

## **Mechanism of nitric oxide induced sympatholysis in rat soleus feed arteries**

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During exercise, the neurotransmitter norepinephrine (NE) binds to arterial adrenergic receptors to cause vasoconstriction, yet arteries and arterioles constrict less to sympathetic stimulation in contracting compared to resting skeletal muscle (sympatholysis). Previous evidence indicates that nitric oxide (NO) can be sympatholytic, but the mechanism is unknown. We hypothesized that NO causes sympatholysis in rat soleus muscle feed arteries, that NO is released from vascular endothelial cells by increased shear stress, and that NO acts through a guanylyl cyclase intracellular signaling pathway. Soleus feed arteries (n = 12 per group) were isolated from male Sprague-Dawley rats and cannulated on two glass micropipettes for in vitro videomicroscopy. We measured the constriction response to the adrenergic agonist phenylephrine (PE;  $10^{-9}$  M to  $10^{-4}$  M, 0.5 log increments) in the presence of varying levels of the nitric oxide donor sodium nitroprusside (SNP; 0 nM, 0.1 nM and 100 nM), shear stress (0 dy/cm<sup>2</sup>, 25 dy/cm<sup>2</sup>, and 135 dy/cm<sup>2</sup>), and SNP + ODQ (0.1 nM), an inhibitor of guanylyl cyclase. SNP reduced constriction to PE in a dose-dependent manner (maximum constriction 77.3 % vs. 70.7 % and 56.7 %), indicating that NO interferes with sympathetic constriction. ODQ restored PE-induced constriction (PE alone 77.5%; with SNP 67.6%; with SNP + ODQ 83.5%), indicating that NO causes sympatholysis through a guanylyl cyclase signaling pathway. However, shear stress did not reduce constriction to PE (67.6 % vs. 68.1 %, and 67.6 %), indicating that increased shear stress during exercise is not the source of the NO causing sympatholysis. We conclude that nitric oxide acting through guanylyl cyclase causes sympatholysis, but the source of the nitric oxide during exercise is not shear stress-induced endothelial cell activation.