Dissociation Between Sympathetic Nerve Traffic and
Sympathetically Mediated Vascular Tone in
Normotensive Human Obesity

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Christine Ann Sinkey, William Geoffrey Haynes

Abstract—Obesity increases the risk of hypertension and its cardiovascular complications. This has been partly attributed to increased sympathetic nerve activity, as assessed by microneurography and catecholamine assays. However, increased vasoconstriction in response to obesity-induced sympatoactivation has not been unequivocally demonstrated in obese subjects without hypertension. We evaluated sympathetic α-adrenergic vascular tone in the forearm by brachial arterial infusion of the α-adrenoreceptor antagonist phentolamine (120 μg/min) in normotensive obese (daytime ambulatory arterial pressure: 123±1/77±1 mm Hg; body mass index: 35±1 kg/m²) and lean (daytime ambulatory arterial pressure: 123±2/77±2 mm Hg; body mass index: 22±1 kg/m²) subjects (n=25 per group) matched by blood pressure, age, and gender. Microneurographic sympathetic nerve activity to skeletal muscle was significantly higher in obese subjects (30±3 versus 22±1 bursts per minute; P=0.02). Surprisingly, complete α-adrenergic receptor blockade by phentolamine (at concentrations sufficient to completely inhibit norepinephrine and phenylephrine-induced vasoconstriction) caused equivalent vasodilatation in obese (−57±2%) and lean subjects (−57±3%; P=0.9). In conclusion, sympathetic vascular tone in the forearm circulation is not increased in obese normotensive subjects despite increased sympathetic outflow. Vasodilator factors or mechanisms occurring in obese normotensive subjects could oppose the vasoconstrictor actions of increased sympatoactivation. Our findings may help to explain why some obese subjects are protected from the development of hypertension. (Hypertension. 2008;52:1-9.)

Key Words: obesity ■ arterial pressure ■ sympathetic nervous system ■ vasoconstriction

Human obesity is associated with the development of hypertension,1 coronary atherosclerosis, myocardial hypertrophy,2 and increased cardiovascular morbidity and mortality.3 Several lines of evidence indicate that obesity activates the sympathetic nervous system.4–6 Sympathoactivation has been demonstrated in human obesity by plasma norepinephrine measurements, 24-hour urinary norepinephrine excretion, measurements of turnover of radiolabeled norepinephrine, microneurographic measurement of muscle sympathetic nerve activity (mSNA), dual α- and β-adrenergic antagonism, and systemic ganglionic blockade.7–12 Furthermore, body fat content is positively correlated with mSNA13 and arterial pressure,14 whereas reductions in body weight from a hypocaloric diet decrease mSNA, plasma norepinephrine,15 and arterial pressure.16 These observations have led to the assumption that augmented sympathetic activity to the skeletal muscle circulation translates into elevated sympathetic vasoconstrictor activity, which could, in turn, contribute to the development of obesity-induced hypertension. However, increased sympathetic nerve traffic has not been proven to cause vasoconstriction in obesity. Egan et al17 demonstrated that overweight subjects, most of them hypertensive, exhibit increased α-adrenergic vascular tone. Nevertheless, hypertension alone could explain this finding.18 No previous studies have examined sympathetic vascular tone in normotensive obese subjects, who may have factors protecting them from the development of hypertension. We designed this study to test the hypothesis that sympathetically mediated vascular tone is increased in obese subjects without hypertension. We used phentolamine, a nonselective α-adrenergic receptor antagonist, in conjunction with microneurographically measured mSNA, to assess the contribution of sympathetic nerve traffic to forearm vascular tone in obese normotensive subjects compared with lean control subjects.

Population and Methods

Participants

Subjects whose body mass index (BMI) was ≥27 kg/m² were considered obese, whereas subjects whose BMI was ≤25 kg/m² were
considered lean. We recruited obese (n=25) and lean (n=25) normotensive subjects, carefully pair matched by age and gender (group 1). Subjects were not formally matched by arterial pressure but had to have systolic and diastolic pressures under 140 and 90 mm Hg, respectively. Metabolic syndrome diagnosed according to National Cholesterol Education Program criteria was present in 5 subjects in the obese group. Subjects in group 1 underwent assessment of body adipose mass, ambulatory blood pressure monitoring, mSNA to leg, and forearm vascular responses to local α-adrenoceptor blockade.

