Reduced plasma volume and mesenteric vascular reactivity in obese Zucker rats

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Reduced plasma volume and mesenteric vascular reactivity in obese Zucker rats. Am J Physiol Regul Integr Comp Physiol 288: R253–R261, 2005. First published September 2, 2004; doi:10.1152/ajpregu.00498.2004.—Obese Zucker rats (OZR) are mildly hypertensive with an apparently elevated sympathetic vasomotor tone compared with lean Zucker rats (LZR). Studies have also suggested enhanced adrenergic pressor reactivity in OZR but assumed comparable baroreflexes, or blood volume-to-body weight ratio, to LZR. In 15-wk-old OZR and LZR, we measured plasma volume and vascular reactivity to norepinephrine (NE) and phenylephrine (PE) with doses evaluated by body weight and plasma volume. Plasma volume measured by dye dilution (Evans blue; 200 μL of 0.5%) showed that OZR had comparable blood volumes to LZR but lower blood volume-to-body weight ratio (3.4 ± 0.2 mL/100 g) than LZR (5.7 ± 0.2 mL/100 g, P < 0.05). Ganglionic blockade (mecamylamine, 4 mg/kg) in isoflurane-anesthetized OZR compared with LZR (52 ± 2 vs. 46 ± 2 mmHg). Pressor responses to NE (0.01–10 μg/kg) were exaggerated with doses analyzed by body weight but not analyzed by drug quantity. Pressor responses to PE (1–24 μg/kg) showed no difference with doses analyzed by body weight, but, analyzed by drug quantity, OZR showed a slight decrease in pressor reactivity. PE-induced increases in vascular resistance were exaggerated in the hindlimb circulation of OZR, normal in the renal circulation, and attenuated in the mesenteric circulation. The timing of the peak pressor response to PE corresponded with the increase in mesenteric vascular resistance, followed by rises in hindlimb and renal resistance. These data suggest that systemic adrenergic pressor reactivity is not enhanced in OZR, despite exaggerated vascular reactivity in the hindlimb of the OZR.

skeletal muscle; blood flow

Exaggerated adrenergically mediated vascular reactivity has been documented in obese rat aortic rings (3, 17, 18) and the microcirculation of the hindlimb (23). In clinical studies, humans with higher adiposity display augmented noradrenergic-mediated reductions in forearm blood flow (16). However, the contribution of vascular reactivity to altered systemic pressor responses is uncertain, as these reactivity measurements have been conducted either in conduit arteries or in the skeletal muscle circulation in which vascular resistance is high, even in normal individuals. Information regarding the adrenergic vascular reactivity in the beds receiving most of the resting cardiac output, the mesenteric and the renal circulations, has been limited to in vitro preparations, yielding conflicting results (13, 14, 25). Furthermore, in vivo studies of adrenergic pressor reactivity in OZR have constructed reactivity curves with the autonomic nervous system intact (1) or from doses based on body weight with the assumption that plasma volume can be comparably estimated from body weight in OZR vs. LZR (19, 29). Given reports of reduced blood mass (21) and impaired baroreflex control in OZR (2, 4, 19), these variables must be considered to determine the true adrenergic pressor reactivity in the setting of obesity.

The objective of the present study was to determine the pressor reactivity to adrenergic stimulation in OZR compared with LZR, with consideration of their blood volumes and in the absence of potentially confounding endogenous sympathetic vasomotor tone and baroreceptor reflexes. MAP, heart rate (HR), blood and plasma volumes, and blood flows in renal, hindquarter, and mesenteric vascular beds were measured in ganglionic-blocked, isoflurane-anesthetized OZR and LZR. The primary findings of this study are that 1) OZR have significantly less blood volume-to-body weight ratio compared with LZR, 2) adrenergically mediated pressor reactivity is not elevated in OZR when doses are normalized by plasma volume, and 3) OZR display enhanced adrenergically mediated vasoconstriction in the hindquarters, but normal responses in the renal circulation, and reduced responses in the mesenteric circulation.

