Impaired dilation of skeletal muscle microvessels to reduced oxygen tension in diabetic obese Zucker rats

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Frisbee, Jefferson C. Impaired dilation of skeletal muscle microvessels to reduced oxygen tension in diabetic obese Zucker rats. Am J Physiol Heart Circ Physiol 281: H1568–H1574, 2001.—This study determined alterations to hypoxic dilation of isolated skeletal muscle resistance arteries (gracilis arteries; viewed via television microscopy) from obese Zucker rats (OZR) compared with lean Zucker rats (LZR). Hypoxic dilation was reduced in OZR compared with LZR. Endothelium removal and cyclooxygenase inhibition (indomethacin) severely reduced this response in both groups, although nitric oxide synthase inhibition (Nω-nitro-L-arginine methyl ester) reduced dilation in LZR only. Treatment of vessels with a PGH2-thromboxane A2 receptor antagonist had no effect on hypoxic dilation in either group. Arterial dilation to arachidonic acid, iloprost, acetylcholine, and sodium nitroprusside was reduced in OZR versus LZR, although dilation to forskolin and aprikalim was unaltered. Treatment of arteries from OZR with oxidative radical scavengers increased dilation to hypoxia and agonists, with no effect on responses in LZR. The restored hypoxic dilation in OZR was abolished by indomethacin. These results suggest that hypoxic dilation of skeletal muscle microvessels from LZR represents the summated effects of prostanoid and nitric oxide release, whereas the impaired response of vessels in OZR may reflect scavenging of PGL2 by superoxide anion.

skeletal muscle microvessel; type 2 diabetes; hypertension; Zucker rat; hypoxia; superoxide

DIABETES MELLITUS is a widespread pathology impacting ~11 million Americans, and while a leading cause of blindness, kidney failure, and limb amputation, it is also a potent risk factor for the development of peripheral vascular disease, a debilitating condition impacting ~60 million Americans (2). A recent study (27) has indicated that type 2 diabetes is a public health challenge of increasing consequence, because, over the last 10 years, the incidence of type 2 diabetes has increased by ~70% in 30- to 39-year-old Americans and has become increasingly common among American children. The obese Zucker rat (OZR) provides a valuable model for examining the effects of type 2 diabetes mellitus. Owing to a nonfunctional leptin receptor gene (10) and increased food consumption, OZR rapidly develops numerous clinically relevant pathological conditions including, in addition to type 2 diabetes, hypertension and obesity (14, 29, 33). Although the progression of these phenotypes has been well documented, the effects of these pathologies, developing concurrently, on peripheral vascular function remain largely uncharacterized.

The small resistance arteries supplying skeletal muscle lie immediately proximal to downstream arterioles and exchange vessels. The ability of these microvessels to alter their active tone is of vital importance in that they are critical regulators of the delivery of blood to downstream microvessel networks. In OZR, previous studies have indicated that intestinal and mesenteric arteriolar dilation to endothelium-dependent agonists and stimuli was reduced compared with responses in control rats (13, 35, 37), an observation that may have been related to an altered tissue sensitivity to nitric oxide (NO) (36) or an increased oxidative stress in tissues of OZR compared with lean Zucker rats (LZR) (3, 17). However, there has been no attempt to determine the reactivity of skeletal muscle microvessels of OZR to the physiological dilator stimulus of hypoxia. The purposes of the present study were to determine whether alterations to the dilator reactivity of skeletal muscle resistance arteries of OZR to reduced PO2 exist and to determine which mechanisms contribute to alterations in this response between LZR and OZR.

MATERIALS AND METHODS

Animals. All experiments used 13- to 15-wk-old male LZR and OZR. Animals were fed standard chow and drank tape water ad libitum. Rats were housed in an animal care facility at the Medical College of Wisconsin approved by the American Association for the Accreditation of Laboratory Animal Care, and all protocols were approved by the institutional Animal Care and Use Committee at the Medical College of Wisconsin. Rats were anesthetized with an injection of pentobarbital sodium (60 mg/kg ip), and a carotid artery was cannulated for determination of arterial pressure. In addition to being heavier than LZR [347 ± 10 g body wt; mean arterial pressure (MAP), 119 ± 3.2 mmHg; blood [glucose], 138 ± 15 mg/dl], OZR (613 ± 18 g body wt; MAP, 165 ± 6.4 mmHg; blood [glucose], 486 ± 48 mg/dl) demonstrated significant hypertension and hyperglycemia.

