Autonomic Blockade Reverses Endothelial Dysfunction in Obesity-Associated Hypertension

Alfredo Gamboa, Rocío Figueroa, Sachin Y. Paranjape, Ginnie Farley, Andre Diedrich, Italo Biaggioni

Abstract—Impaired nitric oxide (NO) vasodilation (endothelial dysfunction) is associated with obesity and thought to be a factor in the development of hypertension. We previously found that NO synthesis inhibition had similar pressor effects in obese hypertensives compared with healthy control during autonomic blockade, suggesting that impaired NO vasodilation is secondary to sympathetic activation. We tested this hypothesis by determining the effect of autonomic blockade (trimethaphan 4 mg/min IV) on NO-mediated vasodilation (increase in forearm blood flow to intrabrachial acetylcholine) compared with endothelial-independent vasodilation (intrabrachial sodium nitroprusside) in obese hypertensive subjects (BMI<40 kg/m²). Acetylcholine and sodium nitroprusside were given at equipotent doses (10, 30, and 50 μg/min and 1, 2, and 3 μg/min, respectively) to 14 obese subjects (49±3.6 years, 34±1 kg/m², 165/94±7/6 mmHg), on separate occasions 1 month apart, randomly assigned. Autonomic blockade increased basal forearm blood flow (from 3.9±0.7 to 5.2±1.2 mL/100 mL per minute, P=0.078). As expected, NO-mediated vasodilation was blunted on the intact day compared with NO-independent vasodilation; forearm blood flow increased from 3.6±0.6 to 10.1±1.1 with the highest dose of nitroprusside, but only from 3.7±0.4 to 7.2±0.8 mL/100 mL per minute with the highest dose of acetylcholine, P<0.05. In contrast, forearm blood flow responses to acetylcholine were restored by autonomic blockade and were no longer different to nitroprusside (from 6.2±1.1 to 11.4±1.6 mL/100 mL per minute and from 5.2±0.9 to 12.5±0.9, respectively, P=0.58). Our results support the concept that sympathetic activation contributes to the impairment in NO-mediated vasodilation seen in obesity-associated hypertension and provides further rationale to explore it as a therapeutic target. (Hypertension. 2016;68:00-00. DOI: 10.1161/HYPERTENSIONAHA.116.07681.)

Key Words: autonomic nervous system ■ hypertension ■ nitric oxide ■ obesity ■ vasodilation

There is increasing evidence supporting a role of the sympathetic nervous system in the development and maintenance of hypertension, and this is particularly true in obesity-associated hypertension. Not all obese subjects have increased sympathetic activity, and in fact there are selected populations (Pima Indians) with high prevalence of obesity and low sympathetic activity as measured by muscle sympathetic nerve activity when compared with whites. Furthermore, it is also possible that in some cases of monogenic obesity, sympathetic activity might not be increased or even could be decreased as is the case in congenital leptin deficiency. Nonetheless, the preponderance of evidence among white population, in whom most of the studies have been done, supports the concept that sympathetic activation accompanies obesity-associated hypertension and that there is a selective increase in sympathetic activity regulating vasomotor tone. Although regional sympathetic nerve activity might be heterogeneous in obesity, and whole-body norepinephrine spillover is not increased in all states of obesity, obese hypertensive subjects have been shown to have increased regional spillover to vascular beds that are relevant to hypertension, such as the kidneys and the heart. Furthermore, microneurographic recordings of sympathetic nerve traffic innervating the skeletal muscle vasculature, which is tightly coupled to baroreflex regulation, have consistently shown a strong positive relationship with body weight, body mass index, or percentage body fat. Local modulation of vascular tone also plays a role in blood pressure regulation. Among the factors involved, nitric oxide (NO) is arguably the most potent local vasodilator; we previously found that endogenous NO can restrain blood pressure by at least 30 mmHg in normal subjects. Previous studies have consistently shown that obesity is associated with impaired NO vasodilatory function, using either intrarrenal infusions of NO-mediated vasodilators (acetylcholine) or responses to shear stress (flow-mediated dilation). Impaired NO vasodilatory function, therefore, is a prime suspect in the development of obesity-associated hypertension.

