Exaggerated Cardiovascular Stress Responses and Impaired \( \beta \)-Adrenergic–Mediated Pressor Recovery in Obese Zucker Rats


Abstract—Clinical studies have demonstrated that the pressor response to acute stress is larger in obese versus lean individuals. We therefore tested the hypotheses that the pressor response to behavioral stress is greater in obese (OZR) versus lean Zucker rats (LZR) and that reduced \( \beta \)-adrenergic–mediated vasodilation contributes to the enhanced pressor response. Animals were restrained and subjected to acute pulsatile air jet stress (3 minutes), followed by a poststress period of 20 minutes; \( \beta \)-adrenergic blockade was achieved with propranolol (5 mg/kg, IV) given 15 minutes before the start of air jet stress. Mean arterial pressure (MAP) was continuously monitored by telemetry. Untreated OZRs responded with a greater integrated pressor response (area under the curve [AUC]) to acute stress (41.2+6.1 versus 21.2+3.3 mm Hg×3 minutes, OZR versus LZR; \( P<0.05 \)) and significantly reduced poststress recovery of MAP. \( \beta \)-Adrenergic blockade had no effect on stress AUC in either LZR or OZR but significantly attenuated the poststress recovery of MAP in LZR only (poststress AUC: -100.1+48.1 versus 49.0+13.5 mm Hg×20 minutes, untreated versus propranolol; \( P<0.05 \)). In anesthetized animals, significantly smaller increases in mesenteric vascular conductance contributed to blunted depressor responses to isoproterenol in OZR versus LZR, suggesting that \( \beta \)-adrenergic stimulation causes a greater reduction in total peripheral resistance in lean versus obese animals. We conclude that \( \beta \)-adrenergic–mediated vasodilation facilitates blood pressure recovery after stress and that this pathway is compromised in an animal model of morbid obesity, resulting in the impaired ability to regulate blood pressure during stress. (Hypertension. 2006;48:1109-1115.)

Key Words: arterial pressure ■ behavioral stress ■ thyroid ■ cardiac output ■ regional blood flow

Obesity is recognized as a major risk factor in the development of metabolic abnormalities, including insulin resistance and dyslipidemia, and is associated with both acute and chronic perturbations in blood pressure regulation. Although chronic hypertension in obese individuals likely reflects a deficit in renal function,1–3 underlying mechanisms of acute blood pressure control have not been fully elucidated. Normally, blood pressure is acutely regulated by adjustments in sympathetic nerve activity and peripheral vascular resistance. Several studies have demonstrated that the pressor response to acute, physical, and mental stressors is elevated in obese versus lean subjects4–8 and that the heightened cardiovascular response depends on the degree and distribution of body fat. Central adiposity seems to be a critical determinant, because it is positively associated with an increase in total peripheral resistance,7,9 as well as impaired poststress recovery of blood pressure.10 Several studies have shown that the increase in total peripheral resistance is attributable at least in part to a significantly smaller vasodilatory response in obese individuals during stress8,11; however, the mechanism responsible for this observed defect remains poorly understood.

The obese Zucker rat (OZR) is a well-established model for the study of cardiovascular and endocrine abnormalities associated with the metabolic syndrome, developing obesity-induced insulin resistance and moderate hypertension.12,13 We13 and others14,15 have shown that autonomic ganglion blockade produces a greater drop in arterial pressure in OZR compared with their lean counterparts, suggesting that heightened sympathetic nerve activity contributes to the elevated pressure in OZR. Sympathetic vasomotor tone reflects the balance between constrictor and dilator actions of catecholamines on vascular smooth muscle through \( \alpha \)- and \( \beta \)-adrenergic receptors, respectively. Previously, our laboratory has shown that whole animal adrenergic pressor reactivity during autonomic ganglion blockade is not enhanced in OZR13 and that, in isolated mesenteric resistance arteries from OZR, constrictor responses to exogenous norepineph-
rine are attenuated. Thus, these data suggest that the elevated peripheral vascular resistance in the face of augmented sympathetic nerve activity may be because of suppressed β-adrenergic–mediated vasodilation.