Subsequently, after determining that the resting total forearm blood flow (FFB) was 60% higher in obese normotensive subjects, we conducted studies in additional 20 obese (5 with metabolic syndrome according National Cholesterol Education Program criteria) and 20 lean normotensive subjects (group 2), who were pair matched with regard to age and gender to participants in group 1. In this subudy, obese normotensive subjects received 60% higher doses of vasoactive medications to achieve equivalent forearm intravascular concentrations as those estimated in the lean normotensive control subjects. We estimated the intravascular concentration of vasoactive agents in lean and obese subjects by dividing the rate of infusion by total FBF, as used in previous studies.19

In addition, we recruited obese (n=9) and lean (n=5) subjects for measurements of mSNA to both the arm and leg (group 3). We did not perform blood tests (except screening tests), ambulatory blood pressure, or vascular reactivity studies in group 3. Exclusion criteria included atherosclerosis, diabetes, heart failure, other clinically relevant diagnoses, and weight change (ie, variation ≥5% of usual body weight) in the past 3 months. No subject, either lean or obese, had evidence of obstructive sleep apnea by diagnosis or Berlin Questionnaire.20 Estrogen-containing medications and vitamin C or E were halted 1 month before study entry. Antiinflammatory, vasoactive, or central nervous system–acting medications were not allowed unless withdrawn for ≥1 week before study sessions. Subjects were asked to refrain from alcohol for 24 hours, caffeine and food for 12 hours, and smoking for 2 hours before study sessions.

The study was approved by the University of Iowa Institutional Review Board, and all of the participants provided written informed consent.

Body Adiposity
BMI, waist:hip ratio, and dual energy X-ray absorptiometry (Hologic QDR-4500) were used to assess adiposity.

Hemodynamics
Ambulatory blood pressure was measured using a validated method (Space labs 90207).21 Daytime (8 AM to 12 AM) and nighttime (12 AM to 8 AM) arterial pressures were used for analysis. During experimental studies, supine arterial pressure was measured by a noninvasive automated oscillometric sphygmomanometer (Lifestat 200, Physio-Control). Heart rate was measured continuously using a lead II ECG. FBF was measured by venous occlusion plethysmography using indium/gallium-in-silastic strain gauges, as described previously.22,23

Microneurographic Assessment of Efferent Sympathetic Neural Activity
Direct intraneural recordings of mSNA to skeletal muscle were obtained by percutaneous insertion of tungsten microelectrodes into the peroneal or radial/median nerves. Well-validated criteria were used to determine that the amplified neurogram represented sympathetic activity to skeletal muscle.24 Sympathetic nerve activity was quantified by determining the burst frequency per minute.25-27

Biochemical Assays
Plasma lipids, glucose, and insulin were measured in all of the subjects using established methods at the University of Iowa Hospitals and Clinics. Insulin was measured by electrochemiluminescence immunoassay (Roche Diagnostics). Plasma renin activity (radioimmunoassay; Perkin-Elmer Life Sciences), leptin (radioimmunoassay; Linco), and norepinephrine (high-performance liquid chromatography with electrochemical detection) were measured in the University of Iowa General Clinical Research Center Core Analytic Laboratory.

Study Design and Procedures
At screening, subjects underwent measurements of body adiposity and 24-hour ambulatory blood pressure. Forearm vascular function and mSNA were assessed on 2 separate visits ≥1 day apart. All of the studies were performed at a constant temperature between 22°C and 24°C. Tracings of electrocardiograms, FBF, and mSNA were recorded to a Macintosh G4 Computer (Apple Inc) using a MacLab data acquisition system (AD Instruments).

Forearm Vascular Reactivity Study
The brachial artery was cannulated with a 27 SWG steel cannula followed by infusion of 0.9% NaCl. In group 1, the following drugs were infused intra-arterially: norepinephrine (48 and 480 pg/ml/min for 6 minutes each), nitroprusside (1 and 10 µg/min for 6 minutes each), isoproterenol (25 and 250 ng/min for 6 minutes each), and phentolamine (12 and 120 µg/min for 18 minutes each). Norepinephrine was infused with phentolamine at the end of the study to confirm that α-adrenoceptor blockade was maximal at the phenolamine dose of 120 µg/min. In group 2, the following drugs were infused intra-arterially: phenylephrine (0.08, 0.80, and 1.29 µg/min for 6 minutes each), nitroprusside (10 and 16 µg/min for 6 minutes each), isoproterenol (250 and 404 ng/min for 6 minutes each), and phentolamine (120 and 194 µg/min for 18 minutes each). Phenylephrine was infused with phentolamine at the end of the study to confirm that α-adrenoceptor blockade was maximal at the phentolamine dose of 194 µg/min. The selective α-adrenergic agonist phenylephrine was used in group 2 to exclude the confounding effect of β-adrenergic–dependent vasodilatation.