These observations raise the possibility for an interaction between sympathetic activity and NO vasodilatory function. In this regard, Hijmering et al found that sympathetic activation induced by lower body negative pressure impaired flow-mediated dilation in healthy subjects. Similarly, Engelke et al showed that sympathetic activation induced by lower body negative pressure resulted in an acute impairment in...
NO-mediated dilation in response to intrabrachial infusion of acetylcholine in the forearm, also in healthy subjects. Furthermore, we previously found that NO synthesis inhibition with L-arginine (L-NMMA) produced similar increases in blood pressure in obese hypertensives compared with healthy controls if autonomic function was blocked, whereas impaired NO-mediated dilation would have resulted in a lower pressor response, as was the case in smokers.19 The objective of this study, therefore, was to test the hypothesis that sympathetic activity contributes to impaired NO-mediated vasodilation in obesity-associated hypertension, so that obese hypertensive subjects would have decreased vasodilation in response to intra-arterial acetylcholine (endothelial-dependent vasodilator) infusion when compared with intra-arterial sodium nitroprusside (SNP, endothelial-independent vasodilator), and that this impairment would disappear with ganglionic autonomic withdrawal with trimethaphan.

Methods

Subjects

The study was reviewed and approved by the Vanderbilt University Institutional Review Board, and written informed consent was obtained from each subject before initiating the study. The study was registered in ClinicalTrials.gov before enrolling (ClinicalTrials.gov identifier: NCT01137253).

We enrolled obese hypertensive volunteers from the Vanderbilt University Clinical Research Center volunteer database and Research Match.18 Subjects 18 to 60 years old of either sex with a body mass index between 30 and 40 kg/m² were considered eligible for the study. Current smokers, subjects with diabetes mellitus, patients with clinically apparent coronary or peripheral vascular disease, and pregnant women were excluded. All medications including antihypertensives were withdrawn at least 7 days before each study day with the exception of oral contraceptives. Subjects abstained from caffeine and other substances that are known to have an effect on the autonomic nervous system for 272 hours before testing. During the screening visit, all subjects underwent a clinical examination, ECG, urinalysis, and routine laboratory testing (ie, blood count and chemistry).

Study Design

Forearm vasodilation was assessed on 2 separate days, 1 month apart using identical instrumentation, as previously described17; once with intact autonomic function and once during autonomic blockade (Figure 1). Both the order of the study days and the infusions were randomized using a single-blind crossover design with a computer-generated randomization code. Subjects were blinded as to which treatment (trimethaphan or saline) would be received; the order of the intra-arterial infusions to allow parameters to return toward baseline values.

Instrumentation

For each study day, subjects were fasted and in the supine position. A catheter was inserted into the right antecubital vein for drug administration. An indwelling catheter was placed into the left brachial artery for intrarterial drug administration and connected through 3-way valves to a pressure transducer for continuous blood pressure measurements. Blood pressure was also measured in the finger using the volume clamp method (BMeye, Nexfin, Edwards Lifesciences), and every 5 minutes with an automated oscilometric brachial cuff (Vital-Guard 450C, Ivy Biomedical Systems). Heart rate was determined from continuous ECG monitoring. Cardiovascular signals were digitized using a Windaq system (DA-220; DATAQ Instruments). Forearm blood flow (FBF) was measured using venous occlusion mercury-in-silastic strain gauge plethysmography18 (Hokanson EC4, DE; Hokanson Inc).

Study Protocol

After instrumentation, subjects were allowed to rest in a quiet room for 15 minutes to ensure that all cardiovascular parameters had returned to resting values before taking baseline measurements (Figure 1). The subjects then received an intravenous infusion of either saline (48 mL/h, intact study day) or trimethaphan (4 mg/min, autonomic blocked day). Infusions were maintained throughout the study. We have shown previously that this dose induces complete autonomic blockade.19 After 15 minutes, a second set of measurements were taken and then increasing dosages of the vasodilator acetylcholine or SNP were administered intrabrachially in random order. Acetylcholine was infused at rates of 10, 30, and 50 µg/min. Nitroprusside was infused at rates of 1, 2, and 3 µg/min. The infusions were given in increasing doses for 5 minutes each, while monitoring the subject’s heart rate, and blood pressure. FBF was measured before infusions and during the last minute of each dose. Sufficient time was allowed between infusions to allow parameters to return toward baseline values.