The aim of the current study was to test the hypothesis that the pressor response to environmental stress is greater in OZRs versus lean Zucker rats (LZRs). Environmental stress was applied by subjecting LZRs and OZRs to air jet stress, a well-established method to evoke a rapid increase in sympathetic nerve activity. Cardiovascular responses to acute air jet stress were examined in animals that were continuously monitored by telemetry. Given our previous results showing that the adrenergic-mediated constrictor responses are not elevated in OZRs, we also tested the hypothesis that the enhanced pressor response to stress is mediated by impaired β-adrenergic–mediated vasodilation by monitoring the pressor response in untreated animals and in those given the nonselective β-adrenergic receptor antagonist propranolol. Finally, changes in vascular conductance and cardiac output were assessed in response to the β-adrenergic agonist isoproterenol in autonomic ganglion-blocked animals to determine whether responsiveness to β-adrenergic stimulation is altered in obesity.

Methods

Animal Model
All of the experiments used 13- to 16-week-old male LZRs and OZRs (Harlan Laboratories, Indianapolis, IN) 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. All of the protocols have been approved by the Institutional Animal Care and Use Committee.

Telemetry
Telemetry transmitters (Data Sciences, Inc) were implanted according to the manufacturer’s specifications. Rats were anesthetized with ketamine/xylazine (50 mg/kg/10 mg/kg, IP). The abdominal aorta was then exposed by a midline incision and briefly occluded. The transmitter catheter was inserted into a hole made by a 21-gauge needle just proximal to the iliac bifurcation and secured in place with tissue glue (Vetbond). The transmitter body was attached to the abdominal wall along the incision line with a 4-O proline suture as recommended by the manufacturer’s specifications. Rats were anesthetized with ketamine/xylazine (50 mg/kg/10 mg/kg, IP). The abdominal aorta was then exposed by a midline incision and briefly occluded. The transmitter catheter was inserted into a hole made by a 21-gauge needle just proximal to the iliac bifurcation and secured in place with tissue glue (Vetbond). The transmitter body was attached to the abdominal wall along the incision line with a 4-O proline suture as the incision was closed. The skin was closed with staples that were removed 7 days after the incision had healed. Rats were allowed to recover from surgery and returned to individual housing for data collection before being subjected to the stress protocol. Animals were housed in a room separate from that used for studying the stress environment and their pressures stabilized. Animals were then exposed by a midline incision and briefly occluded. The transmitter catheter was inserted into a hole made by a 21-gauge needle just proximal to the iliac bifurcation and secured in place with tissue glue (Vetbond). The transmitter body was attached to the abdominal wall along the incision line with a 4-O proline suture as the incision was closed. The skin was closed with staples that were removed 7 days after the incision had healed. Rats were allowed to recover from surgery and returned to individual housing for data collection before being subjected to the stress protocol. Animals were housed in a room separate from that used for studying the stress response. The individual rat cages were placed on top of the telemetry receivers, and mean arterial pressure (MAP) and heart rate (HR) were continuously recorded throughout the study using the Dataquest A.R.T. Acquisition program (Data Sciences International).

Air Jet Stress
LZRs and OZRs (n=7) were quietly brought to a sound-proofed room and allowed to acclimate to their surroundings for 15 to 30 minutes in their cages. Immediately after starting the telemetry recording software, the room was vacated. The animals were then allowed to acclimate to their surroundings for 15 to 30 minutes in their cages, that is, until which time they ceased exploring the new environment and their pressures stabilized. Animals were then placed in tubular Plexiglas restrainers with sufficient aeration, and MAP and HR were continuously monitored by telemetry for ≥15 minutes before initiating air jet stress. When necessary, animals were monitored for up to an additional 10 minutes to allow the animals to adapt to being restrained, such that 3 to 5 minutes of stable MAP and HR recordings were obtained before exposure to air jet stress. Stress consisted of pulses (2-s duration delivered every 10 s for 3 minutes) of compressed air (15 lb/in²) aimed at the forehead from a 1/8-in opening at the front of the tube. After the 3-minute stress period, MAP and HR were monitored for 20 additional minutes while the animals were still in the restrainer, and postair jet values were obtained. At the end of this poststress period, animals were returned to their cages and brought back to their holding room. The effect of β-adrenergic blockade was examined in a separate group of LZRs and OZRs fitted previously with venous catheters that were routed subcutaneously and exteriorized at the back of the neck (n=6 to 7). A bolus infusion of propranolol (5 mg/kg IV) was administered after the animals had been restrained for 15 minutes; animals were subjected to air jet stress 15 minutes after receiving propranolol. Parallel studies indicated that propranolol at 5 mg/kg reduced the pressure decrease to isoproterenol (0.1 μmol) by >60% (30±3 versus 11±1 mm Hg, control versus propranolol; P<0.05; n=3).