MATERIALS AND METHODS

Animals. All experiments used male LZR and OZR (Harlan, Madison, WI), fed standard rat chow and tap water ad libitum. Rats were housed in the animal care facility at the Medical College of Georgia, which is approved by the American Association for the Accreditation of Laboratory Animal Care, and the Institutional Animal Care and Use Committee approved all protocols.

Measurement of blood volume. Anesthesia was induced with 5% isoflurane in 100% O2 and maintained during surgery with 1.9–2.1%

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isoflurane in 100% O2 through a nose cone. The depth of anesthesia was verified by noting the absence of physical responses to firm paw pinch and corneal probing. A catheter was placed in the right femoral artery (PE-50; VWR; www.vwrsp.com) to measure MAP and HR and to withdraw arterial blood. A catheter was placed in the right femoral vein (PV-5; Scientific Commodities; www.sciominc.com) to deliver dye and drugs. To estimate plasma volume, 1 mg of Evans blue dye to withdraw arterial blood. A catheter was placed in the right femoral pinch and corneal probing. A catheter was placed in the right femoral Sigma; www.sigma-aldrich.com) and flushed with 150 μl of saline. After 10 min, 1 ml of blood was withdrawn from the arterial line to measure hematocrit and estimate dilution of the dye in plasma. A small amount was withdrawn into a hematocrit capillary and centrifuged. The remainder of the sample was centrifuged, and 200 μl of plasma were diluted into 1.8 ml of saline in duplicate. The absorbance was measured at 604 nm (27), and the two values were averaged for each rat.

The average value from each rat was compared with a standard curve generated by using 10 ml of donor blood with a comparable hematocrit (27). Ten amounts of dye (0–100 μg) were added to ten 1-ml samples of donor blood. After the samples were centrifuged, 0.2 ml of plasma were diluted into 1.8 ml of saline, and absorbance was measured at 605 nm. Dye concentrations were chosen based on expected concentration in the experimental animals (e.g., 1 mg of dye into a rat with a 20-ml blood volume would yield ∼50 μg dye/ml of blood).

Blood volumes were calculated from the plasma volume in relation to the percentage of packed cells in the hematocrit [blood volume = plasma volume × 100/(100 − hematocrit)] (27).

Pressor reactivity to norepinephrine and phenylephrine. After estimation of blood volume, rats were artificially ventilated. To eliminate endogenous autonomic tone, rats were treated with the autonomic ganglionic antagonist mecamylamine (4 mg/kg iv). This dose effectively eliminates splanchnic nerve activity and baroreceptor reflex-mediated changes in HR for several hours (data not shown). Each rat was given serial doses of either norepinephrine (NE; 0.01–10 μg/kg iv) or phenylephrine (PE; 0.5–100 μg/kg iv). The pressor responses to NE were examined to mimic effects of the endogenous adrenergic ligand, and PE was selected to examine the effects of selective stimulation of the α1-adrenoceptors, the major receptor subtype for adrenergic actions on the vasculature. Each dose was given as a bolus in a randomized order, with each pair of lean and obese rats receiving the doses in the same order. The next dose was given when MAP values had returned to at least 95% of baseline levels. Efficacy of ganglionic blockade was confirmed by an absence of a baroreflex-mediated bradycardia with each dose of NE or PE. The MAP and HR values immediately before each dose (baseline) were subtracted from the peak response to determine changes in MAP and HR. The MAP values were also expressed as a percentage of the maximum MAP response within each rat, which occurred at the highest dose of NE or PE, and sensitivity was assessed by a change in the half-maximal effective dose (ED50). The ED50 was determined by using individual sigmoid curve fits derived with Origin graphic software (Originlab, Northampton, MA).

