Impaired hemorrhage tolerance in the obese Zucker rat model of metabolic syndrome

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Frisbee, Jefferson C. Impaired hemorrhage tolerance in the obese Zucker rat model of metabolic syndrome. J Appl Physiol 100: 465–473, 2006. First published October 13, 2005; doi:10.1152/japplphysiol.01062.2005.—As obese Zucker rats (OZR) manifesting the metabolic syndrome exhibit enhanced vascular adrenergic constriction and potentially an enhanced adrenergic activity vs. lean Zucker rats (LZR), this study tested the hypothesis that OZR exhibit an improved tolerance to progressive hemorrhage. Preliminary experiments indicated that, corrected for body mass, total blood volume was reduced in OZR vs. LZR. Anesthetized LZR and OZR had a cremaster muscle prepared for in situ videomicroscopy and had renal, splanchnic, hindlimb, and skeletal muscle perfusion monitored with flow probes. Arterial pressure, arteriolar reactivity to norepinephrine, and tissue/organ perfusion were monitored after either infusion of phentolamine or successive withdrawals of 10% total blood volume. Phentolamine infusion indicated that regional adrenergic tone under control conditions differed substantially between LZR and OZR, whereas with hemorrhage OZR exhibit decompensation in arterial pressure before LZR. Renal, distal hindlimb, and skeletal muscle perfusion decreased more rapidly and to a greater extent in OZR vs. LZR after hemorrhage. In contrast, hemorrhage-induced reductions in splanchnic perfusion in OZR lagged behind those in LZR, although a similar maximum reduction was ultimately attained. With increasing hemorrhage, cremasteric arteriolar tone increased more in OZR than LZR, and this increase in active tone was entirely due to an elevated adrenergic contribution. Norepinephrine-induced arteriolar constriction was greater in OZR vs. LZR under control conditions and during hemorrhage, with arterioles from OZR demonstrating early closure vs. LZR. These results suggest that a combination of reduced blood volume and elevated peripheral adrenergic constriction contribute to impaired hemorrhage tolerance in OZR.

microcirculation; blood flow regulation; rodent models of the metabolic syndrome; obesity

As recently reviewed by van Baak (24), sympathetic neural activity in general tends to be elevated in obese individuals, and microneurographic recordings from the peroneal nerve (innervating the skeletal muscle circulation) demonstrate a strong positive correlation with body mass index and adiposity (18, 19). Furthermore, whole body norepinephrine spillover has also been demonstrated to be positively correlated with adiposity (25). Although these responses have not been universally observed (15), and much of the variability may reflect alterations in diet and physical activity (5), existing data generally demonstrate an increased level of sympathetic nervous system activity with obesity and that this elevated sympathetic nervous system activity may be associated with the development of other elements of the metabolic syndrome, including insulin resistance, dyslipidemia, and hypertension (13, 24).

We and others have previously used the obese Zucker rat model of the metabolic syndrome to investigate alterations in cardiovascular function that evolve under this pathological condition. One consistent element of these studies that has been observed is an elevated adrenergic constrictor reactivity of conduit arteries (23) and in the renal (1, 20) and skeletal muscle microcirculation (10, 11, 21), with the potential to negatively impact normal patterns of perfusion (10, 11). Based on these previous observations, we hypothesized that the adult obese Zucker rat may have an improved tolerance to progressive hemorrhage, a stress for which the immediate compensation is an increased sympathetic neural activity and a constriction of the peripheral circulation (6). The purpose of the present study was to determine whether an increased sympathetic neural activity (7, 17) and an increased reactivity of peripheral microvessels to adrenergic stimuli would contribute to a protection of the obese Zucker rat from entering into decompensation [i.e., a negative slope for the change in mean arterial pressure (MAP) vs. time] following progressive incremental hemorrhage.