Measurement of Regional Blood Flow
Blood flow responses to isoproterenol were measured using a Transonic T402 Flowmeter. Under isoflurane anesthesia, carotid artery and jugular vein were catheterized for the measurement of MAP and drug delivery, respectively. A midline incision was performed, and the superior mesenteric artery or the distal aorta at the iliac bifurcation was exposed. Adventitial tissue was gently removed, and a 1PRB (mesenteric) or 2PS (aorta) Transonic flow probe was placed around the vessel. Acoustic coupling was achieved by a coating of HR conductance jelly. Autonomic ganglion blockade was achieved with 2 mg/kg of mecamylamine. After ganglionic blockade, arterial pressure was maintained by infusion of angiotensin II to keep the pressure equivalent to the preblocked baseline. Because previous studies from our group have shown that blood volumes are equivalent between LZRs and OZRs, drugs were injected as fixed amounts. Randomized boluses of isoproterenol (0.001 to 0.5 μmol) were administered intravenously and MAP and blood flow recorded. Isoproterenol is a mixed β1/2 agonist with some limited β3 receptor activity. Vascular conductance was calculated as the quotient of flow over pressure (milliliters per minute per millimeters of mercury per gram). The change in vascular conductance (percentage of baseline) was then plotted against actual dose in micromoles.

Measurement of Cardiac Output
Cardiac output was assessed as aortic flow. The surgical preparation was similar to that of regional blood flow with modifications. The animals were mechanically ventilated with a mix of isoflurane and supplemental oxygen to maintain respiration during a thoracotomy. The thoracotomy was performed at the fifth intercostal space, and a 2.5PSB Transonic flow probe was placed around the root of the aortic arch. Acoustic coupling jelly was applied to the thoracic cavity to maintain the flow signal. Randomized boluses of isoproterenol (0.001 to 0.5 μmol) were administered intravenously, and aortic flow was recorded.

Metabolic Measurements
Fasting blood glucose was assessed using an over-the-counter glucometer (Precision XL). Plasma total cholesterol and triglycerides were assessed with colorimetric assays (WakoUSA). Plasma insulin was determined using the Mercodia Rat Insulin ELISA assay (ALPCO Diagnostics). Thyroid hormone levels (total T3 and T4) were measured by ELISA by the animal reference pathology division of ARUP Laboratories. Thyroid-stimulating hormone levels were assessed by ELISA (ALPCO Diagnostics).

Statistical Analysis
Data are expressed as mean±SE. All of the baseline MAP and HR values are reported as 24-hour means. Pressure and HR variability are expressed as the coefficient of variation and were calculated by the equation: 100% × (SD/mean). Total pressor response during the
stress and poststress periods was determined by the equation: \( \Sigma([\text{pressure} - \text{pre-air jet baseline}] \times 0.083) \), where pressure refers to each measurement recorded during the delivery of air jet stress and the 20-minute poststress period, the pre-air jet baseline is the average pressure during the 3 minutes just before the onset of the air pulses, and 0.083 is the 5-s data collection interval. Data are expressed as the area under the curve ([AUC] milligrams of mercury \( \times \) minutes). Analyses of stress and poststress AUCs were made by 2-way ANOVA followed by the Newman–Keuls test for multiple comparisons. Isoproterenol responses were analyzed by 2-way ANOVA with repeated measures. All of the baseline metabolic and cardiovascular measurements were analyzed by unpaired \( t \) test. Differences are considered significant at \( P<0.05 \).