Measurement of regional blood flow. Blood flow responses to PE were measured by using a Transonic T204 flowmeter. Each animal was catheterized for the measurement of MAP (carotid artery) and venous drug delivery (jugular vein), and anesthesia was maintained with isoflurane. A midline incision was performed, and the left renal artery, the superior mesenteric artery, or the distal aorta at the iliac bifurcation was exposed. Adventitial tissue was gently removed, and a 1PRB (renal and mesenteric) or 2PS (aorta) Transonic flow probe was placed around the vessel. Acoustic coupling was achieved by a coating of HR conductance jelly (Supplier). Ganglionic blockade was achieved with 4 mg/kg mecamylamine. Randomized boluses of PE (1–24 μg/kg) were administered intravenously, and MAP and blood flow were recorded. Blood flow responses were normalized to organ weight, as determined by intra-arterial infusion of crystal violet to delineate the perfusion territory. Vascular resistance was calculated as the quotient of pressure over flow (mmHg·ml−1·min−1·g−1).

The change in vascular resistance (% of baseline) was then plotted against actual dose in micrograms, and the slope of the change in resistance vs. dose was derived from a linear fit with Microsoft Excel software. Changes in reactivity were then determined by comparison of slopes between LZR and OZR.

Statistics. Data are expressed as means ± SE. Significant statistical difference was set at P < 0.05. Age, weight, hematocrit, plasma volumes, blood volumes, ED50 values, and slopes of resistance curves for LZR and OZR were compared by t-tests. When changes in MAP and HR produced by NE and PE were reported in microgram per kilogram doses, the OZR and LZR were compared by ANOVA with repeated measures followed by Tukey-Kramer post hoc tests for each dose when a significant F value was obtained.

RESULTS

Age, weight, and baseline MAP of LZR and OZR before and after mecamylamine are shown in Table 1. The ages of the LZR and OZR were comparable, but the average weight of the OZR was significantly higher than that of the LZR. The OZR had a slightly higher baseline MAP compared with LZR, as previously reported (5, 19, 29). Elimination of autonomic tone by intravenous administration of the ganglionic antagonist mecamylamine (4 mg/kg iv) produced a larger decrease in MAP in OZR compared with LZR, as previously reported (5, 19), suggesting either an exaggerated sympathetic vasomotor tone in OZR or enhanced adrenergic vascular reactivity to a comparable sympathetic tone. A significant difference in MAP remained after mecamylamine, suggesting an additional non-autonomic contribution to resting MAP.

Measurements of blood volume in LZR and OZR are reported in Table 2. Although body weight was significantly greater in OZR than in age-matched LZR; plasma volumes and hematocrit volumes were not different between OZR and LZR. Hence the blood volumes in these two groups are comparable. However, the blood volume/100 g body weight was ∼67% higher in LZR compared with age-matched OZR.

Pressor and tachycardic responses to NE. Randomized doses of NE produced reliable dose-dependent increases in

Table 1. Baseline mean arterial pressure in obese Zucker rats and lean Zucker rats and effect of autonomic ganglionic blockade

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age, wk</th>
<th>Weight, g</th>
<th>Baseline MAP, mmHg</th>
<th>MAP After Mecamylamine, mmHg</th>
<th>Change in MAP With Mecamylamine, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>LZR</td>
<td>38</td>
<td>15.2±0.3</td>
<td>367.7±6.0</td>
<td>104.2±2.4</td>
<td>58.5±2.0</td>
<td>45.7±2.8</td>
</tr>
<tr>
<td>OZR</td>
<td>38</td>
<td>15.9±0.6</td>
<td>585.4±10.1*</td>
<td>116.0±3.0*</td>
<td>63.9±2.5*</td>
<td>52.1±2.3*</td>
</tr>
</tbody>
</table>

