**A Mathematical Model for the Role of N2O3 in**

**Enhancing Nitric Oxide Following Nitrite Infusion**

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**Introduction:** The production of nitric oxide (NO) by the nitrite reductase activity of deoxygenated hemoglobin (deoxyHb) has been recently proposed as a major mechanism in hypoxic vasodilation. Infusions of nitrite into the bloodstream in animal and human experiments have been shown to cause vasodilation, reduce hypertension, and protect from ischemia-reperfusion injury. A major challenge to the deoxyHb nitrite reductase hypothesis is to explain how nitrite-derived NO escapes hemoglobin scavenging.1 It has been proposed that a stable intermediate species, dinitrogen trioxide (N2O3), is generated during nitrite reduction which can diffuse away from erythrocytes and release NO in smooth muscle cells (SMC).2 We developed a mathematical model for an arteriole and surrounding tissue to investigate the potential for this pathway to enhance SMC NO, based on rate constants in the literature for production and homolysis of N2O3.

**Methods:** Coupled partial differential equations for an arteriole model were written in cylindrical coordinates and solved to steady state by finite element numerical methods using COMSOL v5.1 (COMSOL, Inc., Burlington, MA). NO was produced by the endothelium through shear stress and O2-dependent eNOS, and deoxyHb reduction of infused nitrite was modeled using the Monod-Wyman-Changeux equation for the oxyhemoglobin equilibrium curve.3 The model predicts how N2O3 produced in the blood by deoxyHb nitrite reductase diffuses away from the erythrocyte trap, and is homolyzed in tissue to release NO. The effect of the N2O3 pathway on SMC NO from infused nitrite was simulated for different conditions of blood flow and oxygen level.

**Results and Discussion:** Our simulations predict that without the N2O3 pathway, nitrite reduction by deoxyHb results in negligible NO elevation. For simulations without the N2O3 pathway, a decrease in blood PO2 is predicted to decrease average SMC NO. With the N2O3 pathway, moderate levels of nitrite infusion can compensate for this lost NO with significant elevation of vascular wall NO during hypoxic conditions. The enhancement of SMC NO increases with more severe hypoxia, reaching a maximum at the lowest blood PO2, and increases nonlinearly with increasing nitrite concentration.4 These results provide insight into the mechanisms by which nitrite infusion can cause vasodilation despite the NO-scavenging environment of RBC hemoglobin.

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**References:**

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