Obesity, a major health problem in industrialized societies, is associated with a high incidence of cardiovascular complications such as hypertension, ischemic heart disease, and stroke. However, the underlying mechanism relating obesity to these cardiovascular events is not clear. In experimental animal models, overfeeding stimulates sympathetic activity and because overfeeding is associated with insulin resistance and hyperinsulinemia, the question of whether these two factors may contribute to sympathetic activation is an intensively researched but unresolved issue. Sympathetic activation could contribute to increased systemic vascular resistance and hypertension through activation of α-adrenergic vasoconstriction and stimulation of the renin-angiotensin system. Such vasoconstriction could be reinforced by sympathetically mediated trophic effects on the vasculature. Furthermore, sympathetic activation has been shown to promote atherosclerosis, and it could trigger acute cardiovascular events by increasing platelet number and aggregability. Surprisingly, however, studies in humans examining the relation between sympathetic activity and body weight have produced conflicting results and shown decreased, normal, or augmented sympathetic activity in overweight subjects. Although many factors may explain such divergent findings in humans, the possibility that regional heterogeneity in sympathetic activity may underlie some of the variability in lean-obese comparisons has received little attention. Microneurography allows direct recording of postganglionic sympathetic nerve action potentials targeted at the skeletal muscle vascular bed and a recent study found a positive relation between sympathetic burst frequency and body fat. We therefore measured sympathetic nerve activity in skeletal muscle in a group of subjects covering a broad spectrum of percent body fat. To examine potential functional consequences of sympathetic nerve discharge, we simultaneously measured calf vascular resistance, arterial pressure, and energy expenditure. Furthermore, because we found that the rate of sympathetic nerve discharge was directly correlated with plasma insulin concentration, we tested whether in lean subjects, acute elevation of plasma insulin concentration to levels similar to those observed in fasting overweight subjects stimulates sympathetic activity.

**Methods**

Healthy lean or overweight subjects 18 to 50 years old were recruited by advertisement. Applicants who had metabolic or cardiovascular disorders, hypertension (sitting blood pressure of >140/90 mm Hg), unstable body weight (change of >1% within the month before the study), or regular ethanol consumption of more than 20 g/d or who were taking any medication were excluded on the basis of an interview. To confirm eligibility for the study, applicants who fulfilled the
above criteria underwent clinical examination by one of the authors, and in overweight subjects, an oral glucose tolerance test (75 g) was performed to document normal glucose tolerance. To ensure that the study population would cover a broad spectrum of body weight, body mass index (BMI; weight in kilograms divided by the square of height in meters) and percent body fat were calculated. Body fat was estimated by measuring skinfold thickness at four sites—biceps, triceps, subscapular, and suprailiac—using Lange calipers (Cambridge Scientific Instruments). As long as morbidly obese subjects are excluded, estimations of body fat obtained by this method correlate closely with those obtained by underwater weighing.16,17 The waist-to-hip ratio was assessed from the minimal waist girth and the maximal hip girth in the standing position. Of the 42 subjects who met all entry criteria, we did not succeed in obtaining a technically acceptable recording of muscle sympathetic nerve activity (MSNA) in 3 lean (BMI <27 kg/m²) and 2 overweight (BMI >27 kg/m²) subjects. The 37 subjects (19 women and 18 men) in whom we succeeded in obtaining a recording had a mean age of 31 ± 1 years (mean ± SEM; range, 19 to 48 years), a BMI of 26.4 ± 1.0 kg/m² (range, 18.6 to 43.7 kg/m²), and percent body fat ranging from 8% to 41% (mean, 25.0 ± 1.6%). All tests were conducted in the morning after the subjects fasted overnight. Subjects had been on a weight-maintaining diet containing at least 4% carbohydrates for 3 days before the test. The protocol was approved by the institutional review board on human investigation, and all subjects provided informed written consent.