**Results**

**Baseline Metabolic and Cardiovascular Parameters**

The baseline metabolic and cardiovascular features of LZRs and OZRs are listed in Tables 1 and 2. OZRs displayed hyperlipidemia, hyperinsulinemia, and obesity (\( P<0.05 \)), consistent with traits observed in patients with syndrome X; plasma glucose was not different between LZRs and OZRs. Conversely, OZRs had significantly lower plasma thyroid hormone levels. Baseline (24-hour) MAP was modestly, yet significantly, higher in OZRs despite no difference in HR.

**Cardiovascular Responses to Acute Stress**

Both moving to a different room and restraint caused transient increases in MAP, which had stabilized during the latter portion of the in-cage acclimation and restraint periods (data not shown). For those animals that remained untreated and those that were given PRP during the restraint period, a comparison of MAP within each strain after it had leveled off revealed no differences between those pressures after room switch and during restraint. HR was also transiently elevated, but by the end of the respective periods, HR during restraint was comparable to that seen after room switch in both untreated and PRP-treated LZRs and OZRs.

Figure 1A shows the MAP values obtained 3 minutes before and during the delivery of the air jet stress in untreated LZRs and OZRs. The average pressure over the 3-minute period before the delivery of the air pulses was used as the pre-air jet baseline pressure, to which the pressures during and after the air jet stress period were compared. In both LZRs and OZRs, there was a rapid initial rise in pressure with the delivery of the first air pulse. This peak then declined to a plateau between 90 s and the end of the response. The AUC, which accounts for all components of the pressor response, revealed that it was nearly doubled in OZRs compared with LZRs and OZRs. Conversely, in OZRs, MAP did not reach a plateau between 90 s and the end of the response. The AUC, which accounts for all components of the pressor response, revealed that it was nearly doubled in OZRs compared with LZRs (41.2 \( \pm \) 6.1 versus 21.2 \( \pm \) 3.3 mm Hg \( \times \) 3 minutes, OZR versus LZR; \( P<0.05 \); Figure 2A).

HR was similar in both groups during the 3-minute period before the start of air jet stress (458 \( \pm \) 19 versus 458 \( \pm \) 13 bpm, LZR versus OZR; \( P \) value not significant). On initiation of air jet stress, there was an abrupt bradycardic response (\( -69 \pm 15 \) versus \( -88 \pm 24 \) bpm, LZR versus OZR; \( P \) value not significant), which was maintained throughout the stress period, such that the average HR during the last minute of the stress period was 412 \( \pm \) 16 and 400 \( \pm \) 12 bpm (\( P<0.05 \) versus respective baselines) for LZRs and OZRs, respectively.

MAP was monitored for 20 minutes after the stress period to assess the extent of recovery (Figure 1B). In untreated LZRs, MAP returned to the pre-air jet baseline within 2 minutes and remained below baseline for all of the subsequent time points. Conversely, in OZRs, MAP did not reach the pre-air jet baseline within the 20-minute poststress period.

### TABLE 1. Baseline Metabolic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LZR</th>
<th>OZR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, wk</td>
<td>12 to 15</td>
<td>12 to 15</td>
</tr>
<tr>
<td>Body weight, g</td>
<td>451 ( \pm ) 54</td>
<td>671 ( \pm ) 44*</td>
</tr>
<tr>
<td>Fasting blood glucose, mg/dL</td>
<td>110 ( \pm ) 15</td>
<td>121 ( \pm ) 20</td>
</tr>
<tr>
<td>Serum cholesterol, mg/dL</td>
<td>51 ( \pm ) 5</td>
<td>95 ( \pm ) 10*</td>
</tr>
<tr>
<td>Serum triglyceride, mg/dL</td>
<td>54 ( \pm ) 4</td>
<td>443 ( \pm ) 80*</td>
</tr>
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<td>Plasma insulin, ng/mL</td>
<td>2.0 ( \pm ) 0.3</td>
<td>16.4 ( \pm ) 1.2*</td>
</tr>
<tr>
<td>Blood HbA1c, %</td>
<td>4.2 ( \pm ) 0.2</td>
<td>5.0 ( \pm ) 0.2</td>
</tr>
<tr>
<td>Thyroid hormone (T3 and T4), ( \mu )g/dL</td>
<td>4.8 ( \pm ) 0.5</td>
<td>3.1 ( \pm ) 0.6*</td>
</tr>
<tr>
<td>Thyroid stimulating hormone, ( \mu )IU/mL</td>
<td>0.49 ( \pm ) 0.03</td>
<td>0.38 ( \pm ) 0.03*</td>
</tr>
</tbody>
</table>