MATERIALS AND METHODS

Animals. Male 15- to 17-wk-old lean and obese Zucker rats (LZR and OZR, respectively) were used for all experiments. Rats were housed in an Association for Assessment and Accreditation of Laboratory Animals Care-accredited animal care facility, were fed standard chow and tap water ad libitum, and all protocols received prior Institutional Animal Care and Use Committee approval. After an

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overnight fast, rats were anesthetized with injections of pentobarbital sodium (50 mg/kg ip) and received tracheal intubation to facilitate maintenance of a patent airway. In all rats, a carotid artery and an external jugular vein were cannulated for determination of arterial pressure and for intravenous infusion of supplemental anesthetic, if necessary. While under anesthetic, an aliquot of blood was drawn from the jugular vein to be used for the biochemical determination of plasma glucose and insulin concentrations (Lincro Research, St. Charles, MO) as well as a plasma lipid profile (ACE Autoanalyzer, Alfa Wasserman, West Caldwell, NJ) from each animal.

**Evaluation of regional adrenergic tone.** To determine the relative degree of adrenergic tone to key organs/tissues and the contribution of this process in regulating blood flow under control conditions, anesthetized rats (n = 5 LZR and n = 5 OZR) had a femoral artery (immediately proximal to the knee) and the contralateral gastrocnemius muscle exposed, and either a renal artery or the superior mesenteric artery isolated (i.e., in no single animal was both the renal and superior mesenteric artery isolated). In addition to chronically measuring MAP, blood flow was measured through the isolated arteries (0.7 PSB; Transonic, Ithaca, NY) or capillary perfusion within the skeletal muscle exposed, and either a renal artery or the superior mesenteric artery isolated. Preliminary experiments demonstrated that the acquisition of a consistent blood flow signal through the superior mesenteric artery could not be reliably performed with the animal and the cremaster muscle in place within the microscope field. After all surgical procedures, each animal received an intravenous infusion of 1,000 IU/kg heparin (Elkins-Sinn, Cherry Hill, NJ), and all exposed surgical areas were covered in PSS-soaked gauze to minimize evaporative water loss.

**Progressive hemorrhage protocol.** In each animal, MAP was continuously monitored via the carotid artery cannula, whereas perfusion through the superior mesenteric artery, renal artery, distal femoral artery, or gastrocnemius muscle was monitored using the respective flow probe.

After the animal was placed within the videomicroscope and a postsurgical equilibration period of 30 min, a second-order arteriole (~60-μm diameter) was identified in a clearly visible region of the cremaster muscle. This vessel was examined along its length until a suitable bifurcation was identified in which a third-order branch of the vessel would serve as the arteriole of interest. Arterioles chosen for study had walls that were clearly visible, a brisk flow velocity, and active tone, as indicated by the occurrence of significant dilation in response to topical application of 10−4 M adenosine. All arterioles that were studied were located in a region of the muscle that was away from any incision.

Subsequently, individual rats were subjected to a blood loss of ~10% of the total circulating blood volume (taken from the estimation derived above). The blood was withdrawn from the carotid artery cannula and occurred over a 3-min period. Subsequently, each rat was allowed 40 min of recovery time before the second blood withdrawal (an additional ~10% of the original blood volume). This process was repeated until the anesthetized rat either died in response to blood withdrawal or demonstrated a decompensation (a negative slope in blood pressure vs. time during the recovery period).

For the experiments involving cremasteric arteriolar reactivity and alterations to arteriolar tone with progressive hemorrhage, the 20 LZR and 20 OZR were each divided into 4 groups of 5 animals. The first