General Procedures

Subjects were studied in the supine position. Heart rate (ECG), respiratory excursions (pneumobelt), blood pressure (Finapres blood pressure monitor, Ohmeda),18 calf blood flow (venous occlusion plethysmography), and effector MSNA were recorded continuously on an electrostatic recorder and on a TEAC R 71 tape recorder (TEAC Corp). Respiratory excursions were monitored to detect inadvertent performance of a Valsalva maneuver or prolonged expiration; these respiratory maneuvers can markedly stimulate MSNA.20 An intravenous catheter was inserted in an antecubital vein for blood sampling. Urine was collected before and at the end of the study for nitrogen determination.

Recording of Sympathetic Nerve Activity

Multunit recordings of sympathetic nerve activity were obtained through the use of unipolar tungsten microelectrodes inserted selectively into muscle nerve fascicles of the peroneal nerve posterior to the fibular head following the microneurographic technique of Vallbo et al.13 The neural signals were amplified (by 20 to 50 × 10⁵), filtered (bandwidth, 700 to 2000 Hz), rectified, and integrated (time constant, 0.1 second) to obtain a mean voltage display of sympathetic activity. A recording of MSNA was considered acceptable when it revealed spontaneous, pulse-synchronous bursts of neural activity, with the largest bursts showing a minimal signal-to-noise ratio of 3:1. In each experiment, we documented that we were recording sympathetic outflow to skeletal muscle by demonstrating that the neural activity did not respond to arousal stimuli (loud noise or skin pinch) but showed a characteristic biphasic response to the Valsalva maneuver.20 This response consists of sympathetic activation during phases II and III (decrease in blood pressure) followed by sympathoinhibition during phase IV (overshoot in blood pressure during release), the latter being used to define the noise level.

Sympathetic bursts were identified by inspection of the filtered and mean voltage neurograms. We analyzed nerve recordings while blinded to patient condition. In our laboratory, the intraobserver and interobserver coefficients of variation of the mean in identifying bursts are <6% and <9%, respectively.21 Nerve traffic was expressed as the number of bursts of sympathetic activity per minute. Sympathetic burst frequency has been shown to be remarkably stable when a given subject is studied on repeated occasions.12 To determine the intrasubject variability in burst frequency in subjects included in the present study, we performed nerve recordings in 17 subjects on two separate occasions 1 to 52 weeks apart. The variability in burst frequency was ±5 bursts per minute.

Calf Blood Flow

While recording sympathetic outflow to calf muscles in one leg, we simultaneously measured calf blood flow in the contralateral leg. Calf blood flow was measured with venous occlusion plethysmography using mercury-in-Silastic strain gauges.19 The calf was elevated 10 to 15 cm above the level of the right atrium to collapse the veins. The circulation to the foot was arrested by inflating a cuff around the ankles during blood flow determinations, which were performed at 15-second intervals for 5 minutes.

Indirect Calorimetry

Resting metabolic rate was calculated from respiratory gas exchanges (determined by a computerized, flow-through canopy gas analyzer system; Deltatrac, Datex) and urinary nitrogen excretion, after correction for changes in body urea nitrogen pool.22,23 The following stoichiometric equations were used:

1 mol Glucose + 134.3 L O₂ → 134.3 L CO₂ + 2821.5 kJ
1 g Lipid + 2.09 L O₂ → 1.47 L CO₂ + 38.9 kJ
6.21 g Endogenous Protein (1 g N) + 6.46 L O₂
→ 5.34 L CO₂ + 114.2 kJ

Predicted energy expenditure was calculated using the equations of Fleisch.24 To determine the variability in an individual subject's resting metabolic rate obtained under these conditions, we measured the resting metabolic rate in 15 of the subjects on two separate occasions 1 to 9 weeks apart. At the time of the second measurement, they were within 1% of their body weight at the initial assessment. The variability in energy expenditure was 0.120 ± 0.028 kJ/min.