*\( P<0.05 \) vs LZR.

### TABLE 2. Baseline Cardiovascular Parameters (Conscious; 24-Hour Average)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LZR</th>
<th>OZR</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mm Hg</td>
<td>100 ( \pm ) 2</td>
<td>122 ( \pm ) 5*</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>396 ( \pm ) 7</td>
<td>388 ( \pm ) 7</td>
</tr>
<tr>
<td>Pressure variability, %</td>
<td>9.2 ( \pm ) 0.4</td>
<td>9.1 ( \pm ) 0.7</td>
</tr>
<tr>
<td>Heart rate variability, %</td>
<td>12.4 ( \pm ) 0.5</td>
<td>10.7 ( \pm ) 0.8*</td>
</tr>
</tbody>
</table>

*\( P<0.05 \) vs LZR.
Figure 2. Summary of total pressor response (AUC) to acute air jet stress (A) and blood pressure recovery during poststress period (B) in LZRs and OZRs. Animals were either left untreated or given the nonselective \( \beta \)-adrenergic antagonist propranolol 15 minutes before the start of air jet stress. Values were calculated as the sum of the MAP data points during or after air jet stress minus the average MAP obtained over the 3 minutes before the initiation of air jet stress. *\( P<0.05 \).

(1B). Thus, MAP recovery, as reflected by the larger poststress AUC, was significantly diminished in OZRs (97.4±33.0 versus \(-100.1±48.1\) mm Hg×20 minutes, OZR versus LZR; \( P<0.05 \); Figure 2B). This is highlighted by the finding that MAP reached a steady-state value of \( 6±1\) mm Hg below the pre-air jet baseline over the 15 minutes of the poststress period for LZRs, whereas that for OZRs remained \( 4±1\) mm Hg above its respective baseline over that same length of time. The change reflects a 12±2% decrease in pressure from the steady-state level, that is, the average pressure over the last 30 s of air jet stress in LZRs compared with a 4±3% drop in OZRs (\( P<0.05 \)).

Treatment with propranolol 15 minutes before the start of air jet stress caused a small but significant increase in MAP in LZRs only (7±2 mm Hg; \( P<0.05 \)), despite eliciting a substantial drop in HR (−102±9 bpm; \( P<0.05 \)). In OZRs, propranolol had no effect on MAP but did produce a large decrease in HR (−125±7 bpm; \( P<0.05 \)). Within each strain, propranolol also had no effect on the peak pressor response to stress or on the average increase during the last minute of stress. Thus, compared with the respective untreated groups, propranolol did not affect the integrated pressor response; the stress AUC, however, remained significantly elevated in propranolol-treated OZRs (32.5±4.8 versus 19.3±4.8, OZR versus LZR; \( P<0.05 \); Figure 2A). There was a significantly smaller decrease in HR in propranolol-treated OZRs that was sustained throughout the 3 minutes of air jet stress (peak: −28±5 versus −60±10 bpm, OZR versus LZR; \( P<0.05 \); average during the last minute: −13±4 versus −33±6 bpm, OZR versus LZR; \( P<0.05 \)). In contrast to the lack of effect on the response during air jet stress, propranolol attenuated the recovery of MAP after stress in LZRs only such that MAP remained at or above the pre-air jet value throughout the poststress period. Thus, poststress AUC was significantly greater in propranolol-treated versus untreated LZRs (49.0±13.5 versus −100.1±48.1 mm Hg×20 minutes, propranolol versus untreated; \( P<0.05 \)) and approximated that found in propranolol-treated OZRs (72.7±20.7, not significant versus LZR; Figure 2B).