Values are means ± SE n, no. of animals. A subset of these rats were used to determine blood volume and pressor reactivity to phenylephrine or norepinephrine. The remainder was used to determine phenylephrine-induced changes in vascular resistance in mesenteric artery, renal artery, or abdominal aorta. LZR, lean Zucker rats; OZR, obese Zucker rats; MAP, mean arterial pressure. *Significant difference from LZR, P < 0.05.
MAP in ganglionic-blocked, isoflurane-anesthetized rats (Fig. 1). With NE doses analyzed by body weight, the pressor responses were significantly larger in OZR compared with LZR (Fig. 1A), as shown previously (19, 29). Pressor sensitivity was also increased in OZR relative to LZR (ED₅₀ = 0.16 ± 0.03 vs. 0.32 ± 0.09 μg/kg; P < 0.05) (Fig. 1B). However, with NE doses analyzed by drug quantity, the pressor sensitivity was similar [ED₅₀ = 0.09 ± 0.01 vs. 0.012 ± 0.03 μg, P = not significant (NS); Fig. 1C].

NE produced reliable dose-dependent increases in HR in ganglionic-blocked, isoflurane-anesthetized rats (Fig. 2). With NE doses analyzed by body weight, there was a trend for larger responses in OZR, but these differences failed to reach statistical significance (Fig. 2A). Analysis of NE doses by drug quantity showed no differences in NE-evoked increases in HR between OZR and LZR (Fig. 2B). Thus any apparent differences in pressor responses to NE observed in OZR vs. LZR are not likely due to differences in chronotropic cardiac responses.

**Pressor and tachycardic responses to PE.** Randomized doses of PE produced reliable dose-dependent increases in MAP in ganglionic-blocked, isoflurane-anesthetized rats (Fig. 3). With PE doses analyzed by body weight, the pressor responses were not different in OZR compared with LZR (Fig. 3A), and sensitivity was similar (ED₅₀ = 3.97 ± 0.7 μg/kg in OZR vs. 3.63 ± 0.6 μg/kg in LZR, P = NS, Fig. 3B). With PE doses analyzed by drug quantity, pressor responses as a percentage of maximum change in MAP showed a slight decrease in sensitivity (ED₅₀ = 2.21 ± 0.3 μg in OZR vs. 1.33 ± 0.2 μg in LZR, P < 0.05, Fig 3C).

PE evoked reliable, dose-dependent increases in HR in ganglionic-blocked, isoflurane-anesthetized rats (Fig. 4), likely due to direct activation of cardiac α-adrenergic receptors (28). With PE doses analyzed by body weight, there was a trend for larger responses in OZR, but these differences failed to reach statistical significance (Fig. 4A). Analysis of PE doses by drug quantity showed no differences in PE-evoked increases in HR between OZR and LZR (Fig. 4B). Thus differences in pressor responses to PE observed in OZR vs. LZR are not likely due to differences in HR.

**Increases in vascular resistance to PE.** Baseline vascular parameters in the mesenteric, renal, and hindquarters circulations are shown in Table 3. Absolute blood flow tended to be elevated in the mesenteric and renal circulations but not the hindlimb circulation of OZR. The increased blood flows likely reflected the splanchnic and renal hypertrophy observed in OZR. Basal renal and mesenteric vascular resistances were similar between LZR and OZR when normalized to tissue mass. In contrast, whereas hindquarter absolute blood flow was similar in LZR and OZR, normalized blood flow was significantly lower and basal vascular resistance in the hindquarter circulation was markedly increased in OZR. The increased hindlimb vascular resistance likely reflects vascular remodeling shown in the hindlimb circulation of OZR (24).

### Table 2. Blood volume in relation to body weight in age-matched OZR and LZR

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age, wk</th>
<th>Weight, g</th>
<th>Hematocrit, %</th>
<th>Plasma Volume, ml</th>
<th>Blood Volume, ml</th>
<th>Blood Volume/100 g Body wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>LZR</td>
<td>16</td>
<td>14.7 ± 0.5</td>
<td>367.7 ± 2.0</td>
<td>41.2 ± 0.3</td>
<td>12.2 ± 0.5</td>
<td>20.8 ± 0.9</td>
<td>5.7 ± 0.2</td>
</tr>
<tr>
<td>OZR</td>
<td>15</td>
<td>15.1 ± 0.6</td>
<td>579.0 ± 17.8*</td>
<td>41.5 ± 0.3</td>
<td>11.3 ± 0.6</td>
<td>19.3 ± 0.9</td>
<td>3.4 ± 0.2*</td>
</tr>
</tbody>
</table>