Preparation of isolated vessels. Gracilis arteries were surgically dissected from the anesthetized rat as described pre-
viously (8). Arteries were placed in a heated (37°C) chamber that allowed the lumen and exterior of the vessel to be perfused and superfused, respectively, with physiological salt solution (PSS) from separate reservoirs. The PSS used in these experiments was equilibrated with 21% O₂-5% CO₂-6% N₂ and had the following composition (in mM): 119 NaCl, 4.7 KCl, 1.17 MgSO₄, 1.6 CaCl₂, 1.18 NaH₂PO₄, 24 NaHCO₃, 0.026 EDTA, and 5.5 glucose. Vessels were cannulated at both ends with glass micropipettes (tip diameter, ~100 μm) and secured to the inflow and outflow pipettes using 10-0 nylon sutures. Any side branches were ligated with a single strand teased from a 6-0 silk suture. The inflow pipette was connected to a reservoir perfusion system that allowed the intraluminal pressure and luminal gas concentrations to be controlled. Vessel diameter was measured using television microscopy and an on-screen video micrometer.

Arteries were extended to their in vivo length and equilibrated at 80% of the animal’s MAP to approximate the perfusion pressure encountered in vivo (21). Any vessel that did not demonstrate active tone at rest was discarded. Active tone at the equilibration pressure was calculated as follows: (ΔD/ΔPmax) × 100, where ΔD is the diameter increase from rest in response to Ca²⁺-free PSS and ΔPmax is the maximum diameter measured at the equilibration pressure in Ca²⁺-free PSS.

Removal of the vascular endothelium. The microvessel endothelium was removed via air bolus perfusion (8, 22). Subsequently, PSS perfusion through the lumen was restored, and the artery was allowed to reequilibrate for 30 min. Endothelium denudation procedures were deemed successful when vessel dilator reactivity to 10⁻⁶ M acetylcholine was eliminated and when the reactivity of the vessel to the endothelium-independent agonist forskolin (10⁻⁷ M) was not altered from responses determined in intact vessels.

Inhibition of cytochrome P-450 4A enzymes. To assess the role of cytochrome P-450 4A-derived arachidonic acid ω-hydroxylation (producing 20-hydroxyeicosatetraenoic acid) and epoxidation (producing epoxyeicosatrienoic acids) in contributing to hypoxic relaxation of arteries, these enzymes were inhibited with 10⁻⁶ M 17-octadecynoic acid (17-ODYA) (1, 8).

Inhibition of prostanooid and NO production. To assess the role of prostanooid or NO release from the microvessel endothelium in regulating hypoxic dilation of isolated arteries, the cyclooxygenase inhibitor indomethacin (10⁻⁶ M) or the NO synthase inhibitor Nω-nitro-l-arginine methyl ester (l-NAME; 10⁻⁴ M) was added to the vessel bath to inhibit the production of prostanooids and NO, respectively (7, 8).

Blockade of PGH₂-thromboxane A₂ receptors. To determine the contribution of activation of PGH₂-thromboxane A₂ (TXA₂) receptors in contributing to altered hypoxic dilation of microvessels from OZR versus LZR, dilator responses of microvessels from both groups were assessed in response to hypoxia and to iloprost (10⁻⁹ g/ml) under control conditions and after application of the PGH₂-TXA₂ receptor antagonist SQ-29548 (10⁻⁵ M) (15).

Dilator agonists and hypoxia. In a separate series of experiments, dilator responses of isolated gracilis arteries from LZR and OZR were assessed in response to challenge with 1) the PGH₂ analog iloprost (10⁻¹⁵–10⁻⁹ g/ml), 2) arachidonic acid (10⁻⁸–10⁻⁶ g/ml), 3) acetylcholine (10⁻⁹–10⁻⁶ g/ml), 4) the adenylyl cyclase activator forskolin (10⁻¹³–10⁻⁷ M), 5) the endothelium-independent NO donor sodium nitroprusside (10⁻⁹–10⁻⁶ M), 6) the ATP-sensitive K⁺ channel agonist aprakalin (10⁻⁹–10⁻⁶ M), and 7) Ca²⁺-free PSS containing 10⁻³ M adenosine to produce maximal dilation and determine the maximum diameter of the microvessel.
the individual pathways to hypoxic dilation of gracilis arteries of LZR and OZR.

