Secondary Pulmonary Hypertension in Chronic Heart Failure

The Role of the Endothelium in Pathophysiology and Management

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Abstract—Pulmonary vascular resistance is frequently elevated in patients with chronic left ventricular failure as a result of dysregulation of vascular smooth muscle tone and structural remodeling. The former is reversible over a period of minutes to days by pharmacological vasodilators, whereas the latter is relatively fixed and may resolve only slowly, over months to years. These abnormalities are due, at least in part, to pulmonary vascular endothelial dysfunction that results in impaired nitric oxide availability and increased endothelin expression. In patients with chronic heart failure, the resulting pulmonary hypertension directly affects right ventricular function and may affect exercise capacity, morbidity, and mortality. New treatment strategies, which include the use of agents that increase nitric oxide availability or oppose the actions of endothelin, may improve the structure and function of the pulmonary vasculature in patients with chronic heart failure. (Circulation. 2000;102:1718-1723.)

Key Words: heart failure ■ hypertension, pulmonary ■ nitric oxide ■ endothelin

The pulmonary circulation is a low-pressure, high-capacity system. At sea level, the normal pulmonary artery systolic pressure is ≤25 mm Hg, and the pulmonary vascular resistance (PVR) averages 67±30 dynes·s·cm⁻², less than one tenth that of the systemic circulation. The pulmonary vasculature can accommodate large increases in blood flow, as during exercise or sudden occlusion of a pulmonary artery, with little or no increase in pressure.

The pulmonary circulation is a major determinant of right ventricular (RV) afterload and thus determines RV output. Although the thin-walled, distensible RV can accommodate large increases in systemic venous return without a rise in pulmonary artery pressures, even modest increases in pulmonary vascular tone, if acute, can result in RV failure. The pulmonary circulation also regulates venous return to the left ventricle (LV) and thus protects the LV against excess preload. In pulmonary hypertension associated with chronic heart failure, RV afterload and LV preload are increased, leading to further myocardial dysfunction.

Pathophysiology of “ Reactive” Pulmonary Hypertension in Heart Failure

Pulmonary hypertension is present when the pulmonary artery systolic pressure exceeds 30 mm Hg or the mean pulmonary artery pressure is ≥19 mm Hg. In patients with chronic LV dysfunction, an elevation in LV filling pressure results in a “passive” increase in pulmonary venous pressure. Pulmonary venous congestion is frequently associated with a “reactive” increase in PVR, which results in an increased transpulmonary pressure gradient that is superimposed on the pulmonary venous pressure. The pulmonary artery pressure further depends on the performance of the RV. Although the normal RV can generate peak systolic pressures of only 45 to 50 mm Hg, much higher pressures may be achieved if pulmonary hypertension develops slowly so that there is RV hypertrophy. Conversely, if there is RV failure, the pulmonary artery pressure may be relatively low despite marked elevation of the PVR.

Secondary pulmonary hypertension may reflect “remodeling” of the arterial wall with abnormalities of elastic fibers, intimal fibrosis, and medial hypertrophy that result in vascular stiffness and reduced vasodilator responsiveness. Although possibly reversible over time (ie, months), the pulmonary hypertension attributable to structural remodeling is generally referred to as “fixed” because it is not rapidly responsive (ie, minutes to days) to reversal with pharmacological maneuvers.

In most patients with chronic heart failure, the major component of pulmonary hypertension is readily reversed by vasodilators. In the pulmonary vasculature, as in the systemic circulation, the endothelium plays a central role in the local control of tone through the regulated release of nitric oxide (NO) and endothelin (ET). There is growing evidence that the dysregulation of pulmonary vascular tone in disease states, including chronic heart failure, involves alterations in these important counterbalancing systems (Figure 1).

NO-Dependent Pulmonary Vasodilation

Pulmonary vascular endothelial cells elaborate NO, which relaxes vascular smooth muscle cells. Under basal conditions,
NO is synthesized by the “constitutive” isoform of NO synthase (NOS), also referred to as NOS3, one of a family of enzymes that catalyze the conversion of L-arginine to L-citrulline. In addition, several substances or physical stimuli act on NOS3 to increase the synthesis and release of NO. NO diffuses from the endothelial cell into adjacent smooth muscle cells, where it activates soluble guanylyl cyclase, thereby increasing the intracellular concentration of cGMP, which in turn causes smooth muscle cell relaxation by inhibiting calcium release from the sarcoplasmic reticulum. Endothelial cell–derived NO also inhibits smooth muscle cell proliferation and hypertrophy and, acting in concert with prostacyclin, inhibits platelet aggregation and adhesion.

