolic rate and energy expenditure.21,23,24 It has been proposed that most experimental forms of obesity are low in sympathetic activity25 and that low sympathetic nervous activity may pose an increased risk for weight gain because of the lower metabolic rate.10,26,27 There is therefore a compelling discordance between these considerations and the high levels of sympathetic nerve traffic reported in obese humans.16–20

Obese subjects have a high prevalence of obstructive sleep apnea (OSA), which may itself be accompanied by increased levels of MSNA.26–28 None of the studies examining the link between obesity and sympathetic nerve activity have adjusted for the potential influence of OSA. Undiagnosed sleep-disordered breathing is highly prevalent and has a wide range of severity among middle-aged adults.29,30 A recent study on the frequency of sleep apnea in a population of obese subjects has provided evidence that even severely or morbidly obese men without a primary sleep complaint are at very high risk for sleep-disordered breathing.31 Thus, studies reporting high MSNA in obese subjects may in fact reflect the high MSNA due not to obesity, per se, but to OSA. The apparent
The relationship between obesity and high MSNA might therefore be due to the inadvertent inclusion of obese subjects with occult sleep-disordered breathing. We tested the hypothesis that obesity, per se, in the absence of OSA is not accompanied by increased MSNA. We measured sympathetic neural outflow to skeletal muscle blood vessels in normal-weight and obese subjects without any sleep-disordered breathing, which was confirmed by complete overnight polysomnography.

Methods

Subjects

Normal-weight and obese subjects were recruited from the University of Iowa and Iowa City community. Informed written consent was obtained from all subjects. The study was approved by the Institutional Human Subjects Review Committee.

We studied 25 normal-weight normal subjects (17 men and 8 women; mean age, 38 ± 2.8 years) and 30 normal sedentary obese subjects (19 men and 11 women; mean age, 40 ± 2.2 years). All subjects were free of any diseases and on no medications. Normal weight was defined as a BMI of 24 kg/m² for females and 25 kg/m² for males. Obesity was defined as a BMI of ≥30 kg/m². The mean BMI, calculated as the weight in kilograms divided by the square of the height in meters, was 23 ± 0.4 kg/m² (range, 19 to 25 kg/m²) for the normal-weight subjects and 36 ± 1.7 kg/m² (range, 30 to 52 kg/m²) for the obese subjects. All subjects were screened to exclude those with hypertension and those with a history suggestive of sleep-disordered breathing (daytime somnolence, disturbed sleep, and loud snoring).

Measurements

Sympathetic activity was measured during the daytime, in the morning or early afternoon, at least 3 hours after the last meal. Sympathetic nerve activity was recorded continuously by obtaining multunit recordings of postganglionic sympathetic activity to muscle, which was measured from a nerve fascicle in the peroneal nerve with the use of tungsten microelectrodes (shaft diameter, 200 μm; tapering to an uninsulated tip of 1 to 5 μm). A subcutaneous reference electrode was inserted 2 to 3 cm away from the recording electrode. Sympathetic bursts were identified by inspection of the mean voltage neurogram. Sympathetic activity was recorded with the subjects awake during 10 minutes of undisturbed supine rest and was expressed as bursts per minute and bursts per 100 heartbeats. Mean blood pressure was measured with a Physio-Control Lifelast 200 sphygmomanometer. Heart rate was measured by electrocardiography.

Continuous measurements of respiration and oxygen saturation were also recorded. None of the subjects had apnea, hypopnea, or oxygen desaturation during these daytime measurements.

Polysomnographic studies to determine whether subjects were free of sleep-disordered breathing were carried out on a separate day, only after daytime measurements of sympathetic nerve activity were obtained. All subjects underwent complete overnight polysomnographic recordings consisting of electroencephalogram, electrooculogram, electromyogram, ECG, chest wall movement, nasal and oral air flow (measured by temperature-sensitive thermocouples), and oxygen saturation. MSNA was not measured during polysomnographic studies.