Drug infusions were separated by the administration of 0.9% NaCl for 20 minutes to prevent drug interactions. FBF responses were measured bilaterally, and forearm vascular resistance (FVR) was calculated by dividing mean arterial pressure (diastolic+1/3 pulse pressure) by FBF and expressed in mm Hg · min · dL/mL. Total FBF and vascular resistance were calculated from forearm volume measured by water displacement, FBF, and FVR. Phentolamine was given last because of its longer duration of action.26 Estimated intravascular concentrations of drugs were calculated in group 2 to allow for the comparison of vascular drug effects at similar concentrations in lean and obese subjects. Estimated intravascular concentrations were calculated from the drug infusion rate and total FBF.19

Microneurographic Study
The microneurography electrode was placed in the peroneal (groups 1 and 3) or radial/median nerves (group 3). Baseline microneurographic recordings were made over 30 minutes in resting supine subjects. Venous blood samples were obtained for biochemical assays after subjects had been supine for 30 minutes. The analysis of mSNA recordings was not blinded.

Sample Size Calculations and Statistical Analyses
The number of subjects was based on a power calculation that 18 subjects in groups 1 and 2 would give 80% power to detect a 6.4%-point difference in vasodilatation to phentolamine at a P value of <0.05, assuming an SD of 6.7. These calculations were based on previous results in hypertensive patients.18 Twenty to 25 subjects were recruited per group to allow for attrition.

Differences in baseline parameters, vascular responses to intra-arterial drugs, and mSNA responses between groups were analyzed by unpaired Student’s t test using Office Excel 2002 (Microsoft Corporation). Repeated FVR responses to the 2 doses of phentolamine in groups 1 and 2 were analyzed through repeated-measures ANOVA, with posthoc Tukey’s test, using SAS 9 (SAS Institute Inc). General linear models were used in multiple regression analyses using SAS 9. All of the group results are reported as means±SEMs, and P values <0.05 were considered statistically significant.
Results

Ambulatory arterial pressure, age, and gender were well matched between lean and obese subjects, whereas casual arterial pressure measured during screening was modestly higher in obese as compared with lean subjects (Table 1). Although in the normal range, low-density lipoprotein cholesterol and triglycerides were significantly higher and high-density lipoprotein cholesterol was significantly lower in obese subjects (Table 2). Glucose levels were similar, but insulin was substantially higher in the obese subjects. As expected, the obes subjects had significantly higher leptin levels. Plasma norepinephrine concentrations and renin activity were not significantly different in obese and lean normotensive subjects.

Peroneal nerve mSNA was significantly higher in obese than in lean normotensive subjects (30±2 vs 22±1 bursts per minute; P=0.02; Table 1). Notably, there was a highly significant correlation between radial and peroneal nerve mSNA (Figure 1) in 14 subjects (group 3) across a wide range of BMIs (23 to 44 kg/m²). No significant interaction between group allocation and gender with regard to mSNA was observed (F value for the interaction = 0.67; P=0.52). Also, adjustment of mSNA by gender did not materially alter the observed (F value for the interaction = 0.67; P=0.52). Also, adjustment of mSNA by gender did not materially alter the results (overal model unadjusted F value = 6.53, P=0.014; adjusted F value = 3.97, P=0.026).