Reactivity to Isoproterenol

In anesthetized animals, baseline MAP and cardiac output were higher in OZRs compared with LZRs; the elevation in cardiac output was attributable mainly to an increase in stroke volume (Table 3). Ganglionic blockade caused a larger drop in blood pressure in OZRs versus LZRs and eliminated the differences in cardiac output and stroke volume, consistent with previous reports of greater baseline sympathetic tone to the cardiovascular system in OZRs. Baseline mesenteric and hind limb flow were similar in LZRs and OZRs (Table 3).

Cardiovascular responses to isoproterenol were examined in anesthetized animals to determine the extent to which \( \beta \)-adrenergic responsiveness is impaired in OZRs (n=10 in each group). In the absence (Figure 3A) and presence (Figure 3B) of autonomic ganglion blockade, whole animal depressor responses to isoproterenol were blunted in OZRs relative to LZRs. Figure 4 illustrates the effect of isoproterenol on cardiac function in the absence of autonomic ganglion blockade. OZRs displayed a reduction in the percentage of increase in cardiac output compared with LZRs (Figure 4). This decrement was partially attributable not only to the higher baseline cardiac output but also to smaller absolute increases (8±1 versus 11±1 mL/min, OZR versus LZR at isoproterenol=0.5 \( \mu \)mol; \( P<0.05 \); n=10). Conversely, changes in HR were not different in ganglion intact or blocked LZRs and OZRs (data not shown). Figure 5 demonstrates the effects of isoproterenol on vascular conductance in ganglion-blocked LZRs and OZRs. Increases in mesenteric vascular conductance in OZRs were markedly blunted at the higher dose range (0.05 to 0.5 \( \mu \)mol) compared with LZRs (Figure 5A), consistent with the reduced depressor responses observed in Figure 3B. In contrast, hind limb vascular responses to isoproterenol were similar between LZRs and OZRs (Figure 5B).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LZR</th>
<th>OZR</th>
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<tbody>
<tr>
<td>Aortic pressure, mm Hg</td>
<td>102±4</td>
<td>114±4*</td>
</tr>
<tr>
<td>Aortic pressure (ganglion block), mm Hg</td>
<td>60±2</td>
<td>58±2</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>418±11</td>
<td>382±22*</td>
</tr>
<tr>
<td>Cardiac output, mL/min</td>
<td>72±6</td>
<td>96±6*</td>
</tr>
<tr>
<td>Cardiac output (ganglion block), mL/min</td>
<td>63±4</td>
<td>60±5</td>
</tr>
<tr>
<td>Stroke volume, µL</td>
<td>161±15</td>
<td>237±22*</td>
</tr>
<tr>
<td>Stroke volume (ganglion block), µL</td>
<td>153±12</td>
<td>160±9</td>
</tr>
<tr>
<td>Mesenteric blood flow, mL/min per g</td>
<td>1.05±0.10</td>
<td>1.03±0.10</td>
</tr>
<tr>
<td>Hind limb blood flow, mL/min per g</td>
<td>0.16±0.01</td>
<td>0.13±0.02</td>
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</tbody>
</table>

*\( P<0.05 \) vs LZR.
Discussion

Previous reports in humans have demonstrated that obesity has profound effects on acute blood pressure regulation. We, therefore, tested the hypotheses that the pressor response to acute stress is larger in OZRs versus LZRs and that impaired β-adrenergic–mediated vasodilation contributes to the elevated response. A key finding of this study is that the total pressor response to a 3-minute episode of pulsatile air jet stress is enhanced in OZRs, an animal model of morbid obesity. A more striking difference was seen after stress, during which time the MAP for LZRs returned to a subbasal level, whereas that for OZRs remained elevated above the prestress value.