Severity of sleep apnea was defined on the basis of the apnea-hypopnea index (AHI). Apnea refers to cessation of both nasal and oral airflow, and hypopnea refers to a reduction in airflow to <50% of baseline in association with oxygen desaturation. To be considered significant, abnormal respiratory events had to persist for a minimum of 10 seconds or had to occur in association with an arousal and/or a decrease in oxygen saturation by ≥3%. Obstruction was confirmed by respiratory effort recorded by thoracic-abdominal strain gauge and electromyogram. The AHI, indicating the number of respiratory irregularities per hour, was calculated as follows: (total number of apneas + hypopneas)/(total sleep time in minutes) × 60. An index of <5 is considered normal.

Statistical Analysis

Results are expressed as mean ± SEM. Statistical analysis consisted of ANOVA and ANCOVA, followed by the Scheffé test for multiple comparisons, to allow pairwise testing for significant differences between the groups. The Fisher exact test was used to compare frequency of occult OSA in normal-weight and obese subjects. The determinants of sympathetic nerve activity were assessed by stepwise multiple linear regression analyses, with MSNA as the dependent variable and BMI, age, and mean blood pressure as the independent variables.

Results

Despite careful screening, of the 30 apparently normal obese subjects, 9 were found to have OSA (AHI, 19 ± 4 events per hour). Only 1 of the 25 normal-weight subjects had OSA (P = 0.015 compared with obese subjects).

Demographic data for normal-weight subjects and obese subjects without sleep apnea and obese subjects with occult OSA are shown in the Table. There were no significant differences.
differences in systolic blood pressure or heart rate among the 3 groups. Although all participants were normotensive, subjects with occult OSA (n=9) had higher diastolic blood pressure (79±2 mm Hg) compared with normal-weight subjects without sleep apnea (n=24) (64±2 mm Hg, P<0.01) but not compared with the obese subjects without sleep apnea (n=21) (72±2 mm Hg, P=0.18). Oxygen saturation levels during MSNA recordings did not differ between obese subjects with occult OSA (96.8±0.5%) and obese subjects without OSA (97.5±0.3%, P=0.45) (Table).

There was no difference in MSNA between normal-weight subjects (41±3 bursts per 100 heartbeats) and obese subjects (42±3 bursts per 100 heartbeats) without sleep apnea (P=0.99) (Figures 1 and 2). Almost identical results were obtained after adjustment for mean arterial pressure (42±3 bursts per 100 heartbeats in normal-weight control subjects and 41±3 bursts per 100 heartbeats in obese subjects). MSNA in obese subjects was also similar to that in normal-weight subjects when the analysis was repeated in a subgroup that included only males (42±4 and 43±5 bursts per 100 heartbeats, respectively) or when values were expressed in bursts per minute (28±2 and 25±2 bursts per minute, respectively).

Whether expressed in bursts per 100 heartbeats or absolute burst frequency, MSNA levels in obese subjects with occult OSA were greater than the levels seen in either normal subjects or obese subjects without sleep apnea (Table, Figure 2). In the only apparently normal normal-weight subject (BMI, 24.7 kg/m²), who was found on polysomnography to have OSA, AHI was 22 events per hour and MSNA was 88 bursts per 100 heartbeats.

Stepwise multiple linear regression analysis revealed that only age was significantly correlated with MSNA in normal-weight subjects without OSA (R²=0.26, P=0.007). Mean arterial pressure, but not BMI or age, was independently linked to MSNA in obese subjects without sleep-disordered breathing (R²=0.17, P=0.05).

**Discussion**

The novel and important finding of the present study is that MSNA is not increased in obese subjects without OSA compared with normal-weight subjects.