Values are means ± SE. *Significant difference from LZR, P < 0.05.
PE evoked reliable, dose-dependent increases in vascular resistance in the mesenteric, renal, and hindquarters circulations. Summary time course data from the second highest dose (16 μg/kg) are shown in Fig. 5. Whereas the pressor response was swift in both LZR and OZR (Fig. 5, A and E), the time courses of responses to PE in various vascular beds were heterogeneous. Figure 5, C, D, G, and H, shows changes in vascular resistance in absolute values, and Fig. 5, B and F, shows relative changes in vascular resistance to account for differences in baseline resistance among different vascular beds. The mesenteric circulation, with a moderate level of baseline vascular resistance (Fig. 5, C and G), demonstrated a rapid increase in resistance in response to PE that parallels the upstroke of the pressor response in both LZR and OZR. The relative change in resistance was largest in the mesenteric circulation in LZR (Fig. 5B), compared with the renal and hindquarters. Changes in resistance in the renal (low resistance, Fig. 5, C and G) and hindquarter (high resistance, Fig. 5, D and H) circulation were smaller and slower in onset, paralleling the more sustained aspect of the pressor response (Fig. 5, B and E). These data show that the PE-induced rapid changes in MAP coincide with changes within the mesenteric circulation in both LZR and OZR.

Figure 6 shows vascular reactivity to PE in all three vascular beds. In LZR, the mesenteric circulation demonstrated the highest degree of reactivity to PE (slope = 0.31 ± 0.02). The change in mesenteric vascular resistance (Fig. 6A) was markedly reduced in OZR relative to LZR (slope = 0.13 ± 0.03 vs. 0.31 ± 0.02; P < 0.05), indicating a reduction in vascular responsiveness to PE. Changes in renal vascular resistance to PE (Fig. 6B) were similar between OZR and LZR (slope =
Determining the relative contributions of increased sympathetic nerve activity and alterations in vascular reactivity is essential for understanding the effects of obesity on the development of hypertension and vascular disease. The goal of the present study was to rigorously determine the pressor reactivity of the total vascular system to adrenergic stimulation (pressor) and assay key sites of resistance (renal, hindquarter, and mesenteric) for sensitivity to adrenergically mediated vasoconstriction. In agreement with previous studies, we observed that OZR had a higher baseline MAP and that blockade of the autonomic nervous system produced a larger decrease in OZR compared with LZR (5, 19). The principle findings of this study are that adrenergically mediated pressor reactivity is not elevated in OZR when doses are normalized by plasma volume. Although OZR displayed enhanced adrenergically mediated vasoconstriction in the hindquarters, responses were normal in the renal circulation and reduced in the mesenteric circulation. These data suggest that the apparently normal adrenergic pressor reactivity in OZR may reflect a compilation of diverse vascular reactivities across beds in OZR compared with LZR. In addition, the lack of a prominent exaggeration in systemic pressor reactivity in OZR after a larger decrease in MAP produced by ganglionic blockade suggests enhanced sympathetic vasomotor tone in OZR compared with LZR.

In the present study, rats were examined under isoflurane anesthesia, because the inhalation route of administration alleviated concerns about the amount of drug by body weight that OZR vs. LZR should be given, considering their disparate blood volume per body weights. The anesthetized preparation allowed for more stable measures with controlled ventilation, thus minimizing total protocol time where rats were maintained in the hypotensive, ganglionic blocked state. Baseline characteristics in OZR of slightly higher baseline MAP, larger decrease in arterial pressure with ganglionic blockade, and exaggerated pressor responses to NE with doses analyzed by body weight are consistent with those previously reported in conscious rats (5, 19). Therefore, this preparation appeared to be suitable for examining blood volume, whole body pressor reactivity, and changes in blood flow in OZR compared with LZR.