β-Adrenergic blockade had no effect on the integrated pressor response but significantly reduced the poststress recovery of MAP in LZRs only. In anesthetized animals, β-adrenergic stimulation elicited smaller depressor responses, most likely through a smaller increase in mesenteric vascular conductance. Isoproterenol caused a smaller rise in cardiac output in OZRs despite no difference in the tachycardic response.

Stemming from a mutation of the leptin receptor rendering the animal incapable of suppressing food intake,21 OZRs become morbidly obese by 15 weeks of age. Because of documented evidence of sympathetic defects in these rats that parallel those in human studies, they provide a useful model to study the effects of obesity on altered pressor reactivity to sympathetically mediated stress.

Cardiovascular Response to Stress

Within the time frame studied, the responses to acute stress are mediated primarily by the sympathetic nervous system and are, thus, determined by the levels of catecholamines released, the responsiveness of the target cardiovascular tissues, and the counterregulatory mechanisms that buffer the pressor response. Previous studies in Zucker rats have documented that stress-mediated rises in catecholamines are either not different22 or are lower23,24 in OZRs in response to immobilization stress or exercise. Moreover, our laboratory has shown that systemic pressor responses to α-adrenergic stimulation are comparable in OZRs versus LZRs13 and that constrictor responses are reduced in isolated mesenteric resistance arteries from OZRs.16 Thus, any involvement of altered adrenergic responsiveness that would lead to an enhanced pressor response to stress or impaired MAP recovery after stress must invoke changes in β-adrenergic responses, that is, either through an increase in cardiac output or a decrease in β-adrenergic–mediated vasodilation. In the present study, β-adrenergic blockade did not affect the response to stress, whereas poststress recovery of MAP was...
significantly attenuated by propranolol in LZRs only; no effects with propranolol treatment were seen in OZRs. These data suggest that neurogenic dilation facilitates blood pressure recovery and that this mechanism is impaired in obesity. This more significant role of β-adrenergic dilation during recovery in LZRs is consistent with our finding that the depressor responses to β-adrenergic stimulation with isoproterenol are greater in these animals compared with OZRs.

Although the impaired recovery is accounted for by impaired β-adrenergic vasodilation, the mechanism of the acute pressor response is unclear. Two general explanations are most likely. The first is an increase is the level of sympathetic nerve activity during stress. Several studies have shown that baseline arterial pressure is more sensitive to ganglionic blockade in OZRs compared with LZRs13–15 implying greater sympathetic contribution to arterial pressure in OZRs. Thus, OZRs may have exaggerated sympathetic responses to inputs such as stress or excitation. The second possibility is that the normal buffering of the baroreflex is impaired in obesity. In the present study, we report that HR variability in OZRs is decreased, suggesting that reflex control of blood pressure is impaired in OZRs. Consistent with these results, Pami-dimikkala and Jandhyala15 have demonstrated that baroceptor sensitivity is compromised in OZRs relative to LZRs, and so it is possible that sympathetically mediated pressor responses may be potentiated by a reduction in the pressure-induced sympathoinhibition.

In the paradigm used, stress caused a reflex decrease in HR in untreated OZRs and LZRs. In OZRs, however, MAP remained higher relative to its respective baseline during air jet stress, suggesting that the decrease in HR is not sufficient to offset the increase in total peripheral resistance. Normally, the drop in HR is the result of sympathetic withdrawal and/or parasympathetic activation. Because β-adrenergic blockade prevents the effect of sympathetic stimulation, i. t. therefore, unmasks that component of bradycardia because of parasympathetic activation. In the presence of propranolol, the decrease in HR during the stress response was severely reduced in OZRs compared with those that were untreated, suggesting that the bradycardic response in these animals is primarily mediated by sympathetic withdrawal, with little recruitment of parasympathetic activity.