### Table 1. Baseline characteristics of lean and obese Zucker rats used for the present study

<table>
<thead>
<tr>
<th></th>
<th>Lean Zucker Rats (n = 30)</th>
<th>Obese Zucker Rats (n = 31)</th>
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<tbody>
<tr>
<td>Mass, g</td>
<td>349±9</td>
<td>605±11*</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>104±4</td>
<td>127±5*</td>
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<tr>
<td>Plasma [glucose], mg/dl</td>
<td>105±10</td>
<td>211±12*</td>
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<tr>
<td>Plasma [insulin], mg/ml</td>
<td>1.6±0.5</td>
<td>15.9±2.1*</td>
</tr>
<tr>
<td>Plasma [cholesterol], mg/dl</td>
<td>78±11</td>
<td>104±12</td>
</tr>
<tr>
<td>Plasma [triglycerides], mg/dl</td>
<td>98±13</td>
<td>358±14*</td>
</tr>
<tr>
<td>Blood, mL/100 g mass</td>
<td>21.6±1.1</td>
<td>23.2±1.3</td>
</tr>
<tr>
<td>Kidney mass, g</td>
<td>6.2±0.2</td>
<td>3.8±0.2*</td>
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<tr>
<td>Mass, g</td>
<td>1.48±0.11</td>
<td>1.87±0.12*</td>
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<tr>
<td>Small intestine mass, g</td>
<td>14.2±1.2</td>
<td>19.0±1.5*</td>
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<tr>
<td>Distal hindlimb mass, g</td>
<td>42.4±4.0</td>
<td>46.8±4.1</td>
</tr>
<tr>
<td>Gastrocnemius mass, g</td>
<td>2.24±0.10</td>
<td>2.10±0.12</td>
</tr>
</tbody>
</table>

Values are means ± SE. MAP, mean arterial pressure. Brackets denote concentration. *P < 0.05 vs. lean Zucker rats.
of these groups (i.e., 5 LZR and 5 OZR) had arteriolar reactivity to norepinephrine \((10^{-10} \text{ to } 10^{-7} \text{ M})\) and active tone determined under control (normovolemic) conditions. The second group had reactivity and active tone assessed after the first bleed only. Similarly, the third and fourth groups had these properties assessed only after the second and third blood withdrawals, respectively. In any individual experiment, after completion of the norepinephrine concentration-response curves, cremaster muscles were treated with \(10^{-5} \text{ M}\) phentolamine in the superfusate to determine adrenergic-dependent vs. -independent components of active tone. Muscles were subsequently treated with \(\text{Ca}^{2+}\)-free PSS and adenosine to determine total active tone as described in Data and statistical analyses. This experimental procedure was necessary because neither treatment with phentolamine nor exposure to \(\text{Ca}^{2+}\)-free PSS/adenosine were determined to be functionally reversible in the setting of increasing hemorrhage.

**Data and statistical analyses.** All data are presented as means ± SE. After completion of a given experiment, the kidney, distal hindlimb, and small intestine, as appropriate, were removed, and the mass was determined for the normalization of all perfusion data. The ability of an animal to recover from progressive hemorrhage was estimated by determining the slope (using basic linear regression) of the MAP vs. time relationship over the 40 min after a given blood withdrawal. The ability of an animal to maintain tissue or organ perfusion after progressive hemorrhage was estimated by determining the percentage of the prewithdrawal perfusion that was present after 40 min of postwithdrawal recovery. Active tone for in situ arterioles was calculated as \((\Delta D/D_{\text{max}}) \times 100\), where \(\Delta D\) is the diameter increase from control in response to \(\text{Ca}^{2+}\)-free PSS containing \(10^{-3} \text{ M}\) adenosine and \(D_{\text{max}}\) is the maximum diameter measured under superfusion with \(\text{Ca}^{2+}\)-free PSS containing \(10^{-3} \text{ M}\) adenosine. To

![Fig. 1. Data describing hemodynamic alterations in adult male lean Zucker rats (LZR) and obese Zucker rats (OZR) (n = 5 animals for each strain) in response to intravenous infusion of the adrenoreceptor antagonist phentolamine (5 mg/kg). Data (means ± SE) are presented for mean arterial pressure (A), renal perfusion (B), splanchnic perfusion (C), distal hindlimb perfusion (D), and gastrocnemius muscle perfusion (E). *P < 0.05 vs. LZR control; †P < 0.05 vs. OZR control.](http://jap.physiology.org/)

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determine the active tone that was independent of adrenergic influences, the identical equation was used, although in this case $\Delta D$ is the increase in arteriolar diameter after treatment of the cremaster with phentolamine ($10^{-5}$ M) in response to Ca$^{2+}$-free PSS containing $10^{-3}$ M adenosine. The adrenergic-dependent component of active tone was calculated as the difference between total active tone and adrenergic-independent active tone.