Pressor responses to activation of the sympathetic nervous system represent the balance of the degree of activation and the sensitivity of the vasculature to adrenergic stimulation. Obesity and associated insulin-resistant states have been suggested to involve both sides of the balance. The elevation of sympathetic nerve activity is a well-documented aspect of obesity (7, 10, 15), although the role of this activation in regulation of arterial pressure has been subject to debate. In agreement with previous studies, we observed that sympathetic nerve activity is a well-documented aspect of obesity (7, 10, 15), although the role of this activation in regulation of arterial pressure has been subject to debate. In our study, we find that the decrease in MAP following ganglionic blockade is larger (Table 1) in OZR compared with LZR. These data are in accordance with Carlson and coworkers (5) in which gangli-
onic blockade with hexamethonium produced a greater reduction in MAP measured by telemetry in OZR compared with LZR. As shown previously (29), after ganglionic blockade, MAP was still higher in OZR, suggesting that sympathetic-independent mechanisms may also be at least partially responsible for baseline MAP in OZR.

The effects of obesity on adrenergically mediated vascular reactivity are less clear. OZR display elevated vascular con-
tractility to adrenergic stimulation in aortas (3, 17, 18), and striking hyperreactivity is also observed in isolated microvessels from the hindlimb (23). However, rapid pressor responses to adrenergic stimulation are mediated less by the aorta or skeletal muscle circulation but more by the mesenteric circulation, as suggested by Fig. 5. In our study, we find that pressor responses to neither NE, the endogenous neurotransmitter, nor PE, an α₁-adrenoceptor-specific agonist, are augmented in OZR compared with LZR. Indeed, the pressor sensitivity to PE is slightly reduced. Thus the greater decrease in MAP observed following sympathetic blockade most likely represents the higher level of sympathetic activity rather than a systemic increase in the pressor reactivity to activation of adrenergic receptors.

Two key features in our conclusion that pressor reactivity is not elevated are the use of sympathetic blockade and the normalization for vascular volume. In animals in which baroreflex control is compromised, variation in reflex control of arterial pressure may inappropriately exaggerate the response to pressor agents (22). Alonso-Galicia et al. (1) reported an increase in the magnitude of the response to adrenergic receptor activation in OZR, but these studies were performed in conscious, sympathetically intact animals. Because OZR have blunted baroreflexes (2, 4, 19), it is likely that this increased pressor response in OZR does not reflect the augmented reactivity of the vasculature but rather the impaired ability of the animals to buffer sudden increases in MAP.

Similarly, accounting for blood volume is essential for accurate assessment of vascular reactivity. Pamidimukkala and Jandhyala (19) examined reactivity to PE in sympathetically blocked animals and reported augmented vascular reactivity with dosing based on body weight. Our data, however, indicate that such an approach is inaccurate because plasma volume-to-body weight ratio is significantly lower in OZR compared with LZR. Thus independent of any change in reactivity, dosing by body weight will likely result in plasma concentrations of ~150–170% of those predicted in OZR. In the present study, without accounting for differences in plasma volume, estimated reactivity to NE appears to be increased, and estimated reactivity to PE is similar in OZR compared with LZR. Analyzing doses by drug quantity shows no difference in NE reactivity and a slight reduction in sensitivity to PE. Accounting for both impaired reflexes (ganglionic blockade) and plasma volume likely provides the best and most accurate accounting for pressor reactivity to adrenergic stimulation in OZR compared with LZR, and thus we conclude that the pressor reactivity to neither adrenergic agonist is augmented in OZR.