Determination of vascular responses to dilator agonists. Subsequent experiments determined vascular responses to dilator agonists associated with the pathways of hypoxic dilation determined in the above experiments. After the hypoxic dilation of vessels was determined, microvessel reactivity was evaluated after application of arachidonic acid, acetylcholine, iloprost, forskolin, sodium nitroprusside, and aprikalim, as described above.

Determination of vascular responses to agonists and hypoxia after treatment with PEG-SOD and catalase. For these experiments, the response of isolated microvessels from LZR and OZR to arachidonic acid, acetylcholine, iloprost, sodium nitroprusside, and hypoxia was determined before and after treatment of the vessel with the oxidative free radical scavengers PEG-SOD and catalase or catalase alone, as described above.

Role of intralumenal pressure in mediating dilator responses. Given that the evaluation of the dilator reactivity of gracilis arteries from LZR and OZR was performed at different intralumenal equilibrium pressures, additional data were collected to address the possibility that the elevated intralumenal pressure employed for OZR may have contributed to alterations in dilator reactivity in these vessels. For these experiments, the dilator reactivity of isolated vessels of OZR in response to 10⁻⁶ M acetylcholine, 10⁻⁶ M sodium nitroprusside, and hypoxia was evaluated at the intraluminal equilibration pressure employed for both LZR (95 mmHg) and OZR (131 mmHg).

Data and statistical analyses. For all concentration-response curves, vascular reactivity data were fit with the following regression equation

\[ y = \alpha + \beta \log(x) \]

where \( y \) is the dilator response (increase in vessel diameter in response to challenge with a specific agonist), \( \alpha \) is an intercept term, and \( \beta \) is the agonist concentration. For all regression equations, \( r^2 > 0.85 \). For this analysis, the \( \beta \) (slope) coefficient represents the change in microvessel diameter for a logarithmic change in agonist concentration.

All data are presented as means ± SE. Differences in \( \beta \)-coefficients and in the responses of isolated vessels to hypoxia were determined using ANOVA, with Tukey’s post hoc test and Student’s t-test where appropriate. For all analyses, \( P < 0.05 \) was considered to be statistically significant.

RESULTS

Under control conditions, resting diameter and active tone of isolated microvessels from LZR and OZR were not different. However, the maximum microvessel diameter, determined during superfusion with Ca²⁺-free PSS, was significantly lower in OZR versus LZR (Table 1).

Mediators of hypoxic dilation. Data describing hypoxic dilation of microvessels from LZR and OZR and the effects of endothelium denudation are presented in Fig. 1. Gracilis arteries from OZR demonstrated a significant impairment in vessel dilation to reduced PO₂ compared with responses in LZR. Removal of the microvessel endothelium with air bolus perfusion abolished the dilator reactivity of vessels of LZR to hypoxia, whereas this response was severely inhibited in vessels of OZR.

Figure 2 presents data describing hypoxic dilation of skeletal muscle microvessels from LZR and OZR after inhibition of NO synthase, cyclooxygenase, or both. In LZR, treatment of vessels with L-NAME or indomethacin significantly reduced hypoxic dilation of vessels from control values, whereas treatment of vessels with both inhibitors abolished this response (Fig. 2A). In contrast, treatment of vessels from OZR with L-NAME had no effect on hypoxic dilation, although application of indomethacin significantly reduced the dilator reactivity of these vessels to hypoxia (Fig. 2B).

![Fig. 1](http://ajpheart.physiology.org/)
versus LZR. In contrast, arterial dilation to these agonists was reduced in OZR, indicating that skeletal muscle.

agonists employed in the present study are summarized in Table 2. Agonists LZR OZR

Table 2. $\beta$ (slope) coefficients from regression equations of skeletal muscle microvessels of LZR and OZR in response to agonists

<table>
<thead>
<tr>
<th>Agonists</th>
<th>LZR</th>
<th>OZR</th>
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<tbody>
<tr>
<td>AA, $\mu M/log \ M$</td>
<td>2.53 ± 0.19</td>
<td>1.50 ± 0.25*</td>
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<tr>
<td>ACh, $\mu M/log \ M$</td>
<td>2.84 ± 0.28</td>
<td>0.54 ± 0.08*</td>
</tr>
<tr>
<td>SNP, $\mu M/log \ M$</td>
<td>5.42 ± 0.42</td>
<td>1.93 ± 0.26*</td>
</tr>
<tr>
<td>Forskolin, $\mu M/log \ M$</td>
<td>1.84 ± 0.17</td>
<td>0.70 ± 0.13*</td>
</tr>
<tr>
<td>Aprikalim, $\mu M/log \ M$</td>
<td>2.74 ± 0.21</td>
<td>2.59 ± 0.27</td>
</tr>
</tbody>
</table>

Values are means ± SE. $\beta$ (slope) coefficients are from the regression equations describing concentration-response curves (see Eq. 1). AA, arachidonic acid; ACh, acetylcholine; SNP, sodium nitroprusside. *P < 0.05 vs. LZR.