Statistically significant differences in basic characteristics, blood volume, and perfused tissue mass between LZR and OZR were determined using Student’s $t$-test. Analysis of variance (ANOVA) was used to determine statistically significant differences in the effects of phentolamine on MAP and tissue perfusion, the slope of the MAP recovery curves following hemorrhage, posthemorrhage perfusion levels, and cremasteric arteriole active tone between LZR and OZR. Repeated-measures ANOVA was used to determine differences in arteriolar responses to norepinephrine between LZR and OZR. In all cases, Tukey’s test was used post hoc, as appropriate, and $P < 0.05$ was taken to be statistically significant.

RESULTS

Baseline animal characteristics. Data describing the baseline characteristics of LZR and OZR under the conditions of the present study are summarized in Table 1. By 15–17 wk of age, OZR were significantly heavier than their LZR counterparts and demonstrated a moderate elevation in blood pressure, as well as hyperglycemia, hyperinsulinemia, and severe hypertriglyceridemia. Total blood volume was not different between LZR and OZR, although when normalized for body mass, blood volume was reduced in OZR vs. lean animals. Some differences in organ mass were evident between LZR and OZR, as the single kidney mass and that of the small intestine was significantly elevated in obese animals. In contrast, distal hindlimb and gastrocnemius muscle mass was comparable between the two rat strains.

Data describing MAP and blood flow through the renal, superior mesenteric, and distal femoral arteries, as well as perfusion within gastrocnemius muscle in LZR and OZR under control conditions and following pharmacological blockade of $\alpha_1$/-$\alpha_2$-adrenoceptors with phentolamine are presented in Fig. 1. Infusion of phentolamine caused a reduction in MAP in both LZR and OZR, although the magnitude of this response was increased in obese animals (Fig. 1A; $19 \pm 4\%$ in LZR vs. $37 \pm 5\%$ in OZR; $P < 0.05$). Perfusion through the renal artery (Fig. 1B) was not different between LZR and OZR under control conditions, and infusion of phentolamine increased perfusion by a comparable amount in both strains. Splanchnic blood flow, as estimated by perfusion through the superior mesenteric artery, was elevated in OZR vs. LZR, despite correction for the hypertrophy of the intestinal tissue of the OZR (Fig. 1C). Adrenergic blockade, although having minimal impact on perfusion in OZR, significantly increased blood flow through the superior mesenteric artery in LZR. Under control conditions, blood flow within the distal femoral artery (Fig. 1D) and within the gastrocnemius muscle (Fig. 1E) was significantly reduced in OZR vs. LZR, and in both cases this difference between strains was reduced after infusion with phentolamine.

Figure 2 presents changes in MAP in LZR and OZR during the progressive hemorrhage protocol. Although higher before the first bleed, MAP fell more sharply in OZR than in LZR, such that no difference in pressure was determined after the first blood withdrawal. Although both groups experienced a recovery in MAP after the first bleed, the rate of recovery was slightly, although not significantly, greater in LZR vs. OZR (Table 2). After both the second and third bleeds, the rate of recovery in LZR significantly exceeded that in OZR. Finally, after the fourth blood withdrawal, LZR still demonstrated a partial recovery in MAP, although OZR entered into a decompensation phase.

Data describing alterations in tissue/organ perfusion during incremental hemorrhage in LZR and OZR are presented in Fig. 3. Although similar under control conditions, renal perfusion