The lack of increase or even reduction in adrenergic pressor reactivity in OZR is surprising, given studies of reactivity in individual vascular beds. However, previous work has primarily evaluated vascular responses in vitro and in beds that contribute little to the systemic pressor response to injected adrenergic agents. Most studies have been performed either in the aorta (6, 17) or large conduits such as the carotid (5). Conduit arteries contribute little to the regulation of vascular resistance, and thus changes in this portion of the circulation may be more relevant to vasospasm than pressor reactivity. Our own laboratory’s previous work (23) has shown elevated reactivity to NE in resistance arteries from the hindlimb, and clinical studies have also shown that blockade of adrenergic receptors produces a greater decrease in forearm vascular resistance (9). However, even in normal resting individuals, skeletal muscle blood flow is low due to the lack of production of metabolic dilators. Thus resistance to the skeletal circulation is high, and changes in resistance in this bed probably are less important in sudden changes in arterial pressure, as suggested by Fig. 5. The observed alterations in skeletal muscle vascular reactivity are more likely important in limiting perfusion during exercise, not regulation of MAP.

Fig. 6. Percent increases in vascular resistance evoked by PE in ganglionic-blocked OZR and LZR with PE doses analyzed by drug quantity. A: PE evoked smaller increases in mesenteric vascular resistance in OZR (n = 6) compared with LZR (n = 7; P <0.05). B: PE evoked comparable increases in renal vascular resistance in OZR and LZR (n = 9/group). C: PE evoked greater increases in hindquarter vascular resistance in OZR compared with LZR (n = 9/group; P <0.05). Values are means ± SE.
In the present studies, we examined the three major distributions of cardiac output and are the first to report in vivo mesenteric, renal, and hindlimb vascular reactivity to adrenergic stimulation in the OZR and LZR. Importantly, our data provide flow measurements in the absence of potentially confounding reflex control, and we further account for differences in blood volume to ensure comparisons at equivalent levels of stimulation. As shown in Fig. 5, in both LZR and OZR, the sharp upstroke of the pressor response to adrenergic stimulation coincides with the increase in resistance in the mesenteric circulation. Mesenteric reactivity to adrenergic stimulation is reduced in the OZR (Fig. 6). Thus we conclude that pressor reactivity to adrenergic stimulation may be slightly, but significantly, reduced because of the less responsive mesenteric circulation. The difference in pressor reactivity is not as exaggerated as the reduction in reactivity observed in the mesenteric circulation, however, as a modest increase in adrenergic reactivity in the hindquarters circulation appears to offset the reduced reactivity of the mesenteric circulation.

In summary, OZR have a higher baseline MAP, and elimination of autonomic tone by ganglionic blockade produces a larger decrease in OZR compared with LZR. With no generation of autonomic tone by ganglionic blockade produces a significant, reduced because of the less responsive mesenteric circulation and lower perfusion of limbs. If these changes contribute to the larger decrease in MAP with sympathetic generation of autonomic tone by ganglionic blockade produces a significant, reduced because of the less responsive mesenteric circulation and lower perfusion of limbs.

REFERENCES
11. Grassi G, Seravalle G, Dell’Oro R, Turri C, Bolla GB, and Mancia G. Adrenergic reactivity to favor higher perfusion of the mesenteric circulation and lower perfusion of limbs. If these changes contribute to the larger decrease in MAP with sympathetic generation of autonomic tone by ganglionic blockade produces a significant, reduced because of the less responsive mesenteric circulation and lower perfusion of limbs. If these changes contribute to the larger decrease in MAP with sympathetic generation of autonomic tone by ganglionic blockade produces a significant, reduced because of the less responsive mesenteric circulation and lower perfusion of limbs.

Perspectives. Obesity is one of the most important factors for cardiovascular disease in modern populations. Obesity is commonly associated with increased sympathetic vaso- motor tone, and how this change affects regulation of vascular function is still poorly understood. The present study provides the most rigorous examination to date of how the vasculature responds to adrenergic stimulation in vivo and the resultant pressor responses. We find that there is a remodeling of adrenergic reactivity to favor higher perfusion of the mesenteric circulation and lower perfusion of limbs. If these changes are paralleled in human populations, they may contribute to the poor regulation of limb blood flow in obese individuals and the higher incidence of peripheral vascular disease on obese diabetics.

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