Treatment of intact vessels from LZR or OZR or endothelium-denuded vessels of LZR with 17-ODYA did not alter the dilation of vessels to reduced PO$_2$ from responses determined in untreated vessels. However, after endothelium denudation, the small residual dilation of vessels from OZR in response to reduced PO$_2$ (3.6 ± 1.1 $\mu M$) was eliminated by subsequent application of 17-ODYA ($-0.3 ± 0.3 \mu M$).

In response to application of the PGH2-TxA2 receptor antagonist, microvessel dilation to hypoxia or to iloprost was not altered in either group from values determined under control conditions. In LZR, microvessels dilated by 18.5 ± 3.9 and 27.5 ± 3.7 $\mu M$ in response to hypoxia and iloprost, respectively. After application of SQ-29548, vessels dilated by 16.9 ± 3.1 and 28.2 ± 4.8 $\mu M$ to these same stimuli. In OZR, under control conditions, vessels diluted by 11.2 ± 2.5 $\mu M$ in response to hypoxia and 13.4 ± 3.6 $\mu M$ after application of iloprost. During blockade of PGH$_2$-TxA$_2$ receptors, microvessels of OZR dilated by 9.4 ± 3.4 and 15.4 ± 4.1 $\mu M$ to hypoxia and iloprost, respectively.

Reactivity to dilator agonists. Data describing the dilator responses of skeletal muscle microvessels to the agonists employed in the present study are summarized in Table 2. $\beta$ (slope) coefficients describing the dilator reactivity of microvessels from OZR to arachidonic acid, acetylcholine, sodium nitroprusside, and iloprost were significantly reduced compared with values determined in LZR, indicating that skeletal muscle arterial dilation to these agonists was reduced in OZR versus LZR. In contrast, $\beta$-coefficients describing dilator responses of these vessels to forskolin and aprikalim were not different between groups, indicating a comparable level of dilator reactivity to direct adenylate cyclase and ATP-sensitive K$^+$ channel activation, respectively, in skeletal muscle resistance arteries of LZR and OZR. In vessels of LZR, treatment of isolated arteries with L-NAME completely abolished the reactivity of the vessels to 10$^{-6}$ M acetylcholine (control vessel dilation, 21.3 ± 3.5 $\mu M$; L-NAME-treated vessel dilation, 2.5 ± 3.1 $\mu M$). Similarly, the small dilation of vessels of OZR in response to acetylcholine (6.4 ± 2.5 $\mu M$) was abolished after treatment of vessels with L-NAME ($-1.5 ± 1.8 \mu M$).

Table 3 presents data describing the effects of treatment of skeletal muscle microvessels from LZR and OZR with PEG-SOD and catalase on dilator responses to arachidonic acid, acetylcholine, sodium nitroprusside, and iloprost. In LZR, application of the free radical scavengers did not significantly alter $\beta$-coefficients describing the concentration-response curves of vessels any to the agonists. In contrast, treatment of vessels of OZR with PEG-SOD and catalase significantly increased $\beta$-coefficients describing the vessel concentration-response curves to each of the agonists, indicating a significant increase in the dilator reactivity of skeletal muscle microvessels to these agonists after treatment with the oxidative free radical scavengers. In additional studies where catalase alone was applied to the isolated vessels, the dilator responses of gracilis arteries from both LZR and OZR to the employed agonists was not significantly altered from levels determined in untreated vessels (Table 3).