The systemic infusion of Nω-monomethyl-L-arginine (L-NMMA), an analog of L-arginine that inhibits NOS, causes pulmonary hypertension and accentuates hypoxia-induced pulmonary vasoconstriction in healthy humans. To avoid potentially confounding systemic effects, investigators have infused NOS inhibitors directly into the pulmonary artery. Celermajer et al found that intrapulmonary infusion of L-NMMA in children with congenital heart disease and normal pulmonary artery pressures caused a dose-dependent fall in pulmonary blood flow velocity as measured with a Doppler-tipped wire. Because L-NMMA was infused into a subsegmental pulmonary artery, there was no change in pulmonary artery pressure; hence, the decrease in flow reflected an increase in local vascular resistance. Using a similar method in normal adults, Cooper et al found that L-NMMA caused dose-dependent vasoconstriction, whereas acetylcholine caused dose-dependent vasodilation. Coadministration of L-NMMA and acetylcholine attenuated the dilator effect of acetylcholine. These studies suggest that endothelium-derived NO plays an important role in determining both basal pulmonary vascular tone and dilation to endothelium-dependent stimuli.

Impaired NO-Dependent Pulmonary Vasodilation in Heart Failure

Studies in both experimental models and patients suggest that NO-dependent pulmonary vasodilation is impaired in heart failure. In vitro in pulmonary artery segments from rats with chronic LV failure following myocardial infarction, Ontkean et al found that the vasodilator response to acetylcholine was impaired, whereas that for nitroglycerin was normal, suggesting impaired endothelium-dependent relaxation.

In humans, Porter et al used intravascular ultrasound to assess pulmonary artery diameter. They found that intrapulmonary infusion of acetylcholine caused constriction, which was accentuated by inhibition of guanylate cyclase in patients with heart failure and normal pulmonary artery pressures but failed to cause dilation in patients with heart failure and pulmonary hypertension. The endothelium-independent vasodilator nitroglycerin caused pulmonary vasodilation in both groups. Cooper et al extended these observations by measuring pulmonary blood flow velocity during intrapulmonary infusion of L-NMMA. In normal control subjects or patients with heart failure and a normal PVR, L-NMMA caused vasoconstriction, whereas in patients with heart failure and pulmonary hypertension, the vasoconstrictor response to L-NMMA was attenuated. The vasoconstrictor responses to phenylephrine were similar in the 3 groups. Taken together, these clinical studies suggest that basal pulmonary artery NO production is relatively deficient in patients with heart failure and secondary pulmonary hypertension and that the loss of NO-dependent vasodilation may contribute to the development of pulmonary hypertension.

Role of ET in the Regulation of Pulmonary Vascular Tone

ET is a 21-residue vasoactive peptide first isolated in 1988 from endothelial cells by Yanagisawa and colleagues. Besides being a potent arterial and venous vasoconstrictor, ET exerts long-term effects on cellular phenotype. There are 2 subtypes of receptors for ET, ETₐ and ETₐ. In the vasculature, ETₐ receptors are located on vascular smooth muscle cells where they mediate both vasoconstriction and growth (Figure 2). In contrast, ETₐ receptors, found primarily on vascular endothelial cells, mediate vasodilation via the release of NO and prostacyclin. Some ETₐ receptors, which may differ pharmacologically from those on endothelial cells, appear to be located on vascular smooth muscle cells where they directly mediate contraction. ETₐ receptors also play an important role in ET-1 clearance. The ratio of ETₐ to ETₐ receptors on human resistance and conduit pulmonary arteries is approximately 9:1 and the net effect of ET-1 in pulmonary arteries is constriction.

The availability of several nonpeptide ET receptor antagonists that may be selective or nonselective has helped to clarify the roles of the ET receptor subtypes (the Table). In dogs, vasoconstriction stimulated by ET-1 is attenuated by infusion of an ETₐ-selective antagonist. However, an ETₐ-selective antagonist may either potentiate or antagonize the vasoconstrictor effect of ET-1. In one study in normal humans, infusion of the ETₐ-selective antagonist BQ-123 into the brachial artery caused dose-dependent vasodilation, and...
infusion of the ET<sub>B</sub>-selective agonist sarafotoxin S6c caused vasoconstriction. However, in another study in healthy humans, brachial artery infusion of an ET<sub>B</sub>-selective antagonist caused mild vasoconstriction. These studies suggest that in the human forearm ET<sub>A</sub> receptors uniformly mediate vasoconstriction, whereas ET<sub>B</sub> receptors may mediate either dilation or constriction.