Measurements

Subjects were warned ahead of time of all procedures done, and that they may produce discomfort, to avoid anticipatory reactions. To measure FBF, the forearm was elevated to at least 10 cm above the level of the right atrium to ensure that the forearm veins were drained at the beginning of each flow measurement. The wrist cuff was inflated to 200 mmHg 30 s before each series of forearm flow measurements to exclude blood flow through the hand. Four consecutive measurements were performed within 1 minute, and the last 3 measurements were averaged for the determination of the FBF for each study period. Mean arterial pressure (MAP) was calculated as systolic blood pressure×2/diastolic blood pressure and measured immediately after FBF measurements using intrabrachial blood pressure recordings. Forearm vascular resistance was calculated as MAP/ FBF, whereas forearm vascular conductance was calculated as FBF/ MAP×100 and expressed as arbitrary units.

Statistical Analysis

Unless noted otherwise data are presented as means±SEM. The main outcome selected at priori was endothelial function measured as the difference in the deltas in FBF in response to acetylcholine (endothelial-dependent vasodilator) versus SNP (endothelial-independent vasodilator) with intact autonomic nervous system (treatment 1) or with the autonomic nervous system blocked (treatment 2). Wilcoxon signed-rank test was used to prove the null hypothesis that there will be no differences in the deltas in FBF between interventions (intact versus blocked).

| H0: | \(\Delta_{\text{Blocked}} - \Delta_{\text{Intact}} = 0\) |
| where |
| \(\Delta_{\text{Intact}} = [\Delta FBF_{\text{Intact}}] - [\Delta FBF_{\text{NMMA}}]\) |
| \(\Delta FBF_{\text{Intact}} = FBF_{\text{PeakACh}} - FBF_{\text{Baseline}}\) |
| \(\Delta FBF_{\text{SNPIntact}} = FBF_{\text{PeakSNP}} - FBF_{\text{Baseline}}\) |
| \(\Delta_{\text{Blocked}} = [\Delta FBF_{\text{NMMA}}] - [\Delta FBF_{\text{NMMA}}]\) |
| \(\Delta FBF_{\text{AChBlocked}} = FBF_{\text{PeakACh}} - FBF_{\text{Baseline}}\) |
| \(\Delta FBF_{\text{SNPBlocked}} = FBF_{\text{PeakSNP}} - FBF_{\text{Baseline}}\) |

Sample size was determined using FBF in response to acetylcholine from our previous studies. With an SD of 3.4 mL/100 mL per minute, during intrabrachial infusion of acetylcholine (30 µg/min), using a paired t test with a 2-sided type I error probability of 0.05, it was determined that studying 14 subjects will have >95% power to detect a difference in FBF of 4 mL/100 mL per minute when comparing the before and after response to autonomic blockade. In addition, to adjust for sex and age, a random mixed-effects model was used to take into account correlations among repeated measures, to examine whether and to what extent the change in FBF differed by dose and drug (acetylcholine or SNP) in each of the 2 study days (intact versus blocked). All of the tests were 2-tailed, and a P value of <0.05 was
considered significant. Analyses were performed with SPSS statistical software (version 22.0.0, SPSS Inc).

Results

Demographics

We screened a total of 38 subjects. Twenty of them did not qualify because they were either no longer hypertensive after 2 weeks of medication withdrawal or were taking >3 antihypertensive medications. Eighteen subjects were qualified and enrolled in the study, but 4 were not able to complete both study days. Fourteen (8 males, 49±2.7 years of age, Table 1) obese (body mass index, 34±0.9 kg/m²) hypertensive subjects completed both study days. As expected, the percentage of body fat (measured by DEXA scan) was high (40±1.4%). Other parameters are shown in Table 1. Seven subjects were on antihypertensive medications and the others were medication-naive. Seated blood pressure was 131±3.6/83±3.1 mm Hg at screening day while on treatment and 156±6.2/90±3.9 mm Hg after medication withdrawal of at least 1 week.

Study Day Results

At baseline, there were no differences between study days in any of the variables measured (Table 2). Supine blood pressure was 153±5/88±3 and 156±5/90±4 mm Hg in the intact and blocked days, respectively, and FBF was 2.8±0.3 and 3.2±0.4 mL/100 mL per minute, respectively.

Autonomic blockade lowered blood pressure, stroke volume, total peripheral resistance, and forearm vascular resistance and conductance, while increasing heart rate and FBF, not only at baseline but during intra-arterial infusions of both vasodilators (acetylcholine and SNP), shifting upward the dose–response curve (Figure 2). Cardiac output was not different, neither between days nor before and after autonomic blockade.

