OONO
Rebounding From Nitric Oxide
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I
nhaled nitric oxide is an elegantly simple therapy for idiopathic pulmonary hypertension. Breathing small amounts of nitric oxide directly activates guanylyl cyclase in pulmonary resistance vessels to counteract hyperten-
sion. In patients who respond to inhaled nitric oxide, either the endogenous synthesis of nitric oxide is not sufficient to overcome the hypertensive stress or nitric oxide is being inactivated too rapidly to act on guanylate cyclase. Certainly, both processes could be operating simultaneously.

Although nitric oxide has a reputation for being highly toxic, in reality the risk of toxicity with inhaled nitric oxide is minor because nitric oxide itself is unreactive with most biological molecules and the amounts administered are low enough to minimize the formation of nitrogen dioxide. Nitric oxide becomes toxic when converted to secondary reactive nitrogen species. Nitric oxide itself is swept away from the vasculature by rapid reactions with hemoglobin. In the high oxygen environment of the lung, nitric oxide will also not significantly inhibit mitochondrial respiration. By now, many patients have been breathing nitric oxide for weeks and even months without overt harm.

However, sudden termination of inhaled nitric oxide occasion-
ally causes a potentially life-threatening hypertensive rebound, even when treated for a few hours. Hypertensive rebound can occur in individuals who showed no initial vasodilation in response to nitric oxide. In this issue of Circulation Research, Wedgwood et al1 have shown that endothelin, the most potent vasoconstrictor known, may contribute to rebound hypertension by inducing superoxide synthesis in the pulmonary vasculature. The increased flux of superoxide will react with nitric oxide to form peroxy-

The authors further show that endothelial nitric oxide syn-

The non–heme iron in cyclooxygenase must initially be oxidized to an unstable and reactive ferryl state to be able to oxidize arachidonic acid. Marnett and colleagues have shown that peroxynitrite can activate a variety of signaling pathways, which tend to be proinflammatory and hypertensive (see Figure).

Peroxynitrite promotes the inflammatory synthesis of pro-
staglandin. The conjugate acid of peroxynitrite (ONOHH) plays an important role in vivo in the activation of cyclooxygenase by providing the peroxide tone necessary for enzyme activity. The non–heme iron in cyclooxygenase must initially be oxidized to an unstable and reactive ferryl state to be able to oxidize arachidonic acid. Marnett and colleagues have shown that peroxynitrite is the major peroxide responsible for activating cyclooxygenase in vivo.8,10 The product of cyclo-

Accumulating PGH₂ from cyclooxygenase can activate thromboxane receptors with similar potency as thromboxane itself. Thus, the reaction of superoxide with nitric oxide in the vasculature can help subvert the principal vasodilating mech-

Peroxynitrite induces longer-lasting changes in the vasculat-

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Inhaled nitric oxide will rapidly diffuse through the pulmonary epithelium to activate guanylyl cyclase in vascular smooth muscle. It will further diffuse through endothelium to react with hemoglobin, principally forming met-hemoglobin and nitrate. However, when tissues produce superoxide, some of the nitric oxide will be converted to peroxynitrite that will cause some tissue damage. Certain proinflammatory pathways are particularly reactive to peroxynitrite. Consequently, peroxynitrite can increase the formation of PGH2 from arachidonate (AA) by stimulating cyclooxygenase while decreasing the formation of prostacyclin by inhibiting prostacyclin synthase (PGIS). Peroxynitrite can also increase the phosphorylation and activation of JNK.

signaling cascades. Peroxynitrite is particularly effective with inactivated tyrosine kinases such as CD45.13 CD45 is a JAK phosphatase that appears to have a central role in downregulating proinflammatory responses.14 The binding site for the phosphate on phosphotyrosine can easily accommodate peroxynitrite and orient it to attack the crucial sulfhdryl in the active site. Cultured endothelium responds to increased shear stress by activating NADPH oxidase and endothelial nitric oxide synthesis.15 The resulting endogenous formation of peroxynitrite activates c-Jun-NH2-terminal kinase (JNK), which induces a wide range of stress-related responses. The peroxynitrite formation in endothelium does not induce apoptosis. However, peroxynitrite-induced activation of JNK does induce apoptosis in neurons. Peroxynitrite is acting far upstream to activate apoptosis in these studies, and activation of the antiapoptotic serine/threonine kinase Akt (protein upstream to activate apoptosis in these studies, and activation does induce apoptosis in neurons. Peroxynitrite is acting far upstream, it is simultaneously oxidizing an electron spin resonance spin-trapping study. FEBS Lett. 1997;403:127–130.


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