<table>
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<tr>
<th>Bleed 1</th>
<th>MAP</th>
<th>Renal Perfusion</th>
<th>Splanchnic Perfusion</th>
<th>Distal Hindlimb Perfusion</th>
<th>Gastrocnemius Capillary Perfusion</th>
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<td>LZR</td>
<td>1.42±0.2</td>
<td>69.7±4.2</td>
<td>50.0±5.4</td>
<td>82.4±5.8</td>
<td>67.3±4.5</td>
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<td>OZR</td>
<td>1.13±0.2</td>
<td>56.3±4.1*</td>
<td>87.2±4.9*</td>
<td>70.0±5.5</td>
<td>42.9±5.1</td>
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<th>MAP</th>
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<th>Distal Hindlimb Perfusion</th>
<th>Gastrocnemius Capillary Perfusion</th>
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<tr>
<td>LZR</td>
<td>1.22±0.1</td>
<td>51.5±4.6</td>
<td>36.8±5.1</td>
<td>67.6±5.1</td>
<td>41.2±4.9</td>
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<tr>
<td>OZR</td>
<td>0.55±0.1*</td>
<td>29.7±4.2*</td>
<td>58.1±5.6*</td>
<td>45.1±4.8*</td>
<td>12.9±4.6*</td>
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<th>MAP</th>
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<th>Distal Hindlimb Perfusion</th>
<th>Gastrocnemius Capillary Perfusion</th>
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<td>LZR</td>
<td>0.91±0.1</td>
<td>30.0±5.1</td>
<td>14.7±4.8</td>
<td>48.2±4.6</td>
<td>15.5±4.6</td>
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<tr>
<td>OZR</td>
<td>0.36±0.1*</td>
<td>13.1±3.2*</td>
<td>21.7±3.9</td>
<td>9.0±4.9*</td>
<td>17.3±4.9</td>
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<tr>
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<th>MAP</th>
<th>Renal Perfusion</th>
<th>Splanchnic Perfusion</th>
<th>Distal Hindlimb Perfusion</th>
<th>Gastrocnemius Capillary Perfusion</th>
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<tr>
<td>LZR</td>
<td>0.43±0.1</td>
<td>22.7±3.5</td>
<td>8.5±2.1</td>
<td>18.8±3.9</td>
<td>14.5±4.1</td>
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<td>OZR</td>
<td>0.25±0.1†</td>
<td>11.6±3.0*</td>
<td>3.1±0.9</td>
<td>2.5±1.6*</td>
<td>17.1±4.8</td>
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Values are means ± SE. For MAP, data are presented as the slope of MAP recovery over 40 min posthemorrhage (mmHg/min). For all perfusion parameters, data are presented as the recovery in perfusion (as a percentage of the initial control value) after 40 min of posthemorrhage recovery. LZR, lean Zucker rat; OZR, obese Zucker rat. *$P < 0.05$ vs. LZR; †$P < 0.05$ vs. zero slope.
decreased to a greater extent in OZR vs. LZR after the first bleed and stabilized at a lower level (Fig. 3A). After a second bleed, renal perfusion fell further in OZR vs. LZR and demonstrated no significant recovery with time (Table 2). In response to each of the first two hemorrhage periods, splanchnic perfusion (Fig. 3B) fell to a greater extent in LZR vs. OZR, although the subsequent levels of perfusion were comparable between the two groups. After the third bleed, blood flow in the splanchnic perfusion fell more strongly in OZR than in LZR, and the very low perfusion was similar between the two groups. With regard to both distal hindlimb (Fig. 3C) and gastrocnemius muscle microvascular (Fig. 3D) perfusion, this process was reduced in OZR vs. LZR, and the very low perfusion was similar between the two groups. Regarding arteriolar reactivity for in situ cremaster muscle of OZR and LZR in response to increasing concentrations of norepinephrine. Figure 4A presents the constrictor responses of in situ arterioles after challenge with norepinephrine under control conditions. As evidenced in this panel, arterioles in OZR demonstrated an increased reactivity to the adrenergic agonist compared with responses of vessels from LZR. After the first bleed (Fig. 4B), arterioles from LZR exhibited a similar reactivity to norepinephrine as determined under control conditions, although vessels in OZR exhibited an increased tone before challenge with norepinephrine and an earlier incidence of closure with application of the agonist (Fig. 4C). This pattern was further exacerbated in response to the second bleed, where arteriolar diameter was considerably reduced in OZR vs. LZR, and most vessels closed completely in response to challenge with norepinephrine. Regardless of hemorrhage status, treatment of the cremaster muscle with 10^−5 M phentolamine abolished constrictor reactivity to norepinephrine (data not shown).