Table 1. Demographic, Body Adiposity, Blood Pressure, mSNA, and Resting Vascular Data

<table>
<thead>
<tr>
<th>Subject Characteristics</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obese</td>
<td>Lean</td>
<td>Obese</td>
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<tr>
<td>Male/female, n/n</td>
<td>5/20</td>
<td>5/20</td>
<td>5/15</td>
</tr>
<tr>
<td>Smokers, n</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Age, y</td>
<td>39±2</td>
<td>39±2</td>
<td>39±3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>35±1†</td>
<td>22±1</td>
<td>34±1†</td>
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<tr>
<td>DEXA body fat, %</td>
<td>40±1†</td>
<td>27±1</td>
<td>38±1†</td>
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<tr>
<td>Waist:hip ratio</td>
<td>0.85±0.02*</td>
<td>0.79±0.02</td>
<td>0.90±0.02*</td>
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<tr>
<td>Daytime SAP, mm Hg</td>
<td>123±1</td>
<td>123±2</td>
<td>126±3</td>
</tr>
<tr>
<td>Daytime DAP, mm Hg</td>
<td>77±1</td>
<td>77±2</td>
<td>78±2</td>
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<tr>
<td>Nighttime SAP, mm Hg</td>
<td>113±2</td>
<td>112±2</td>
<td>115±2</td>
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<tr>
<td>Nighttime DAP, mm Hg</td>
<td>67±1</td>
<td>66±2</td>
<td>66±1</td>
</tr>
<tr>
<td>24-hour heart rate, bpm</td>
<td>82±2†</td>
<td>74±2</td>
<td>83±2</td>
</tr>
<tr>
<td>Casual SAP, mm Hg</td>
<td>122±2*</td>
<td>115±2</td>
<td>123±3†</td>
</tr>
<tr>
<td>Casual DAP, mm Hg</td>
<td>79±2†</td>
<td>71±2</td>
<td>75±2*</td>
</tr>
<tr>
<td>Leg mSNA, burst per minute</td>
<td>30±3*</td>
<td>22±1</td>
<td>N/A</td>
</tr>
<tr>
<td>Arm mSNA, burst per minute</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Forearm volume, mL</td>
<td>1232±49†</td>
<td>845±44</td>
<td>1111±85†</td>
</tr>
<tr>
<td>Resting FBF, mL/min · dL</td>
<td>3.4±0.3</td>
<td>3.1±0.2</td>
<td>4.3±0.4*</td>
</tr>
<tr>
<td>Resting FVR, mm Hg · min · dL/mL</td>
<td>32±2</td>
<td>29±2</td>
<td>27±2</td>
</tr>
<tr>
<td>Resting total FBF, mL/min</td>
<td>42±7†</td>
<td>26±2</td>
<td>52±8*</td>
</tr>
<tr>
<td>Resting total FVR, mm Hg · min/mL</td>
<td>2.8±0.2</td>
<td>3.5±0.2</td>
<td>2.5±0.3*</td>
</tr>
</tbody>
</table>

DELA indicates dual energy X-ray absorptiometry; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; casual SAP and DAP, blood pressures measured during screening; N/A, not available. Data are means ± SEMs unless otherwise specified.

*P<0.05 obese vs lean.
†P<0.01 obese vs lean.
‡P<0.001 obese vs lean.

Table 2. Blood Biochemical Assay Results (Group 1)

<table>
<thead>
<tr>
<th>Biochemical Assay</th>
<th>Obese</th>
<th>Lean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol, mg/dL</td>
<td>186±8</td>
<td>168±6</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>107±11*</td>
<td>80±7</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>45±2*</td>
<td>56±3</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>119±6†</td>
<td>96±6</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>88±2</td>
<td>86±1</td>
</tr>
<tr>
<td>Insulin, μU/mL</td>
<td>10±2†</td>
<td>4±1</td>
</tr>
<tr>
<td>HOMA index</td>
<td>35±4†</td>
<td>17±4</td>
</tr>
<tr>
<td>Leptin, ng/mL</td>
<td>30±3†</td>
<td>10±2</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>260±50</td>
<td>310±45</td>
</tr>
<tr>
<td>PRA, ng/mL per hour</td>
<td>0.8±0.1</td>
<td>0.9±0.2</td>
</tr>
</tbody>
</table>

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; HOMA, homeostasis model assessment; PRA, plasma renin activity. Data are means ± SEMs.

*P<0.05 obese vs lean.
†P<0.001 obese vs lean.
As expected, forearm volume was substantially higher in obese subjects than in lean subjects in all of the groups (Table 1). Resting FBF per unit of arm volume (mL/min · dL) was similar in obese and lean subjects in group 1. Thus, total resting FBF was ≈60% higher in obese versus lean subjects in group 1 (Table 1). Based on these data, obese normotensive subjects in group 2 received 60% higher maximal doses of infused drugs than lean subjects to allow comparison of vascular responses to equivalent estimated intravascular drug concentrations. Resting FVR per unit of arm volume was similar in obese and lean subjects in all of the groups (Table 1).