Neither intrabrachial infusions of acetylcholine nor SNP had a statistically significant systemic vasodepressor effect (no dose, drug or interaction effect for MAP, Table 3). It is worth noticing, however, that during autonomic blockade, the highest dose of SNP tended to reduce MAP by 9 mm Hg, whereas acetylcholine only reduced it by 3 mm Hg. As expected, FBF increased with both drugs, but the vasodilatation induced by acetylcholine was blunted compared with SNP on the intact day (Figure 2, *P* dose=0.001, *P* drug<0.001, *P* drug×dose=0.016, by mixed effects model). This difference was no longer observed on the blocked day (*P* dose<0.001, *P* drug=0.318, *P* drug×dose=0.873, by mixed-effects model). Acetylcholine of 50 µg/min increased FBF from 3.17±0.44 to 7.16±0.54 mL/100 mL per minute during the intact (saline infusion) day, and from 5.66±0.71 to 13.24±1.35 mL/100 mL per minute during the blocked (trimethaphan infusion) day (Figure 3A). SNP of 3 µg/min increased FBF from 3.36±0.42 to 10.17±0.74 mL/100 mL per minute during the intact day and from 5.19±0.57 to 11.75±1.02 mL/100 mL per minute during the blocked (trimethaphan infusion) day (Figure 3A).

Table 1. Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, F/T (%)</td>
<td>6/14</td>
</tr>
<tr>
<td>Age, y</td>
<td>48.8±2.5</td>
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<tr>
<td>Weight, kg</td>
<td>102.0±3.9</td>
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<tr>
<td>BMI, kg/m²</td>
<td>34.1±0.9</td>
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<tr>
<td>Body fat, %</td>
<td>40.2±1.4</td>
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<td>Systolic BP, mm Hg</td>
<td>156.6±6.2</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>90.0±3.9</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>69.6±3.3</td>
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<tr>
<td>Glucose, mg/dL</td>
<td>92.9±4.2</td>
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<tr>
<td>Insulin, mU/dL</td>
<td>14.3±2.6</td>
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<tr>
<td>Triglycerides, mg/dL</td>
<td>125.1±25.2</td>
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<td>Cholesterol, mg/dL</td>
<td>174.6±12.3</td>
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<tr>
<td>HDL cholesterol, mg/dL</td>
<td>43.4±3.8</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>104.0±10.7</td>
</tr>
<tr>
<td>Systolic BP off medications*</td>
<td>155.5±6.2</td>
</tr>
<tr>
<td>Diastolic BP off medications*</td>
<td>89.6±3.9</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM and were obtained during the screening visit, except for those marked with an asterisk (*), which were obtained at baseline the first study day. BMI indicates body mass index; BP, blood pressure; LDL, low-density lipoprotein; and HDL, high-density lipoprotein.
The peak increase in FBF induced by these drugs was statistically significant between study days only for acetylcholine (3.99±0.49 versus 7.58±1.47 mL/100 mL per minute, for the intact versus block days, \(P=0.032\), Figure 3B). In contrast, the differences in vasodilation induced by SNP was minimal between study days (6.90±0.70 versus 6.56±0.89 mL/100 mL per minute, for the intact and blocked days, \(P=0.105\)). The difference in \(\Delta FBFI\) intact day (\(\Delta FBFAchI\)) between acetylcholine and SNP (\(\Delta FBFSNP\)) and \(\Delta FBF\) blocked day (\(\Delta FBF\ blocked\)) between acetylcholine and SNP (\(\Delta FBFAch\ blocked\)) was statistically significant (3.43±1.13 versus −0.80±1.63 mL/100 mL per minute, for the intact and blocked days, respectively, \(P=0.027\) by Wilcoxon signed-rank test).

### Discussion

Our results suggest that acute removal of sympathetic nervous system activity in obese hypertensive subjects, results in reversal of endothelial dysfunction, as assessed by NO-mediated vasodilation induced by intrarterial infusion of acetylcholine. When obese hypertensive subjects were studied with an intact autonomic nervous system, forearm vasodilation to intrarterial acetylcholine was blunted compared with SNP, but this difference was no longer present when the autonomic nervous system was pharmacologically blocked.