Experimental Protocol

To ensure a stable level of baseline values, after instrumentation all subjects rested quietly for at least 30 minutes. Then, respiratory gas exchanges were measured for two consecutive 30-minute periods, and nerve activity, calf blood flow, blood pressure, and heart rate were measured continuously during three 5-minute periods. In addition, three venous blood samples obtained through an indwelling cannula in the forearm were obtained at 15-minute intervals for determination of plasma catecholamine and plasma insulin concentrations. The samples were collected in prechilled tubes treated with heparin and immediately centrifuged at 4°C. For technical reasons, respiratory gas exchanges could not be obtained in five subjects.

To examine whether in lean subjects elevation of plasma insulin concentration to levels commonly observed in overweight subjects stimulates sympathetic nerve activity, we performed in 19 subjects (three women and two men; age, 36 ± 5 years; BMI, 22.4 ± 0.9 kg/m²; body fat, 23.8 ± 1.5%) a primed continuous low-dose (0.15 mU · kg⁻¹ · min⁻¹) infusion of crystalline insulin (Actrapid HM, Novo Industri S/A) for 2 hours. Euglycemia was maintained by determining plasma glucose concentration every 10 minutes and periodically adjusting a variable infusion of 20% dextrose.25 Sympathetic nerve activity was recorded for 5 of every 15 minutes throughout the infusion.
Statistical analysis was performed using the JMP program (SAS Institute Inc). Comparisons between lean and overweight subjects were done using unpaired two-tailed t tests. The relation between MSNA and body fat, plasma insulin levels, plasma lactate concentration, and age was assessed by multiple linear regression analysis. Correlation coefficients were calculated according to the method of least squares. A value of P<.05 was considered significant. Data are given as mean±SEM.

Results

Fig 1 shows representative recordings of sympathetic nerve activity in four subjects with percent body fat ranging from low normal to markedly elevated. Because multivariate regression analysis with MSNA as the dependent variable in a model including BMI and sex revealed that sex was not a significant (F ratio, 1.63; prob >F, 0.21) predictor of MSNA, male and female subjects were pooled.

A correlation matrix of relevant variables is shown in Table 1. The resting rate of sympathetic nerve discharge to skeletal muscle was strongly and directly correlated with both BMI (r=.67, P<.0001; Fig 2) and percent body fat (r=.71, P<.0001). Such a relation was present in both sexes, and the r values for the correlation between the rate of sympathetic firing and BMI were .69 in women (P=.001) and .59 in men (P=.009). In addition to body fat, sympathetic nerve activity was directly correlated with plasma insulin concentration (r=.34, P<.04; Fig 3), age (r=.40, P<.02), and plasma lactate concentration (r=.35, P<.04). With multiple linear regression analysis with MSNA as the dependent variable, a model that included BMI, age, and plasma insulin and plasma lactate concentrations determined 58% of the variability of MSNA, with BMI (P<.0001) and plasma insulin concentration (P<.05) but not age and plasma lactate concentration remaining independent determinants of sympathetic activity (Table 2). When logarithmic transformation of MSNA, lactic acid, and plasma insulin was used in the same model, lactate (P=.008) together with BMI (P=.0002) and insulin (P=.05) but not age (P=.30) were independent determinants of MSNA.

Increased body weight was associated with marked sympathetic activation. For example, using a BMI of 27 kg/m² to separate lean from obese subjects, we found that the rate of sympathetic discharge in obese subjects was 1.8-fold that of lean subjects: 32±2 compared with 18±2 sympathetic bursts per minute (P<.0001).

In contrast to sympathetic discharge to skeletal muscle, venous plasma norepinephrine concentrations were not significantly correlated with BMI and percent body fat (Table 1). Venous plasma epinephrine concentrations were inversely related to percent body fat (r=-.32, P=.05). We found no significant relation between heart rate and BMI or percent body fat.