Although ours is the first study to examine stress activation of arterial pressure in OZRs, other sympathetic inputs have been examined. Timofeeva et al.15 determined that activation of the paraventricular nucleus by food restriction is greater in OZRs versus LZRs. Projections from the paraventricular nucleus can affect autonomic pathways governing blood pressure. Edwards et al.26 documented a 7-fold increase in plasma corticosterone in OZRs compared with LZRs in response to foot shock stress, arguing further than OZRs are inherently more stress prone than LZRs. Nevertheless, further study of autonomic control of blood pressure is warranted to dissect out the possible contribution of altered sympathetic function in the enhanced pressor reactivity of OZRs.

Cardiovascular Responses to β-Adrenergic Stimulation
The magnitude of the change in arterial pressure produced by β-adrenergic stimulation is dictated by the relative responsiveness of receptors in the heart and vascular smooth muscle, where they mediate an increase in cardiac output and vasodilation, respectively. We found that isoproterenol elicited a smaller increase in cardiac output and a reduced depressor response in OZRs, suggesting that β-adrenergic signaling is impaired in both cardiac myocytes and vascular smooth muscle. Yet, the finding that isoproterenol caused a smaller increase in cardiac output, with no difference in HR, suggests that the deficit may be specific to the inotropic but not the chronotropic effect of β-adrenergic signaling in the myocardium of OZRs. It is tempting to speculate that the reduction in β-adrenergic–mediated responses is related to the lower thyroid hormone levels, given that thyroid hormone increases cardiac output and lowers peripheral vascular resistance.27

Regardless, the reductions in β-adrenergic–mediated inotropy and vasodilation cannot explain the augmentation of pressor responses to air jet stress in OZRs but are more likely to be associated with impaired recovery mechanisms after stress.

In the present study, reduced depressor responses were not found in all of the vascular beds examined. Specifically, we found that the depressor responses were attenuated in the mesenteric but not hindquarter circulation. This difference may reflect a different distribution of β-adrenergic receptors, such as β1 versus the β2 receptor. Indeed, in a recent study from Chruscinski et al.28 femoral arteries from mice in which β1 receptors were genetically deleted were unresponsive to isoproterenol, whereas deletion of β2 receptors had no effect. In contrast, deletion of β2 receptors significantly impaired vasodilation in the carotid artery and the aorta. The distribution of β-adrenergic receptors in the peripheral microcirculation and the effects of obesity on the expression of these receptors warrant future study.

Perspectives
Clinical studies have demonstrated that there is a higher incidence of cardiovascular events in the immediate aftermath of an acute life stress.29–32 Studies have also shown that an excessive cardiovascular response to3,34 and delayed recovery of blood pressure after acute stress35,36 are associated with the increased cardiovascular risk. Obese individuals show impaired blood pressure regulation during and after stress,4–8 perhaps contributing to the increased cardiovascular morbidity in this population. The mechanisms of this defect are unknown but may involve impaired regulation of vascular resistance. Our results suggest that the ability to normalize blood pressure after stress is mediated by β-adrenergic vasodilation and that this vasodilation is compromised in an animal model of obesity. The impaired vasodilation is concomitant with an inability to recover normal arterial pressure after a stressful stimulus. These data indicate that the loss of β-adrenergic vascular responsiveness may be a key factor in the inability of the obese population to regulate cardiovascular function during periods of stress and may represent a novel point of therapeutic intervention.

Acknowledgment
We gratefully acknowledge the excellent technical assistance of Hiram Ocasio.
Sources of Funding
This study was supported by grants from the National Heart, Lung, and Blood Institute (D.W.S.: HL-67303 and D.M.P.: HL-64776) and from the American Heart Association (G.D.: Scientist Development Grant 0530361N; D.W.S.: Scientist Development Grant 0030370Z; and D.M.P.: Established Investigator 0340443N).

Disclosures
D.M.P. serves as a consultant to Speedel Pharma, not related to this study. The remaining authors report no conflicts.

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Exaggerated Cardiovascular Stress Responses and Impaired β-Adrenergic–Mediated Pressor Recovery in Obese Zucker Rats
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Hypertension. 2006;48:1109-1115; originally published online October 16, 2006; doi: 10.1161/01.HYP.0000247306.53547.d4
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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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