These results are in agreement with previous studies showing that transient increases in sympathetic activity result in acute impairment of NO-mediated vasodilation function in healthy subjects.13,14 We believe this study shows for the first time that sympathetically mediated vasoconstriction might be at least partly responsible for the apparent endothelial dysfunction seen in obesity-associated hypertension. This is also in agreement with our previous observation that blockade of NO synthase with L-NMMA results in similar increases in blood pressure in normotensive and hypertensive individuals studied during autonomic blockade,20 whereas a primary NO impairment would result in a blunted increase in blood pressure in response to L-NMMA, as we observed in smokers.15

Taken together, these findings support the hypothesis that

### Table 2. Differences in Hemodynamic Parameters Between Study Days and Between Baseline and During Infusions

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>Saline</th>
<th>Baseline</th>
<th>Trimethaphan</th>
<th>(P) (Saline-Trimt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mmHg</td>
<td>153±5.0</td>
<td>153±5.2</td>
<td>156±5.3</td>
<td>111±4.5(0.03)</td>
<td>0.003</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>88±3.0</td>
<td>89±3.2</td>
<td>90±3.8</td>
<td>70±2.8(0.03)</td>
<td>0.003</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>65±3.6</td>
<td>62±2.4</td>
<td>65±3.5</td>
<td>78±2.6(0.03)</td>
<td>0.008</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>6.2±0.6</td>
<td>6.5±0.6</td>
<td>6.6±0.7</td>
<td>5.7±0.4</td>
<td>0.779</td>
</tr>
<tr>
<td>SV, mL</td>
<td>94±5.7</td>
<td>97±5.6</td>
<td>99±7.3</td>
<td>77±3.8(0.016)</td>
<td>0.05</td>
</tr>
<tr>
<td>TPR, dyn×s×cm(^{-5})</td>
<td>1571±128</td>
<td>1503±121</td>
<td>1567±131</td>
<td>1255±86.3(0.02)</td>
<td>0.036</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>110±3.3</td>
<td>111±3.5</td>
<td>112±4.0</td>
<td>84±3.1(0.03)</td>
<td>0.003</td>
</tr>
<tr>
<td>FBF, mL/100 mL/min</td>
<td>2.8±0.3</td>
<td>3.2±0.4</td>
<td>3.2±0.4</td>
<td>5.4±0.7(0.01)</td>
<td>0.016</td>
</tr>
<tr>
<td>FVR, AU</td>
<td>49.7±7.4</td>
<td>42.5±6.7</td>
<td>44.8±6.8</td>
<td>20.0±3.2(0.03)</td>
<td>0.004</td>
</tr>
<tr>
<td>FVC</td>
<td>2.5±0.3</td>
<td>2.9±0.4(4.14)</td>
<td>2.6±0.3</td>
<td>1.97±0.8(0.03)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM. The \(P\) (before–after) column reflects differences between study days (intact vs blocked) during the infusions (saline or trimethaphan). No significant differences were observed between study days at baseline. CO indicates cardiac output; DBP, diastolic blood pressure; FBF, forearm blood flow; FVC, forearm vascular conductance; FVR, forearm vascular resistance; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure; SV, stroke volume; and TPR, total peripheral resistance.

\*\(P<0.05\) for the comparison between baseline and infusion for each study day.

Figure 2. Effect of increasing doses on sodium nitroprusside (SNP) or acetylcholine (ACh, x axis) on forearm blood flow (FBF, y axis) in obese hypertensive subjects studied on 2 separate occasions, during intravenous infusion of saline (intact autonomic nervous system [ANS], left) or the ganglionic blocker trimethaphan (blocked ANS, right). FBF dilation to ACh was significantly decreased compared with SNP when the ANS was intact (\(^*\)\(P<0.05\) by mixed effects model), but not if ANS was blocked by trimethaphan.
sympathetic activation, known to occur in obesity, tonically contributes to a reduction in NO function.

Ex vivo studies using arterioles from hypertensive and prehypertensive subjects have shown a normal response to NO-mediated vasodilators. Deng et al,23 using precontracted small arteries dissected from gluteal subcutaneous fat biopsies, have shown that response to acetylcholine was normal in prehypertensive subjects. Angus et al21 have shown the same in resistance arteries taken from hypertensive subjects. Furthermore, Angus et al21 found an increased reactivity to norepinephrine in these subjects. Taken together with our results, these observations suggest that early in the hypertensive disease process there is a functional state of endothelial dysfunction as a consequence of increased sympathetically mediated vasoconstriction, and that it can be reversed by sympathoinhibition. In this regard, it has been shown that transient increase in sympathetic activity achieved by lower body negative pressure, impairs both acetylcholine and SNP vasodilation in healthy subjects, and that local sympatholysis, reverses this effect. Engelke et al14 proposed that the sympathetic activity could restrain pharmacological vasodilation. Furthermore, it has been proposed that physiological increases in sympathetic activity (aging) could also result in a reduction of the vasodilatory effect of intra-arterial acetylcholine or SNP.21 The molecular mechanisms by which sympathetic activity impairs NO-mediated dilation cannot be inferred from our studies. It is possible that removal of sympathetic vasoconstriction with ganglionic blockade improves NO production by increasing sheer stress. The lack of improvement in endothelial-independent vasodilation with SNP (Figure 3B) demonstrates the selectivity of this effect and that it was not simply the result of a nonspecific increase in basal blood flow.

