Focused Perspective

A Novel Mechanism for Pulmonary Arterial Hypertension?

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The pathophysiology of primary pulmonary hypertension (PPH) involves alterations in vascular reactivity, vascular structure, and interactions of the vessel wall with circulating blood elements. An imbalance of vasodilator and vasoconstrictor influences is likely to be an early derangement. Progressive intimal and medial thickening, due to proliferation and migration of vascular smooth muscle cells and fibroblasts, reduces the cross-sectional area of the pulmonary microvasculature, causing fixed alterations in pulmonary resistance. Contributing to the progressive increase in pulmonary resistance is thrombosis of the small pulmonary vessels, which explains the benefit of anticoagulation in these patients. In advanced disease, “plexiform arteriopathy” of the small pulmonary vessels is observed. These lesions proliferate into the lumen, creating high-resistance, convoluted endoluminal channels. There is some controversy regarding the nature of the cells constituting these lesions, one group suggesting they are of endothelial origin, whereas more recent evidence indicates that they are myofibroblasts.

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The normal pulmonary endothelium maintains a low vascular resistance, suppresses vascular smooth muscle growth, inhibits platelet adherence and aggregation, and stems inflammation. In patients with PPH, the endothelium has lost these vasoprotective functions. The endothelium of the PPH patient is characterized by the increased elaboration of vasoconstrictors, mitogens, and prothrombotic and proinflammatory mediators (such as thromboxane, endothelin, plasminogen activator inhibitor, and 5-lipoxygenase). These endothelial alterations promote the pathophysiology of PPH. Furthermore, there is less influence of the countervailing factors prostacyclin and NO.

Role of NO Synthase Expression and Activity

Endothelium-derived NO plays a critical role in pulmonary vascular homeostasis. The pathological changes that occur in pulmonary hypertension are in part due to impaired bioactivity and/or synthesis of vascular NO. The mechanisms of this impairment are undoubtedly multifactorial and may vary from patient to patient. For example, endothelial NO synthase (NOS) expression has been reported to be decreased, unchanged, or increased in patients with severe pulmonary hypertension. However, patients with PPH have low levels of NO in their exhaled breath, and endothelium-dependent vasodilation to acetylcholine is impaired. An impairment of NOS activity in the face of normal or increased NOS expression can be explained if the NOS enzyme was dysfunctional. In hypoxia-induced pulmonary hypertension in rats, NOS activity is inhibited by abnormal coupling with caveolin, which is known to prevent NOS activation. In fetal lambs, experimentally induced pulmonary hypertension is in part due to reduced association of HSP 90 with endothelial NOS. A different mechanism of impaired NOS activity has been proposed in the pulmonary hypertension associated with sickle cell disease. In addition to elevated plasma levels of cell-free hemoglobin that can scavenge NO, patients with sickle cell disease have increased plasma levels of arginase. Arginase converts arginine to ornithine and urea, limiting the availability of the NO precursor. In patients with sickle cell disease, the increased arginase activity may reduce pulmonary NO conversion of arginine to NO. If so, supplementary arginine could theoretically reverse this abnormality. Indeed, oral arginine supplementation has been shown to reduce pulmonary pressures in these patients by ~15 mm Hg.

Low plasma L-arginine concentrations may also contribute to persistent pulmonary hypertension of the newborn, which is also associated with reduced levels of plasma nitrogen oxides. L-Arginine infusion has decreased pulmonary vascular resistance and improved blood oxygenation in infants with this disease process.

DDAH and the NOS Pathway

In this issue of Circulation, Millat et al highlight another mechanism that may contribute to reduced NO synthesis in PPH. In a rodent model of chronic hypoxia-induced pulmonary hypertension, Millat et al find that the pulmonary vascular expression of endothelium-derived NOS is increased 2-fold. By contrast, there is a significant decline in the NO content of the lung extracts from hypoxic mice. These discordant observations are resolved by their finding that there is a >2-fold increase in lung tissue levels of the endogenous NOS inhibitor, asymmetric dimethylarginine (ADMA; see below). Millat and colleagues hypothesized that the increase in ADMA might be related to a dysregulation of dimethylarginine dimethylaminohydrolase (DDAH) the enzyme that metabolizes ADMA. Accordingly, they assessed pulmonary expression of DDAH by Western analysis and also measured DDAH enzyme activity in pulmonary homogenates. These studies revealed significant reductions in DDAH expression and activity in the rats with pulmonary artery hypertension. The observations of Millat et al are consistent with an earlier observation that DDAH expression and activity is reduced in an experimental model of hypoxia-induced pulmonary hypertension.

A similar mechanism may be at work in pulmonary hypertension in humans. L-Arginine supplementation improves pulmonary artery pressures and hemodynamics in patients with primary and secondary pulmonary hypertension. Finally, it has recently been ob-
erved that plasma ADMA levels are elevated in individuals with pulmonary hypertension due to congenital heart disease. These studies provided the impetus for a large, randomized clinical trial of arginine therapy for pulmonary hypertension that is underway in Europe and North America.

**ADMA: An Endogenous Inhibitor of Endothelium-Derived NOS**

Accumulating evidence indicates that ADMA is an important regulator of endothelial NOS activity (for review, see Cooke). ADMA is derived from the catabolism of proteins containing methylated arginine residues (as is monomethylarginine, a less common species of NOS inhibitor that has the same effect and metabolic fate as ADMA). Subsequently, ADMA is excreted in the urine or metabolized by DDAH. In renal failure, high plasma levels of ADMA contribute to the severe endothelial dysfunction observed in this disorder. Elevated plasma levels of ADMA may contribute to the endothelial vasodilator dysfunction observed in hypercholesterolemia, hypertension, diabetes mellitus, insulin resistance, hyperhomocystinemia, and vascular disease. Indeed, we propose that ADMA acts as a transducer by which these conditions impair the NOS pathway. We have shown that risk factors for cardiovascular disease elevate plasma ADMA levels by increasing its accumulation. Specifically, each of these risk factors for cardiovascular disease is associated with endothelial oxidative stress and inactivation of DDAH, thereby reducing the metabolism of ADMA.

**Therapeutic Manipulation of the NOS Pathway for Pulmonary Hypertension**

Currently, administration of NO gas is probably the most effective and specific therapy for PPH. However, NO gas can generate toxic free radicals and oxides of NO, and technical difficulties have also limited its widespread use. Another approach is to boost the effect of endogenous NO by the administration of oral or inhaled sildenafil. Sildenafil is a cGMP phosphodiesterase inhibitor that augments the action of endogenous NO by reducing the breakdown of its second messenger, cGMP. This agent has been shown to reduce pulmonary pressures and improve symptoms in patients with primary and secondary pulmonary hypertension. Another approach is to administer NO donors by inhalation; these are under development. Gene transfer of NOS has successfully reduced pulmonary pressures in animal models, but viral or cell vectors need to be improved to reduce inflammation and to provide persistent and regulated expression of NOS. Another approach may be to increase DDAH activity or expression so as to reduce circulating levels of the NOS inhibitor. Increased NO synthesis and bioactivity would be expected to acutely reduce pulmonary pressures by its effects on vasoreactivity and to chronically reduce the progression of disease as a result of the inhibition by NO of medial hypertrophy, intimal hyperplasia, and thrombosis. Accordingly, restoration of endogenous NOS activity in the pulmonary endothelium is a therapeutic avenue worthy of further exploration.

**References**


**Key Words:** Editorials ■ hypertension, pulmonary ■ nitric oxide synthase ■ endothelium
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