Brachial artery infusion of vasoactive drugs did not change blood pressure, heart rate, or noninfused FBF (results not shown). Norepinephrine caused similar vasoconstriction in obese and lean normotensive in group 1 (ΔFVR in response to the high dose of norepinephrine: obese +39±6% versus lean +33±5%; P = 0.61; Table 3 and Figure 2A). To exclude a confounding effect of β-adrenergic vasodilatation from norepinephrine, phenylephrine was used in group 2, with similar vasoconstriction at equivalent intravascular concentrations in obese and lean subjects (ΔFVR: obese +26±4% versus lean +26±7%; P = 0.99; Table 4).

Phentolamine completely prevented forearm vasoconstriction to norepinephrine and phenylephrine in groups 1 (Figure 2A) and 2 (Figure 2B). In fact, modest vasodilatation was observed with both norepinephrine and phenylephrine in lean and obese subjects in groups 1 and 2 (Tables 3 and 4 and Figure 2A and 2B). The dilator response to norepinephrine when confused with phentolamine was significantly greater in lean normotensive subjects in group 1 (Table 3 and Figure 2A). Vasodilatation to phenylephrine when confused with phentolamine was similar in obese and lean normotensive subjects in group 2 (Table 4 and Figure 2B).

Importantly, the decrease in FVR caused by phentolamine infusion was identical in obese and lean normotensive subjects in group 1 (ΔFVR in response to the high dose of phentolamine: obese −57±2% versus lean −57±3%; P = 0.84; Table 3 and Figure 3A). The presence of metabolic syndrome did not change the vasodilatatory response to phentolamine in group 1 (ΔFVR in obese subjects with metabolic syndrome: −59±3%). Vasodilatation to equivalent estimated intravascular concentrations of phentolamine was also similar in obese and lean normotensive subjects in group 2 (ΔFVR: obese: −47±4% versus −53±5%; P = 0.48; Table 4 and Figures 3B and 4). The presence of metabolic syndrome did not change the vasodilatory response to phentolamine in group 2 (ΔFVR in obese subjects with metabolic syndrome: −43±8%). When the analysis of vascular responses to similar estimated intravascular concentrations of phentolamine was repeated only in women, there were similar results (please see the data supplement available at http://hyper.ahajournals.org).

Forearm vasodilatation to isoproterenol and nitroprusside was significantly lower in obese subjects in group 1 (Table 3). This was likely because of insufficient dosing of these drugs, because vasodilatation to isoproterenol and nitroprusside at equivalent estimated intravascular concentrations was similar in obese and lean subjects in group 2 (Table 4).

### Discussion

The main finding of this study is that normotensive obese subjects do not exhibit an increased sympathetic vasoconstrictor contribution to forearm vascular tone, despite elevated sympathetic nerve traffic to skeletal muscle. Our mSNA results confirm previous studies demonstrating that normotensive obese subjects have increased mSNA as com-