Based on the data presented in Fig. 4, a calculation of active tone of in situ cremaster muscle of LZR and OZR can be made during the incremental hemorrhage (Fig. 5). Additionally, the contribution of adrenergic-dependent vs. -independent...
elements of arteriolar tone during these conditions in LZR and OZR can also be estimated after pharmacological blockade of α-adrenoreceptors with phentolamine. As shown in Fig. 5A, active tone of in situ cremasteric arterioles under control conditions was not different between LZR and OZR. However, after the initial bleed, arteriolar tone increased significantly in OZR, whereas this parameter was stable in LZR. After the second bleed, active tone increased in both rat strains, although this increase was more pronounced in OZR than in LZR. After treatment with phentolamine, where adrenergic influences are blocked, data presented in Fig. 5B suggest that adrenergic-independent elements contributing to active tone (e.g., myogenic activation) are not different for in situ cremasteric arterioles between LZR and OZR and that this relationship is not altered by progressive hemorrhage. In contrast, the percentage of active tone that is adrenergic dependent was significantly greater in arterioles of OZR vs. LZR and progressive hemorrhage increased this disparity between the two strains even further (Fig. 5C).

**DISCUSSION**

Recent investigations in our laboratory (10, 21) and by others (20) have demonstrated an increased vasoconstrictor reactivity in response to adrenergic stimuli in both multiple organs and tissues of the obese Zucker rat. Given that additional studies have also suggested that activity within the adrenergic system can also be elevated with the development of obesity in both humans (5, 18, 24) and rodents (7, 17), the present study sought to determine whether these alterations could contribute to an improved ability of the obese Zucker rat to tolerate progressive hemorrhage, a physiological challenge to the cardiovascular system as a whole, the response to which is immediately dependent on sympathetic compensation (6).

The data presented in Fig. 1 suggest that the moderate hypertension that develops in OZR at this age (15–17 wk) may reflect an increased contribution through the sympathetic nervous system (Fig. 1A). Although, in some contrast to earlier investigation of hypertension within the OZR (2), this observation supports previous results from our laboratory and from others where intravenous infusion of α-adrenoreceptor antagonists (21) and ganglionic blockers (7) eliminated differences in MAP between LZR and OZR and partially alleviated differences in peripheral vascular resistance under resting conditions between the two strains (10, 11, 21). The additional panels in Fig. 1 suggest that this contribution of elevated adrenergic tone to increased MAP may reflect a preferential...
be reduced in OZR vs. LZR, since blockade of α-adrenergic receptors had a minimal impact on perfusion in OZR, whereas blood flow was significantly elevated in LZR.

A recent study by Scheihofer et al. (20) provided evidence that blood volume, relative to body weight, is reduced in OZR compared with LZR. This observation was repeated in the present study, wherein blood volume (normalized to body mass) was reduced by nearly 40%. The obvious implication of this observation is that the volume withdrawal of blood during hemorrhage between OZR and LZR must be based on total blood volume, not on body mass (otherwise the severity of effects of each blood withdrawal will be biased against the obese animal). When corrected for this discrepancy, the results of the present study clearly suggest that the ability of OZR to tolerate hemorrhage is reduced compared with that determined in LZR (Fig. 2). OZR initially suffer a more severe fall in MAP after the first blood withdrawal (Fig. 2A) and consistently exhibited a reduced ability to restore normal blood pressure during the 40-min recovery period (Table 2). Additionally, OZR routinely demonstrated decompensation by the fourth blood withdrawal period, a condition that did not present itself in LZR.

The data presented in Fig. 3 provide some evidence describing how incremental hemorrhage impacts perfusion of specific tissues and organs within OZR. In this regard, the kidney (Fig. 3A), the hindlimb (Fig. 3C), and the skeletal muscle (Fig. 3D) all behave similarly in response to incremental blood loss. With systemic hemorrhage, perfusion to these regions of the body is reduced more rapidly in OZR than in LZR, ultimately resulting in a premature reduction in perfusion in these tissues of OZR vs. LZR. This premature reduction in perfusion may contribute to the impaired hemorrhage tolerance in OZR owing to a more rapid loss of the “buffer capacity” associated with hemorrhage tolerance. When incorporated with previous studies, this increased sensitivity in the reduction of perfusion with hemorrhage may be most closely associated with an increased vascular reactivity in response to adrenergic stimuli in these beds (10, 19, 21).

