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⁻⁵, less than one tenth that of the systemic circulation.¹ The pulmonary vasculature can accommodate large increases in blood flow, as during exercise² or sudden occlusion of a pulmonary artery,³ 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,
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 measured 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, ET, and ET. In the vasculature, ET receptors are located on vascular smooth muscle cells where they mediate both vasoconstriction and growth (Figure 2). In contrast, ET receptors, found primarily on vascular endothelial cells, mediate vasodilation via the release of NO and prostacyclin. Some ET receptors, which may differ pharmacologically from those on endothelial cells, appear to be located on vascular smooth muscle cells where they directly mediate contraction. ET receptors also play an important role in ET-1 clearance. The ratio of ET to ET 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 ET-selective antagonist. However, an ET-selective antagonist may either potentiate or antagonize the vasoconstrictor effect of ET-1. In one study in normal humans, infusion of the ET-selective antagonist BQ-123 into the brachial artery caused dose-dependent vasodilation, and...
infusion of the ET_b-selective agonist sarafotoxin S6c caused vasoconstriction. 19 However, in another study in healthy humans, brachial artery infusion of an ET_b-selective antagonist caused mild vasoconstriction. 20 These studies suggest that in the human forearm ET_A receptors uniformly mediate vasoconstriction, whereas ET_B 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 ETA-selective antagonist BQ-123, whereas the ET_B-selective agonist sarafotoxin S6c does not cause contraction.21 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 ETA receptors, although there is some evidence that ET_B receptors may contribute at low ET-1 concentrations.18 ET-1–stimulated proliferation of human pulmonary artery smooth muscle cells is mediated by ETA receptors.22

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.23 Cody et al24 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 al25 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.26 There is increased preproendothelin-1 mRNA and ET-1 staining in pulmonary vascular endothelial cells from rats with chronic heart failure and pulmonary hypertension.27 Likewise, ET-1 immunoreactivity is abundant in pulmonary vascular endothelial cells from patients with primary and secondary pulmonary hypertension.28 In vivo and in vitro data suggest that ET_B receptors mediate ET-1 clearance. Zolk et al29 have recently shown that ET_A 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.30

ET-1 causes concentration-dependent contraction of pulmonary arteries and veins in vitro31 and increases in PVR in vivo,32 effects that are mediated predominantly by ETA receptors.21 Vasoconstriction to ET-1 may be enhanced in heart failure because of upregulation of ET_A receptors.33 ET-1 may also contribute to pathological pulmonary vascular remodeling by causing proliferation and hypertrophy of vascular smooth muscle cells and increased collagen synthe-

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**Figure 2.** Physiological interaction between pulmonary endothelial and vascular smooth muscle cells involves a balance between ET-1 and NO production. A relative increase in ET-1 and/or decrease in NO may cause vasoconstriction and smooth muscle cell proliferation. Ach indicates acetylcholine; prepro-ET, preproendothelin; pro-ET, proendothelin; arg, arginine; and SMC, smooth muscle cell.

**Figure 3.** Relationship between mean pulmonary artery pressure (PA) and plasma ET-1 levels in patients with symptomatic chronic heart failure. Reproduced with permission from Reference 24.
sis. ET-1–induced proliferation of pulmonary artery smooth muscle cells appears to be mediated primarily by the ET<sub>A</sub> 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 (VO<sub>2</sub>) 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 increasing RV afterload. This thesis is supported by a positive correlation between RV ejection fraction (RVEF) at rest and increasing RV afterload. This thesis is supported by a positive correlation between RV ejection fraction (RVEF) at rest and increasing RV afterload.

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 RV ejection fraction (RVEF) and peak VO<sub>2</sub> in patients referred for cardiac transplant evaluation. 40 peak VO<sub>2</sub> in patients with LV failure 39 and between exercise correlation between RV ejection fraction (RVEF) at rest and increasing RV afterload. This thesis is supported by a positive reduced exercise capacity in patients with LV failure by observations led to the suggestion that pulmonary hypertension was associated with excess mortality in patients with severe heart failure. After successful cardiac transplantation, there is rapid resolution of elevated pulmonary arterial pressures.

PVR. The long-term administration of prostacyclin via a continuous infusion, although useful in patients with primary pulmonary hypertension, was associated with excess mortality in patients with severe heart failure. After successful cardiac transplantation, there is rapid resolution of elevated pulmonary arterial pressures.

Nitric Oxide

Based on the pathophysiology of pulmonary hypertension, strategies to increase NO in the pulmonary vasculature have been developed. We and others found that short-term inhalation of NO lowers PVR in patients with moderate to severe heart failure caused by LV dysfunction. The baseline PVR strongly predicted the magnitude of the PVR response to inhaled NO (Figure 4). Surprisingly, inhaled NO did not lower pulmonary artery 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\textsubscript{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\textsubscript{A}-selective antagonist decreased PVR, whereas an ET\textsubscript{B}-selective antagonist had the opposite effect. 17 The implication from this finding is that in heart failure pulmonary ET\textsubscript{A} receptors exert a vasoconstrictor effect, whereas ET\textsubscript{B} receptors mediate vasodilation. ET\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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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