<table>
<thead>
<tr>
<th>Vasoactive Agent</th>
<th>Obese</th>
<th>Lean</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE 48 pmol/min, ΔFVR%</td>
<td>+14±4</td>
<td>+15±4</td>
</tr>
<tr>
<td>NE 48, absolute FVR, mm Hg · min · dL/mL</td>
<td>39±2</td>
<td>37±2</td>
</tr>
<tr>
<td>NE 480 pmol/min, ΔFVR%</td>
<td>+39±6</td>
<td>+33±5</td>
</tr>
<tr>
<td>NE 480, absolute FVR, mm Hg · min · dL/mL</td>
<td>45±3</td>
<td>46±3</td>
</tr>
<tr>
<td>NTP 1 μg/min, ΔFVR%</td>
<td>−54±2*</td>
<td>−60±2</td>
</tr>
<tr>
<td>NTP 1, absolute FVR, mm Hg · min · dL/mL</td>
<td>16±1</td>
<td>13±1</td>
</tr>
<tr>
<td>NTP 10 μg/min, ΔFVR%</td>
<td>−74±2†</td>
<td>−80±2</td>
</tr>
<tr>
<td>NTP 10, absolute FVR, mm Hg · min · dL/mL</td>
<td>9±1*</td>
<td>6±1</td>
</tr>
<tr>
<td>ISO 25 ng/min, ΔFVR%</td>
<td>−51±3</td>
<td>−56±3</td>
</tr>
<tr>
<td>ISO 25, absolute FVR, mm Hg · min · dL/mL</td>
<td>17±1</td>
<td>15±1</td>
</tr>
<tr>
<td>ISO 250 ng/min, ΔFVR%</td>
<td>−68±2†</td>
<td>−76±2</td>
</tr>
<tr>
<td>ISO 250, absolute FVR, mm Hg · min · dL/mL</td>
<td>10±1</td>
<td>7±1</td>
</tr>
<tr>
<td>ISO/NTP ratio</td>
<td>0.93±0.02</td>
<td>0.95±0.02</td>
</tr>
<tr>
<td>PHEN 12 μg/min, ΔFVR%</td>
<td>−47±2</td>
<td>−48±3</td>
</tr>
<tr>
<td>PHEN 12, absolute FVR, mm Hg · min · dL/mL</td>
<td>20±2</td>
<td>19±1</td>
</tr>
<tr>
<td>PHEN 120 μg/min, ΔFVR%</td>
<td>−57±2</td>
<td>−57±3</td>
</tr>
<tr>
<td>PHEN 120, absolute FVR, mm Hg · min · dL/mL</td>
<td>15±1</td>
<td>16±1</td>
</tr>
<tr>
<td>NE/PHEN coinfusion, ΔFVR%</td>
<td>−13±3*</td>
<td>−24±3</td>
</tr>
<tr>
<td>NE/PHEN, absolute FVR, mm Hg · min · dL/mL</td>
<td>13±1</td>
<td>11±1</td>
</tr>
<tr>
<td>PHEN/NTP ratio</td>
<td>0.78±0.03</td>
<td>0.72±0.04</td>
</tr>
</tbody>
</table>

FVR responses to norepinephrine (NE), nitroprusside (NTP), isoproterenol (ISO), and phentolamine (PHEN) are calculated as percentage changes from baseline. FVR response to NE/PHEN coinfusion is calculated as the percentage change from phentolamine infusion. Data are means ± SEMs.

*P < 0.05 obese vs lean.
†P < 0.01 obese vs lean.
Surprisingly, we found that vasodilatation of forearm resistance vessels to complete α-adrenergic blockade is not exaggerated in obese normotensive subjects. These results cannot be explained by α-adrenergic receptor downregulation in obesity, because obese and lean subjects had similar vasoconstrictor responses to both norepinephrine (Figure 2A) and phenylephrine (Figure 2B). Two previous studies by Egan et al. demonstrated increased forearm vasodilatation to phenolamine in lean hypertensive subjects compared with normotensive control subjects and in overweight, mostly hypertensive subjects compared with lean individuals, although mSNA was not recorded. These studies suggested that lean hypertensive and mostly hypertensive overweight subjects have increased sympathetic vascular tone. However, it has never been demonstrated whether the increase in mSNA observed in normotensive obesity leads to augmented sympathetically mediated vascular tone. Our results of no increase in sympathetic vascular tone in obesity contrast with those reported by Egan et al. in overweight subjects. However, the presence of hypertension in most overweight participants in the studies by Egan et al. could account for this difference.

Our conclusions rely on evidence that the achieved concentrations of phenolamine were sufficient to completely block vascular α-adrenergic receptors. Maximal α-adrenergic receptor blockade was achieved in lean and obese subjects because phenolamine completely blocked the vasoconstrictor effect of both norepinephrine and phenylephrine (Figure 2A and 2B). This was further confirmed by the lack of further vasodilatation with higher doses of phenolamine (ie, from 120 to 194 μg/min) in obese and lean subjects (Table 4 and Figure 3B). Interestingly, infusion of phenolamine with either norepinephrine or phenylephrine caused vasodilatation as compared with phenolamine alone (Figure 2A and 2B). It is presumed that such a vasodilatory effect was caused by the preferential activation of vascular β2-adrenergic receptors during profound inhibition of α1-adrenergic receptors.