The relative roles of ET receptor subtypes in regulating pulmonary vascular tone in vivo in humans has not been directly studied with intrapulmonary infusion techniques. However, in vitro in human endothelium-denuded pulmonary arteries, ET-1 stimulates contraction, which is inhibited by the ET<sub>A</sub>-selective antagonist BQ-123, whereas the ET<sub>B</sub>-selective agonist sarafotoxin S6c does not cause contraction. Likewise, other studies that have used human pulmonary resistance arteries and endothelium-denuded intralobar pulmonary arteries have confirmed that ET-1 causes pulmonary artery vasoconstriction predominantly via ET<sub>A</sub> receptors, although there is some evidence that ET<sub>B</sub> receptors may contribute at low ET-1 concentrations. ET-1–stimulated proliferation of human pulmonary artery smooth muscle cells is mediated by ET<sub>A</sub> receptors.

ET and Reactive Pulmonary Hypertension in Heart Failure

Plasma ET-1 levels are elevated in children with pulmonary hypertension secondary to congenital heart disease and adults with primary or secondary pulmonary hypertension. Cody et al found that patients with severe heart failure had significantly elevated plasma ET-1 levels that correlated best with pulmonary artery pressures and PVR (Figure 3) but not with several other measures of systemic hemodynamics, including cardiac index, pulmonary capillary wedge pressure, and systemic vascular resistance (SVR). These data suggested that ET-1 may be a mediator of, or a marker for, reactive pulmonary hypertension in patients with LV failure.

Elevated ET-1 levels in heart failure may be due to increased local production and/or decreased pulmonary clearance. Dupuis et al demonstrated that ET-1 is both produced and cleared by the lungs and that ET-1 spillover in the lungs correlates with PVR in patients with heart failure. There is increased preproendothelin-1 mRNA and ET-1 staining in pulmonary vascular endothelial cells from rats with chronic heart failure and pulmonary hypertension. Likewise, ET-1 immunoreactivity is abundant in pulmonary vascular endothelial cells from patients with primary and secondary pulmonary hypertension. In vivo and in vitro data suggest that ET<sub>B</sub> receptors mediate ET-1 clearance. Zolk et al have recently shown that ET<sub>B</sub> receptors are downregulated in failing human myocardium, which may explain, in part, elevation of circulating and tissue ET-1 levels in heart failure. Conversely, cytokines such as tumor necrosis factor-α that are upregulated in heart failure can stimulate ET-1 production.

ET-1 causes concentration-dependent contraction of pulmonary arteries and veins in vitro and increases in PVR in vivo, effects that are mediated predominantly by ET<sub>A</sub> receptors. Vasoconstriction to ET-1 may be enhanced in heart failure because of upregulation of ET<sub>A</sub> receptors. ET-1 may also contribute to pathological pulmonary vascular remodeling by causing proliferation and hypertrophy of vascular smooth muscle cells and increased collagen synthe-
ET-1--induced proliferation of pulmonary artery smooth muscle cells appears to be mediated primarily by the ETα receptor. In addition, ET-1 may be involved in mediating angiotensin-stimulated vascular hypertrophy and may act in an autocrine or paracrine manner to increase local concentrations of norepinephrine or other pulmonary vasoconstrictors or to inhibit the expression of NOS. Conversely, NO produced by pulmonary vascular endothelium may inhibit the expression or activity of ET-1.

Clinical Implications of Secondary Pulmonary Hypertension in Heart Failure

Exercise Capacity

Measures of resting LV function correlate poorly with exercise capacity in patients with chronic heart failure, and there is evidence that the pulmonary vasculature may play a more important role in determining exercise capacity through its effects on RV function. In patients with heart failure, there is an inverse relationship between peak oxygen consumption (VO₂) and resting pulmonary arterial pressure or PVR. In addition, although exercise results in a fall in SVR, total pulmonary resistance and PVR remain elevated. These observations led to the suggestion that pulmonary hypertension reduced exercise capacity in patients with LV failure by increasing RV afterload. This thesis is supported by a positive correlation between RV ejection fraction (RVEF) at rest and RV ejection fraction during exercise as well as between exercise RVEF and peak VO₂ in patients referred for cardiac transplant evaluation.

Of note, recent studies have demonstrated that elevated levels of ET-1 (but not of norepinephrine or vasopressin) measured during exercise correlate inversely with peak exercise capacity in patients with heart failure and that inhaled NO may increase exercise capacity in selected patients with secondary pulmonary hypertension. Thus, increased ET-1, decreased NO, or both may contribute to exercise intolerance in heart failure by attenuating pulmonary and/or peripheral vasodilation.