To further investigate the extent to which enhanced in situ skeletal muscle arteriolar constriction in response to a hemorrhagic stimuli could contribute to the premature reduction in perfusion, the reactivity of in situ cremasteric arterioles in response to norepinephrine (Fig. 4) and the adrenergic-dependent component of active tone (Fig. 5) were determined after each stage of incremental hemorrhage. While under control conditions, arterioles from OZR demonstrated an increased constrictor reactivity in response to norepinephrine and basal tone was not different between the two strains, suggesting that the cause of the reduced perfusion under resting conditions in skeletal muscle likely reflects an elevated vascular tone at larger resistance arterioles (10). As the severity of hemorrhage was increased, the tone of the distal arterioles of in situ cremasteric arterioles increased more rapidly in OZR than in LZR, resulting in a greater preponderance of vessels that achieved closure either before or after application of norepinephrine. Further analyses of these data and the respective contributions to the increased active tone suggested that this increased tone predominantly reflected an increase in the adrenergic-dependent elements of net vascular tone rather than the elements that are not dependent on adrenergic influences (Fig. 5).
In contrast to these data, adrenergic influences controlling vascular tone appear to be blunted in the splanchnic circulation of OZR vs. LZR, since perfusion of these tissues under control conditions was elevated in obese animals and the effect of adrenoceptor blockade was attenuated. This observation is in general agreement with that from Schreihofer et al. (20) where phenylephrine-induced increases in vascular resistance were reduced in the splanchnic circulation of OZR vs. LZR. Interestingly, and in contrast to the other monitored tissues, incremental hemorrhage did not immediately result in a reduction in perfusion through the superior mesenteric artery of OZR. Rather, this response was less sensitive to blood withdrawal in OZR than in LZR for the initial bleed and only resulted in comparable reductions in perfusion after three hemorrhage periods. It remains to be determined whether the present results during hemorrhage reflect differences in the activity of the sympathetic nervous system within the splanchnic circulation of OZR relative to LZR, differences in the intrinsic reactivity of the splanchnic vasculature to adrenergic agonists, or a combination of both. Speculating a reduced sensitivity of the splanchnic circulation to hemorrhage-induced blood redistribution contributes to the premature reductions in perfusion with hemorrhage determined in the skeletal muscle, hindlimb, and renal circulations of OZR relative to LZR. It is conceivable that a more sensitive response in terms of the reduction in splanchnic perfusion following hemorrhage in OZR could minimize this premature reduction in renal and skeletal muscle perfusion and allow for a more normal hemorrhage tolerance. Further investigation into mechanisms of this disparity between the sensitivity of vascular beds to hemorrhage and adrenergic challenge in OZR and the implications for this in terms of whole body hemodynamics, blood pressure regulation, and hemostasis may be warranted.

The original hypothesis underlying this study was that the previously demonstrated enhanced adrenergic reactivity of the peripheral circulation, when combined with a normal or enhanced function of the sympathetic nervous system, would improve the ability of the adult OZR afflicted with the metabolic syndrome to withstand the physiological challenge to the cardiovascular system of progressive hemorrhage. Clearly, the results of the present study refute this original hypothesis. When taken together, it seems likely that, in the OZR, the combination of a reduced total blood volume (relative to body mass), an increased adrenergic constrictor reactivity in both the renal and skeletal muscle circulations, and a blunted adrenergic sensitivity in the splanchnic circulation impairs hemorrhage tolerance relative to that in LZR. The relative hypovolemia in OZR, when combined with an elevated adrenergic tone in the peripheral circulation of these animals, suggests that they may already exist in a state that is comparable to that of a mild hemorrhage. This condition, when combined with a loss of the buffer capacity to tolerate hemorrhage in terms of reducing peripheral perfusion and an imbalance in sympathetic responses between the splanchnic circulation and that of the renal and skeletal muscle circulations, results in a condition wherein the obese animal has lower reservoir of blood with which to perfuse vital organs and a compromised ability to adequately redirect perfusion to those vital organs during periods of hypovolemic stress.

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GRANTS

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