Importantly, our findings suggest that microneurographic mSNA cannot be assumed to directly correlate with sympa-
Theoretically mediated vascular tone, because higher mSNA is not associated with increased vasodilation to phentolamine in the forearm of obese normotensive subjects (Figure 3A). It is intriguing to speculate that this dissociation between sympathetic vascular tone and mSNA may act to protect this subset of obese subjects from developing hypertension.

Although increased mSNA did not appear to directly elevate vascular tone in the forearm in our studies, sympathetic activation may still play a role in blood pressure regulation in obesity. Indeed, mSNA is highly correlated with cardiac and renal norepinephrine spillover in healthy subjects.35,36 Moreover, increased renal norepinephrine spillover has been documented in obese normotensive and hypertensive subjects, whereas cardiac norepinephrine spillover is increased in obese hypertensive subjects but reduced in obese normotensive subjects.37 Therefore, cardiorenal sympathetic activation could be important for the development and maintenance of obesity-related hypertension in humans even in the absence of increased \(\alpha\)-adrenergic vasoconstrictor tone to skeletal muscle.

Several mechanisms could explain the inability of increased mSNA to augment sympathetically mediated vascular tone in the forearm. First, we measured forearm vascular responses while mSNA was recorded from the peroneal nerve. However, we also measured resting mSNA in the radial/median and peroneal nerves in the same subjects and found a strong positive correlation between mSNA in the forearm and leg (Figure 1). Also, other investigators have shown that resting arm and leg mSNA measurements are concordant at rest and during lower-body negative pressure.38,39 These results indicate that mSNA recorded at the peroneal nerve most likely reflects sympathoactivation to the forearm.

Second, the vascular effects of increased mSNA in obesity may be opposed by vasodilator compensatory factors, such as insulin or leptin. Serum insulin was elevated in obese subjects in group 1 (Table 2) and has been shown previously to produce vasodilation while increasing mSNA in healthy subjects.26 However, insulin does not appear to oppose the vasoconstrictor effect of exogenous norepinephrine in obese hypertensive subjects, consistent with vascular insulin resistance.40 As expected, the adipocyte-derived hormone leptin was also substantially elevated in obese subjects in our study (Table 2). Although leptin causes vasodilation in vitro and in vivo,41–43 experimental hyperleptinemia increases arterial pressure, indicating a predominant sympathoexcitatory effect.44 Interestingly, a novel soluble vasodilatory factor derived from the perivascular fat tissue has been described recently.45,46 This molecule has not been isolated but acts through NO- and peroxide-dependent mechanisms to induce vasodilation47 and could potentially oppose the constrictor effects of increased sympathetic nerve output in obese subjects.

Third, endothelial and/or vascular smooth muscle dysfunction associated with obesity could lead to increased vascular tone, which, in turn, could attenuate phentolamine-induced vasodilation. However, we found that vasodilation to the selective \(\alpha_1\)-adrenoceptor agonist, isoproterenol (ie, partly endothelium dependent), and the NO donor, nitroprusside (ie,
endothelium independent), is not reduced in obese normoten-
sive subjects at equivalent estimated intravascular concen-
trations (Table 4). Thus, our data suggest that obesity without hypertension is not associated with forearm endothelial and/or smooth muscle dysfunction.

Fourth, sustained elevation of mSNA in obesity could downregulate adrenergic receptors and potentially blunt vascular responses to endogenous or exogenous adrenergic stimulation. However, our results show preserved adrenergic vasoconstrictor sensitivity in obese normotensive subjects (Tables 3 and 4 and Figure 2A and 2B).

Fifth, the contribution of endogenous norepinephrine to vascular tone depends not only on nerve traffic but also on the amount of norepinephrine released per sympathetic burst and presynaptic norepinephrine reuptake. Indeed, whereas whole-body norepinephrine spillover tends to be greater in obese women, norepinephrine spillover from abdominal subcutaneous adipose tissue and forearm skeletal muscle is greater in lean control subjects. Thus obesity-related changes in the production, storage, and clearance of norepinephrine in obesity could account for the observed discrepancy between sympathetic nerve activity and sympathetically mediated vascular tone.