The effects of treatment of vessels from LZR and OZR with PEG-SOD and catalase on hypoxic dilation are presented in Fig. 3. In LZR, application of both free radical scavengers did not alter hypoxic dilation of skeletal muscle microvessels from levels under control conditions (Fig. 3A). In contrast, treatment of vessels of OZR with the scavengers significantly increased dilator reactivity to hypoxia from levels in untreated vessels (Fig. 3B). However, compared with the hypoxic dilation of isolated vessels of OZR under control conditions (8.7 ± 2.2 $\mu M$), application of catalase alone had no significant effect on vessel responses to reduced PO$_2$ (9.4 ± 2.8 $\mu M$). Subsequent application of L-NAME to vessels of OZR that had been treated with PEG-SOD and catalase had no effect on the enhanced dilator response to reduced PO$_2$. However, application of indomethacin to vessels of OZR after treatment with the

Table 3. $\beta$ (slope) coefficients from regression equations of skeletal muscle microvessels of LZR and OZR in response to agonists under control conditions and after treatment with PEG-SOD and catalase

<table>
<thead>
<tr>
<th></th>
<th>LZR</th>
<th>OZR</th>
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<tr>
<td></td>
<td>Control</td>
<td>PEG-SOD + Catalase</td>
</tr>
<tr>
<td>AA, $\mu M/log \ M$</td>
<td>2.68 ± 0.24</td>
<td>2.80 ± 0.29</td>
</tr>
<tr>
<td>ACh, $\mu M/log \ M$</td>
<td>2.72 ± 0.29</td>
<td>3.18 ± 0.34</td>
</tr>
<tr>
<td>SNP, $\mu M/log \ M$</td>
<td>6.49 ± 0.96</td>
<td>6.58 ± 0.75</td>
</tr>
<tr>
<td>Iloprost, $\mu M/log \ g/ml$</td>
<td>2.17 ± 0.19</td>
<td>2.25 ± 0.26</td>
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</table>

Values are means ± SE. $\beta$ (slope) coefficients are from the regression equations describing concentration-response curves (see Eq. 1). *P < 0.05 vs. control.
oxidative free radical scavengers completely abolished hypoxic dilation.

The effects of elevated intraluminal equilibration pressure on the dilator reactivity of isolated skeletal muscle resistance arteries from OZR are presented in Fig. 4. When the intraluminal pressure employed for vessels of OZR (131 ± 6 mmHg) was reduced to that used for vessels of LZR (95 ± 5 mmHg), the dilator responses of vessels to acetylcholine, sodium nitroprusside, and reduced PO2 were not significantly different from those determined at the normal equilibration pressure for OZR.

DISCUSSION

The primary observation of the present study was that hypoxic dilation of gracilis arteries of OZR was impaired relative to LZR (Fig. 1). This impaired reactivity to hypoxia, a novel observation of the present study, is in general agreement with existing observations of impaired endothelium-dependent dilation of intestinal and mesenteric microvessels (13, 35, 37) and skeletal muscle arterioles of OZR (9). Interestingly, in OZR, a significant reactivity of skeletal muscle microvessels to hypoxia was retained. The persistent dilator response to reduced PO2 despite the development of hypertension is in agreement with a recent study (8) by the author investigating the effects of Dahl hypertension but contrasts with a previous study (21) investigating the reduced renal mass model of hypertension. These observations suggest that substantial heterogeneity exists regarding the regulation of microvessel tone with hypoxia across different models of hypertension.

The results of the present study suggest that the release of NO and/or prostanoids from the vascular endothelium are responsible for hypoxic dilation of skeletal muscle microvessels from LZR and OZR. While these data are in agreement with previous studies (7, 8, 16, 24, 30) indicating that hypoxic dilation in normotensive rats is mediated by the release of these substances, the present results contrast with a recent study (8) suggesting an endothelium-independent cytochrome P-450 Ψ-hydroxylase-dependent component contributing to this response in gracilis arteries of hypertensive Dahl rats. The results of the present study support only a minimal role for cytochrome P-450 enzymes in mediating hypoxic dilation in skeletal muscle microvessels of Zucker rats. It is important to note, however, that the present study employed only one level of hypoxia for the isolated vessels. Additional studies, with more mild or more severe levels of hypoxia, could elucidate additional contributing mechanisms underlying the dilation of skeletal muscle microvessels to reduced PO2.