Morbidity and Mortality

The extent of secondary pulmonary hypertension may be a determinant of morbidity and mortality in patients with chronic heart failure. In patients with chronic heart failure, pulmonary artery systolic pressure was an independent predictor of the need for cardiac transplantation. Likewise, death and hospitalization for heart failure were increased in patients with echocardiographic evidence of pulmonary hypertension. Presumably, a major impact of pulmonary hypertension is on RV function, which is a strong predictor of overall and event-free survival in chronic heart failure. Plasma ET-1 levels predict mortality in chronic heart failure.

Therapeutic Approaches to Secondary Pulmonary Hypertension

Effects of Standard Therapy

Conventional therapies for heart failure, including ACE inhibitors, β-blockers, digoxin, and most vasodilators, reduce pulmonary artery systolic pressure in patients with primary pulmonary hypertension who have normal LV function. The baseline PVR strongly predicted the magnitude of the PVR response to inhaled NO (Figure 4). Surprisingly, inhaled NO did not lower pulmonary arterial pressure. Rather, the decreases in transpulmonary gradient and PVR were associated with an increase in pulmonary capillary wedge pressure. LV filling pressure does not increase with inhaled NO in patients with primary pulmonary hypertension who have normal LV function. The increase in LV filling pressure appears to reflect the effect of increased pulmonary venous return to a poorly compliant LV. The experience with inhaled NO highlights the important interaction between PVR and LV filling in heart failure. Presumably, LV filling pressure does not increase with pulmonary vasodilators such as nitroprusside because they cause a concomitant decrease in LV afterload.

Because inhaled NO is associated with an increase in LV filling pressure in patients with heart failure and has even been associated with acute pulmonary edema, it has little or no role in primary therapy. However, inhaled NO may be used as a test for pulmonary vasoreactivity before cardiac transplantation, as perioperative support in high-risk patients undergoing CABG or valve replacement, or to pre-
vent or treat RV failure after cardiac transplantation or implantation of an LV assist device.\(^{51}\)

**ET Receptor Antagonists**

The development of ET receptor antagonists has provided an important tool to define the role of ET-1 in the pathophysiology of heart failure. Both ET\(_A\)-selective and nonselective antagonists improve hemodynamics, ameliorate LV remodeling, and improve survival in animal models of heart failure.\(^{54}\) To date, there is relatively little information about the effects of ET-1 antagonists on pulmonary hemodynamics in heart failure. However, in dogs with pacing-induced heart failure and secondary pulmonary hypertension, an ET\(_A\)-selective antagonist decreased PVR, whereas an ET\(_B\)-selective antagonist had the opposite effect.\(^{17}\) The implication from this finding is that in heart failure pulmonary ET\(_A\) receptors exert a vasoconstrictor effect, whereas ET\(_B\) receptors mediate vasodilation. ET\(_A\)-selective antagonists also decrease pulmonary hypertension, pulmonary vascular remodeling, and RV hypertrophy in animals with monocrotaline- or hypoxia-induced pulmonary hypertension.\(^{55}\)

**ET Antagonists in Patients With Heart Failure**

Bolus administration of the nonselective ET antagonist bosentan to patients with moderate heart failure decreased arterial, right atrial, pulmonary artery, and pulmonary capillary wedge pressures; decreased SVR and PVR by 17\% and 33\%, respectively; and increased cardiac index.\(^{56}\) Two weeks of oral bosentan caused further reductions in SVR and PVR.\(^{57}\)

In a small, uncontrolled study, a 1-hour infusion of the ET\(_A\)-selective antagonist BQ-123 caused modest decreases in SVR and PVR and a small increase in cardiac index.\(^{58}\) An intravenous bolus of sitaxsentan,\(^{59}\) an ET\(_A\)-selective antagonist, in patients with chronic stable heart failure decreased pulmonary artery systolic pressure and PVR but had no effect on SVR, pulmonary capillary wedge pressure, cardiac index, or heart rate (Figure 5).

Given the circumstantial evidence that implicates ET-1 in the pathophysiology of reactive pulmonary hypertension in heart failure, ET antagonists may be particularly effective for the amelioration of pulmonary hypertension and the reversal of RV and pulmonary vascular remodeling. Limited existing data suggest that ET\(_A\) selectivity may be desirable with regard to pulmonary vasodilation in heart failure. However, much remains to be learned about both the pharmacology of ET blockade in heart failure and the clinical consequences of this potential new form of therapy.

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**References**


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