Sixth, mSNA elevations observed in the obese subjects in group 1 (Table 1) were modest. Thus, it is possible that modest changes in sympathetic nerve activity may not be high enough to directly increase vascular tone, instead impacting arterial pressure through effects on the heart, kidney, and/or renin-angiotensin-aldosterone system.49 Finally, the pattern of single sympathetic nerve fiber activation has been shown recently to be different in lean and obese hypertensive subjects. In lean hypertensive subjects, the frequency of single nerve firing is elevated. In obese hypertensive subjects, the recruitment of active single nerve fibers is increased, whereas the frequency of firing is not altered. This result suggests that the distribution of sympathetic output to the skeletal muscle is altered in obesity-related hypertension. Therefore, increased mSNA in obesity could mainly target metabolic functions, namely, thermogenesis and lipolysis, rather than the skeletal muscle circulation.

Our study has several potential limitations. First, forearm sympathetic vascular tone may not reflect sympathetic regulation of other vascular beds, including the lower limb. Nonetheless, sympathetic nerve activity is elevated in the limbs of subjects with obesity. Second, plethysmographic assessment of FBF does not discriminate between blood flow to skeletal muscle and nonmuscular tissues in the forearm, and obese subjects have more subcutaneous adipose tissue. However, blood flow to subcutaneous adipose tissue is substantially lower in obese than in lean subjects (12% versus 19% of total FBF, respectively), suggesting little or no increase in total subcutaneous adipose tissue flow in obese subjects. Applying the estimates provided by Blaak et al to current results, absolute blood flow to subcutaneous fat would have been ≈5 mL/min in both lean and obese subjects. Similar findings have been observed in other adipose depots given that blood flow to the subcutaneous abdominal fat tissue is inversely proportional to the adipose mass. Thus, plethysmographic measurement of FBF appears to accurately reflect skeletal muscle blood flow despite obesity.

Another limitation of this study is that results mostly represent vascular and mSNA responses in women. However, there was no significant effect of gender on mSNA or phen tolamine response. Different phases of the menstrual cycle, which were not controlled for in this study, could have altered endothelial function results. Nonetheless, it can be assumed that any measurement error potentially derived from differences in menstrual cycle was distributed randomly between the obese and lean groups. Thus, it is unlikely that the lack of control for menstrual cycle could have biased the results.

One final limitation is that we specifically recruited obese normotensive participants. Thus, our findings are most applicable to obese subjects who may be inherently protected from the development of hypertension through sympathetically mediated vascular mechanisms.

In conclusion, we have demonstrated that, although mSNA is higher in normotensive obese subjects, sympathetically mediated vasoconstriction in the forearm is not enhanced. This dissociation could be because of opposing local factors (eg, insulin or leptin) or a different target of limb sympatho-activation (eg, metabolism versus vasculature). In obese normotensive subjects, our results suggest that increased microneurographic mSNA cannot always be assumed to reflect increased sympathetically mediated vascular tone in the skeletal muscle circulation. Indeed, the dissociation between vascular tone and sympathetic outflow may explain why some obese human subjects do not develop hypertension.

Perspectives
We observed no increase in sympathetic vascular tone in obese normotensive subjects. This population might be protected from the development of clinical hypertension by unknown factors or mechanisms that dissociate neural sympathetic outflow from vasoconstriction induced by the activation of adrenergic receptors. Obesity complicated with hypertension could be associated with increased sympathetic vascular tone. Alternatively, increased sympathetic outflow to organs or tissues other than the peripheral circulation, such as the kidneys, might play a more important role in arterial pressure elevation in human obesity, either directly or indirectly.

Acknowledgment
We are grateful to Dr Allyn L. Mark for his insightful comments on the article.

Sources of Funding
This work was supported by National Institutes of Health grant Hls14388 and 1UL1RR024979. M.L.d.G.C. was partly supported by the State University of Rio de Janeiro.
Disclosures

None.

References


Dissociation Between Sympathetic Nerve Traffic and Sympathetically Mediated Vascular Tone in Normotensive Human Obesity
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Hypertension, published online August 11, 2008;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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DISSOCIATION BETWEEN SYMPATHETIC NERVE TRAFFIC AND
SYMPATHETICALLY-MEDIATED VASCULAR TONE IN
NORMOTENSIVE HUMAN OBESITY

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Short title: Sympathetic Vascular Tone in Normotensive Obesity

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Similar forearm vasodilatation to 120 and 194 μg/min phentolamine infusion is depicted for obese (closed circles) and lean (open triangles) normotensive women. FVR, forearm vascular resistance. Data are means ± SEM.