To examine potential functional consequences of sympathetic nerve discharge, we performed simultaneous measurements of regional vascular resistance and energy expenditure. Calf vascular resistance was directly related to the rate of sympathetic nerve discharge to the same vascular bed (r=.40, P<.02; Fig 4). In contrast, we found no correlation between resting metabolic rate (expressed as percent of the predicted value) and the rate of sympathetic nerve discharge to skeletal muscle (r=.22, P=.19 for all subjects; r=.03, P=.92 and

Analytical Methods

Plasma glucose was determined in duplicate by the glucose oxidase method with a Beckman glucose analyzer (Beckman Instruments). Plasma insulin was measured by radioimmunoassay,26 catecholamines by high-performance liquid chromatography,21 blood urea nitrogen by a Beckman urea analyzer (Beckman Instruments), and urinary nitrogen by the Kjehldahl method. Lactate was measured enzymatically.27

Data Analysis

Mean arterial pressure was calculated as diastolic pressure plus one-third pulse pressure. Vascular resistance in the calf was calculated as mean arterial pressure (in millimeters of mercury) divided by blood flow (in milliliters per minute per 100 mL tissue) and expressed in units.

The values for sympathetic activity, calf blood flow, blood pressure, and heart rate represent the mean of the three 5-minute measurement periods. The values for energy expenditure represent the mean of the second 30-minute measurement period. The values for venous plasma catecholamine and plasma insulin concentrations represent the mean value of the three determinations.
TABLE 1. Correlation Matrix Showing Pairwise Associations of Relevant Variables

<table>
<thead>
<tr>
<th></th>
<th>MSNA</th>
<th>Calf Vascular Resistance</th>
<th>Plasma Insulin</th>
<th>Plasma Norepinephrine</th>
<th>Plasma Lactate</th>
<th>Body Mass Index</th>
<th>Percent Body Fat</th>
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<tr>
<td>MSNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Calf vascular</td>
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<td>.32</td>
<td>.33</td>
<td>.21</td>
<td>.41</td>
<td>.64</td>
<td>.41</td>
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<td>(NS)</td>
<td>(.046)</td>
<td>(.095)</td>
<td>(.061)</td>
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<tr>
<td>Plasma insulin</td>
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<td>.33</td>
<td>.21</td>
<td>.41</td>
<td>.64</td>
<td>.41</td>
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<td>(NS)</td>
<td>(NS)</td>
<td>(NS)</td>
<td>(NS)</td>
<td>(.016)</td>
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<tr>
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<td>.05</td>
<td>.22</td>
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<td></td>
<td>(NS)</td>
<td>(NS)</td>
<td>(NS)</td>
<td>(NS)</td>
<td>(NS)</td>
<td>(.012)</td>
<td>(NS)</td>
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<tr>
<td>Plasma lactate</td>
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<td>.33</td>
<td>.21</td>
<td>.41</td>
<td>.64</td>
<td>.41</td>
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<td>(NS)</td>
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<td>(NS)</td>
<td>(.095)</td>
<td>(.061)</td>
<td>(.0000)</td>
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<tr>
<td>Percent body fat</td>
<td>.64</td>
<td>.39</td>
<td>.59</td>
<td>.22</td>
<td>.31</td>
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<td>.64</td>
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<td>(.0000)</td>
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<td>(NS)</td>
<td>(.095)</td>
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<td>(.0000)</td>
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<tr>
<td>Mean arterial pressure</td>
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<td>.41</td>
<td>.04</td>
<td>.08</td>
<td>.64</td>
<td>.64</td>
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<td>(NS)</td>
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<td>(NS)</td>
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<td>(.012)</td>
<td>(NS)</td>
</tr>
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</table>

MSNA indicates muscle sympathetic nerve activity. Values represent r values, and corresponding P values are given in parentheses. n=37.

r=.17, P=.52, respectively, when analyzed separately for men and women.

There was a close correlation between BMI and the percent body fat (r=.83, P<.0001), and overall, the strength of the various relations examined did not differ greatly between BMI and percent body fat (Table 1).