Hypoxic dilation of skeletal muscle resistance arteries of LZR appeared to be wholly dependent on NO and prostanoid release from the vascular endothelium are responsible for hypoxic dilation of skeletal muscle microvessels from LZR and OZR. While these data are in agreement with previous studies (7, 8, 16, 24, 30) indicating that hypoxic dilation in normotensive rats is mediated by the release of these substances, the present results contrast with a recent study (8) suggesting an endothelium-independent cytochrome P-450 Ψ-hydroxylase-dependent component contributing to this response in gracilis arteries of hypertensive Dahl rats. The results of the present study support only a minimal role for cytochrome P-450 enzymes in mediating hypoxic dilation in skeletal muscle microvessels of Zucker rats. It is important to note, however, that the present study employed only one level of hypoxia for the isolated vessels. Additional studies, with more mild or more severe levels of hypoxia, could elucidate additional contributing mechanisms underlying the dilation of skeletal muscle microvessels to reduced PO2.
metabolites via cyclooxygenase in addition to release of PGI2 (i.e., PGH2 and TxA2, see Refs. 4 and 31) or to an inappropriate activation of PGH2-TxA2 receptors by PGI2 (23). Furthermore, a recent study (32) has indicated that blockade of PGH2-TxA2 receptors in the cheek pouch of spontaneously hypertensive hamsters restores microvessel dilator reactivity to acetylcholine and vasoactive intestinal peptide. However, the results of the present study suggest that these processes do not contribute to the impaired hypoxic dilation of gracilis arteries of OZR, because application of the PGH2-TxA2 receptor antagonist SQ-29548 did not alter hypoxia- or iloprost-induced responses of vessels from LZR or OZR.

It has been suggested that tissue oxidant stress levels are elevated in OZR, compromising dilator responses of microvessels to NO-dependent stimuli (3, 17). Furthermore, the author (9) has previously demonstrated that vascular superoxide anion levels were increased in OZR versus LZR and that treatment of vessels with PEG-SOD and catalase reduces vascular oxidant stress in OZR to levels that are not distinguishable from LZR. As presented in Table 3, vascular oxidant stress levels in OZR were correlated with dilator reactivity of skeletal muscle microvessels to NO- and PGI2-dependent dilator agonists. When compared with the agonist-induced dilator responses of vessels from LZR, these data suggest that reduced vascular smooth muscle reactivity to NO and PGI2 in OZR may reflect increased scavenging of these signaling molecules by oxidative radicals and their conversion to peroxynitrite (34) and isoprostanes (6, 17–19, 28), respectively. However, the results of the present study suggest that the primary source of the oxidant stress-induced impairment in dilator reactivity in OZR was due to superoxide anion and not hydrogen peroxide, because treatment of vessels from OZR with catalase alone had no significant effect on the dilation of vessels from these rats to either reduced PO2 or to the employed agonists.

After normalization of vascular oxidant stress in OZR, hypoxic dilation of skeletal muscle microvessels was increased compared with responses determined under control conditions (Fig. 3). Subsequent application of L-NAME to vessels of OZR treated with PEG-SOD and catalase did not alter hypoxic dilation, although application of indomethacin to these vessels abolished this response. These data suggest that, despite normalization of vascular oxidant stress and restoration of dilator reactivity of these vessels to NO-dependent pharmacological agents (Table 3), the ability of skeletal muscle microvessels to produce and/or release NO in response to hypoxia may be compromised in OZR.

Interestingly, restoration of the prostanooid-dependent component of hypoxic dilation of gracilis arteries of OZR after application of PEG-SOD and catalase suggests that degradation of PGI2 by superoxide anion may represent a primary mechanism underlying the impaired dilation of skeletal muscle microvessels to reduced PO2. However, it is important to note that results from the present study do not rule out the possibility that an elevated vascular oxidant stress level might contribute to impaired endothelial release of PGI2, degradation of prostacyclin receptors, or interference at additional sites in the signal transduction pathways associated with PGI2 that were alleviated after treatment of the isolated gracilis artery of OZR with free radical scavengers.

Summary and conclusions. The results of the present study indicate that hypoxic dilation of skeletal muscle microvessels from OZR is impaired compared with responses in microvessels from LZR. In LZR, hypoxic dilation is mediated by the combined effects of NO and prostanooid release from the vascular endothelium, whereas in OZR, microvessel dilation to reduced PO2 is largely dependent on endothelium-dependent prostanooid release. Normalization of tissue oxidant stress improves dilator responses of microvessels from OZR to NO- and PGI2-dependent dilator agonists and restores the prostanooid-dependent component of hypoxic dilation. These data may represent the first observations suggesting impairment of a PGI2-dependent vasodilator response due to an inactivation of endothelium-derived prostacyclin by superoxide anion.

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