The recent report of the National Commission on Sleep Disorders suggested that 40 million Americans suffer from sleep disorders and that the vast majority of these patients remain undiagnosed. Among specific sleep disorders, the most serious in terms of cardiovascular morbidity and mortality is OSA. Population-based data from the Wisconsin Sleep Cohort Study indicate that 9% of middle-aged men have ≥15 episodes of apnea and hypopnea per hour of sleep. The prevalence of sleep-disordered breathing rises dramatically in obese subjects. An increase of 1 SD in any measure of body habitus is related to a 3-fold increase in the risk of undiagnosed sleep-disordered breathing. Significant sleep apnea has been reported in 40% of severely and morbidly obese men without any primary sleep complaint. Furthermore, history and physical examination are of limited value as screening tools for sleep apnea, and complete overnight...
polysomnographic monitoring has been proposed as the “gold standard” for diagnosing sleep apnea.18,19

Previous studies examining the effects of BMI on MSNA suggested that sympathetic overactivity might constitute a mechanism by which obesity predisposes to cardiovascular disease.16,20 A significant positive correlation between body fat and MSNA has been reported.16,18,19 Other studies17,20 found that obese subjects had significantly higher rates of sympathetic discharge to skeletal muscle tissue compared with normal-weight subjects. That human obesity should be associated with increased sympathetic activity is in conflict with animal models of obesity, which show low sympathetic activity.21,22 Furthermore, sympathetic activation, by increasing energy expenditure, would be expected to oppose the development and maintenance of obesity.23,24

Previous studies of direct or indirect measurement of sympathetic activity in obese human subjects did not address the potential influence of sleep apnea in their populations.16–20 Thus, those studies are likely to have been influenced by the inclusion of significant numbers of subjects with OSA in the obese study populations. Given the high prevalence of OSA in obese subjects and the lack of reliable screening tests for the disorder, our study was designed to assess MSNA in obese subjects in whom sleep-disordered breathing was ruled out by complete overnight polysomnographic evaluation. In the present study, despite careful screening by history to exclude subjects with OSA, 30% of our obese subjects were found on overnight polysomnography to have occult OSA.

Our data show that MSNA is not increased in obese subjects without sleep apnea. Whether the analyses were carried out on unadjusted data, after adjustment for mean arterial pressure, or separately for men, the normal-weight control subjects and obese subjects without sleep apnea had comparable mean values of MSNA. MSNA was high even in obese subjects with mild occult sleep apnea. Thus, even low levels of severity of occult OSA in obese subjects may help explain the previously reported associations between obesity and high sympathetic neural activity. However, all subjects in our study were screened to exclude those with a history suggestive of sleep-disordered breathing. Thus, the criteria used to select obese subjects for our study do not allow us to demonstrate definitively that inclusion of subjects with occult OSA in unselected obese populations explains the high MSNA.

Increased sympathetic drive may be independently implicated in atherosclerotic vascular disease and adverse cardiovascular events.40 In our study, high levels of sympathetic nerve traffic were evident even in subjects with mild OSA. These findings are consistent with epidemiological studies examining the relationship between blood pressure and mild sleep apnea. Young et al41 have shown that subjects with even very mild sleep apnea (AHI between 5 and 15 events per hour) have ambulatory daytime systolic and diastolic blood pressures 10 and 5 mm Hg higher than blood pressures recorded in normal subjects without sleep apnea.

The mechanism underlying the increased MSNA in obese subjects with occult OSA is not known. Differences in oxygen saturation during wakefulness do not explain our findings of higher MSNA in these subjects. There were no apneic or hypopneic events during daytime recordings. Oxygen saturation averaged 98.3±0.3% in normal-weight control subjects and 96.8±0.4% in obese subjects with sleep-disordered breathing. We have previously shown that in free-breathing subjects, decreases in oxygen saturation to 91% are insufficient to elicit increases in MSNA.42

The strengths of our study include complete overnight polysomnographic recordings in both normal-weight and obese subjects. One of the limitations was that the diagnosis of sleep apnea was provided by a study based on a single night in a sleep laboratory. However, this is the standard procedure followed for the diagnosis of sleep apnea in the clinical setting.

In conclusion, our findings show that obesity alone, in the absence of OSA, is not accompanied by increased sympathetic activity to muscle blood vessels. Other investigators have shown that OSA is accompanied by increased cardiovascular morbidity and mortality.35,36 Since studies of cardiovascular risk associated with obesity have not taken into account the possible influence of OSA, our data provide a precedent for the concept that unrecognized OSA may contribute, in part, to the metabolic and cardiovascular derangements that are thought to be linked to obesity and to the association between obesity and cardiovascular risk.

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References

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