Low-Dose Insulin Infusion Studies

Insulin infusion in five lean subjects at a rate of 0.15 mU·kg⁻¹·min⁻¹, which increased plasma insulin concentrations from 6.6±1.3 μU/mL at basal to 20.8±1.8 μU/mL at the end of the 2-hour infusion (P<.05), evoked marked sympathetic activation; sympathetic burst frequency increased from 11±1 at basal to 21±2 bursts per minute at the end of insulin/glucose infusion (P<.05). Plasma insulin concentrations at the end of low-dose insulin infusion in these lean subjects were comparable (P>.1) to fasting plasma insulin concentrations observed in the 17 overweight (BMI, >27 kg/m²) subjects included in this study (18.3±1.1 μU/mL).

Discussion

We used intraneural recordings to measure resting sympathetic nerve discharge in healthy, normotensive subjects covering a broad spectrum of percent body fat. The principal new conclusion is that sympathetic nerve activity is closely and directly related to percent body fat and BMI. These results indicate that in healthy subjects, body fat is a major determinant of resting sympathetic nerve activity and accounts for roughly 50% of the interindividual variation in the rate of sympathetic firing in skeletal muscle. Using simultaneous measurements of vascular resistance to examine potential functional consequences of such overweight-associated sympathetic activation, we found that the rate of sympathetic discharge to skeletal muscle tissue was directly correlated with calf vascular resistance.

Previous attempts to examine the effects of body weight on sympathetic activity were based mainly on

Fig 2. Plot of relation between body mass index (BMI) and rate of sympathetic nerve discharge to skeletal muscle vasculature. MSNA indicates muscle sympathetic nerve activity.

Fig 3. Plot of relation between rate of sympathetic nerve discharge to skeletal muscle and plasma insulin concentrations. To convert values for plasma insulin concentration to picomoles per liter, multiply by 7.175. MSNA indicates muscle sympathetic nerve activity.
measurements of plasma norepinephrine concentrations and urinary norepinephrine excretion that ranged from low to normal to high. In the present study, plasma norepinephrine concentrations varied markedly among both lean and overweight subjects and were not correlated with body fat. In contrast, increases in the rate of sympathetic firing to skeletal muscle with increasing body fat were a robust finding in our subjects. Using a BMI of 27 as a cutoff value between normal and overweight, we found that obese subjects had almost twofold higher rates of sympathetic discharge to skeletal muscle tissue than lean subjects. Such increases in the rate of sympathetic firing with increasing body weight were present in both sexes and occurred independent of the age of the subjects.

There is increasing evidence that sympathetic outflow to various organs may be highly differentiated, and our data regarding body fat–associated sympathetic activation in skeletal muscle tissue cannot be extrapolated to other vascular beds. Indeed, our finding of an inverse correlation between plasma epinephrine levels and body fat, which is in agreement with previous reports, suggests that overweight-associated sympathetic activation may not be uniform and, together with a possible overweight-associated stimulation of norepinephrine clearance, offers one likely explanation for the discrepancy between increased rates of sympathetic discharge to skeletal muscle and normal plasma norepinephrine values. On the other hand, and of potential pathophysiologic relevance, recent data in humans suggest that there may exist a close positive correlation between microneurographic measurements of resting sympathetic discharge to skeletal muscle and cardiac norepinephrine spillover.

Sympathetic activation in skeletal muscle could be of functional importance in several regards. For example, in experimental animals, increases in arterial pressure evoked by diet-induced sympathetic activation are prevented by concomitant administration of clonidine, indicating that in this model, sympathetic activation contributes to diet-induced pressor effects. In the present study in humans, using simultaneous measurements of sympathetic activity and vascular resistance in the same vascular bed, we found that the rate of sympathetic discharge to calf muscles was directly correlated with vascular resistance. Such increases in peripheral vascular resistance could represent one of the factors contributing to the positive correlation between BMI and arterial pressure found in our subjects. Potential mechanisms by which sympathetic activation could increase vascular resistance may include activation of α-ergic vasoconstriction, stimulation of renin and subsequent angiotensin II release, trophic effects on the vasculature, and potentiation of vascular responsiveness to vasoconstrictor stimuli.