It is equally likely that as the disease progresses, a structural endothelial dysfunction state develops as a result of vascular damage. We should note that we excluded patients with clinically apparent coronary or peripheral vascular disease. Our findings, therefore, in no way contradict the impact that atherosclerosis, inflammation, immunity, and oxidative stress have on endothelial dysfunction and hypertension. It should be noted that sympathetic activation could contribute to inflammation with formation of reactive oxygen species and consequent reduction in NO production.23 Sympathetic activity can also impair NO signaling by reducing endothelial NO synthase activity.25

Studies in autonomic failure patients have validated the specificity of trimethaphan actions through a autonomic blockade; patients with supine hypertension because of pure autonomic failure have exaggerated responses to most vasodilators25—30 but not to trimethaphan,11 suggesting that the nonspecific effects of high-dose trimethaphan (eg, histamine release) are not seen at the doses used in these studies.35 The clinical relevance of our finding is that targeting sympathetic activity in the treatment of hypertension should result in improved NO function. An obvious limitation of our proof of concept study is that only acute effects were studied. It is encouraging, however, that uncontrolled studies suggest that chronic treatment with the central sympatholytic moxonidine appears to improve flow-mediated dilation.32 The use of traditional central sympatholytics is limited by their side effect profile, and there has been little interest in the development of new drugs that reduce sympathetic activity. There is, however, renewed interest in targeting sympathetic activity in hypertension. After disappointing initial results, a multicenter trial of renal denervation is under way (EnlightHTN IV, clinicaltrials.gov identifier: NCT01745172), and novel experimental approaches are being developed, such as reducing chemoreceptor input surgically (clinicaltrials.gov identifier: NCT01745172) or pharmacologically.34 Furthermore, we have recently showed that autonomic blockade improves insulin sensitivity in obese hypertensives probably through an increase in glucose uptake by the muscle.35 This effect could also be explained by an improvement in substrate availability.
resulting from insulin-mediated vasodilation, which is NO dependent. This hypothesis requires validation, but regardless of the mechanism, it is possible that targeting sympathetic activation in obesity-associated hypertension would have beneficial vascular (endothelial dysfunction) and metabolic (insulin resistance) effects.

In conclusion, we report that acute autonomic withdrawal results in apparent reversal of endothelial dysfunction, as evidence by improvement of acetylcholine-mediated dilation in obese hypertensives. These results are consistent with the concept that sympathetic activation contributes to impaired NO-mediated dilation in obesity, and we hope that they add to the renewed interest in targeting sympathetic activation in the treatment of obesity-associated hypertension.

**Perspectives**

Endothelial dysfunction is one of the earliest markers for the development of arteriosclerosis and cardiovascular disease; it can be predictive of subsequent development of acute coronary syndrome. Increased sympathetic activity could elicit an endothelial dysfunction state, which we believe to be reversible. Identifying and, therefore, being able to prevent the progression of endothelial dysfunction to endothelial damage is of the utmost importance. The mechanism by which increased sympathetic activity induces endothelial dysfunction in obesity has not been elucidated, not fully studied. Here we propose the first approximation to a better understanding of the phenomena and propose that an increased sympathetic activity is responsible early in the disease process for developing endothelial dysfunction.

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**Disclosures**

None.

**References**


Sympathetic Activity and Endothelial Function

Gamboa et al

Novelty and Significance

What Is New?

- Increased sympathetic activity, as seen in obesity-associated hypertension, can be responsible early in the disease process for developing endothelial dysfunction.
- We are showing that endothelial dysfunction can be reversed during autonomic blockade.

What Is Relevant?

- Increased sympathetic activity could elicit an endothelial dysfunction state, which has the potential of being reversible by targeting the sympathetic nervous system.
- This, in turn, will help prevent the progression of endothelial dysfunction to endothelial damage.

Summary

In this randomized crossover study, the effect of autonomic blockade on endothelial function has been studied. We have shown that acute pharmacological autonomic blockade, restores endothelial function in the forearm of obese hypertensive human subjects.
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