

## **Elevated Vascular Thromboxane Generation Impairs Dilation of OZR Arterioles with Reduced O<sub>2</sub> Tension**

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We determined if altered vascular PGI<sub>2</sub> or TxA<sub>2</sub> production with reduced PO<sub>2</sub> contributes to impaired hypoxic dilation of skeletal muscle arterioles of obese Zucker rats (OZR) vs. lean Zucker rats (LZR). Mechanical responses were assessed in isolated arterioles following reduced PO<sub>2</sub> under control conditions and with pharmacological interventions inhibiting arachidonic acid metabolism, NO synthase, and alleviating vascular oxidant stress. Hypoxic dilation, endothelium-dependent in both, was attenuated in OZR; NOS inhibition had no impact on dilation in either strain. COX inhibition attenuated hypoxic dilation in LZR and abolished responses in OZR. Treating arterioles from OZR with PEG-SOD improved hypoxic dilation; the improvement was entirely COX-dependent. Vascular PGI<sub>2</sub> production with hypoxia was similar between strains, although TxA<sub>2</sub> production was increased in OZR; a difference that was attenuated by treatment with PEG-SOD. Both blockade of PGH<sub>2</sub>/TxA<sub>2</sub> receptors and inhibition of TxA<sub>2</sub> synthase increased hypoxic dilation in OZR arterioles. These results suggest that a contributor to impaired hypoxic dilation of arterioles of OZR may be increased TxA<sub>2</sub> production, which opposes the dilator influences of PGI<sub>2</sub>. These results also suggest that elevated vascular oxidant stress may contribute to the increased TxA<sub>2</sub> production and may blunt vascular sensitivity to PGI<sub>2</sub>.