The sympathetic nervous system is involved not only in cardiovascular control but also in the regulation of energy expenditure, and sympathetic activation has been shown to stimulate energy expenditure. Recent research in humans suggests that skeletal muscle metabolism may account for part of the variance in basal metabolic rate among individuals. In the present study, we did not find a direct relation between sympathetic discharge to skeletal muscle and the deviation from predicted energy expenditure as determined by indirect calorimetry. This conclusion differs from that of a recent report by Spraul et al., indicating that there is not only, in agreement with the present data, a positive correlation between body fat and sympathetic nerve activity but also a significant relation between MSNA and energy expenditure. However, our findings are in agreement with recent data of the same group, indicating that there is no relation between sympathetic activity and resting metabolic rate in men. Although the reason for the difference between findings of the present study and of the study by Spraul et al is not clear, it does not appear to be related to the fact that our study included both men and women, because when we analyzed the data separately for each sex, we did not find a correlation between MSNA and energy expenditure in either group. Thus, although the present findings suggest that the rate of sympathetic discharge to skeletal muscle tissue may not be a major determinant of the interindividual variability of basal metabolic rate as measured by indirect calorimetry, this evidence is conflicting, and further studies are needed to examine whether such discharge is a determinant of resting muscle metabolism.

Although the mechanism by which overweight could lead to sympathetic activation remains unknown, at least two possibilities might be considered. In experimental rats, the sympathetic activation evoked by overfeeding is associated with insulin resistance and hyperinsulinemia. In both experimental animals and humans, acute hyperinsulinemia triggers sympathetic activation in skeletal muscle tissue. Thus, the present observation of a positive correlation between fasting plasma insulin concentration and the rate of sympathetic firing could be consistent with the hypothesis that hyper-

| Table 2. Regression Analysis With Muscle Sympathetic Nerve Activity as Dependent Variable |
|---------------------------------|-----------------|-------|---------|
| Independent Variables          | Sum of Squares | F     | Probability |> F  |
| Body mass index                | 1111.8         | 22.12 | .0000       |
| Plasma insulin concentration   | 209.3          | 4.17  | .049        |
| Age                            | 190.8          | 3.80  | .060        |
| Plasma lactate concentration   | 172.3          | 3.43  | .073        |

n=37.
insulinemia may be one of the factors contributing to sympathetic activation in overweight humans. This interpretation is supported by the present finding in lean subjects that low-dose insulin infusion (resulting in plasma insulin concentrations similar to those observed in fasting overweight subjects) markedly stimulates sympathetic activity.

An alternative mechanism may be suggested by the finding of a positive correlation between plasma lactate concentration and both body fat and MSNA. Increases in lactate with increasing body weight may reflect a disproportionate increase in skeletal muscle anaerobic glycolysis.39 In experimental animal models, infusion of lactic acid into skeletal muscle tissue stimulates metabolically sensitive muscle afferents,40 the activation of which evokes increases in sympathetic nerve traffic and blood pressure. In humans, anaerobic glycolysis–related decreases in intracellular pH in contracting skeletal muscle during static exercise are correlated with sympathetic activation.41 Thus, stimulation of chemosensitive afferent nerve endings by lactic acid could contribute to sympathetic activation in overweight subjects. Alternatively, sustained sympathetic activation may result in augmented glycolysis in skeletal muscle tissue and thereby stimulate lactic acid production.

Although undoubtedly many factors contribute to the increased incidence of cardiovascular complications in overweight subjects, sympathetic activation could be one important mechanism and could either trigger acute events or—possibly in conjunction with an impairment in insulin-induced vasodilation—contribute to sustained elevation of arterial pressure. With regard to the latter, recent data suggest that in overweight subjects, weight loss–induced reductions in arterial pressure are associated with decreases in both sympathetic vasoconstrictor outflow to skeletal muscle and peripheral vascular resistance.45 Finally, sympathetic activation could also represent a potential link between essential hypertension and insulin resistance in lean subjects.46,47

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