Endothelin Mediates Increased Pulmonary Vascular Tone in Patients With Heart Failure
Demonstration by Direct Intrapulmonary Infusion of Sitaxsentan

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**Background**—In patients with chronic heart failure (HF), the pulmonary circulation is a major source of endothelin-1 (ET), and ET levels correlate with pulmonary vascular resistance (PVR). The role of ET in causing pulmonary vasoconstriction in HF is not known, however, in part because of the confounding effects of ET receptor antagonists on systemic hemodynamics.

**Methods and Results**—To directly test the hypothesis that ET causes pulmonary vasoconstriction in patients with HF, we infused the selective ET_A receptor antagonist sitaxsentan at increasing rates (0.3125 to 10 mg/min) into a left lower-lobe segmental pulmonary artery in 8 patients with left ventricular (LV) systolic failure (LV ejection fraction, 24/1100 to 4%) and 4 control subjects with normal LV function. Changes in local PVR distal to the infusion site were assessed by measuring the change in pulmonary blood flow velocity with a Doppler-tipped wire and the mean pulmonary artery pressure (MPAP). Total PVR at baseline was elevated in HF patients (177±23 dyne · s · cm⁻²) versus controls (89±21 dyne · s · cm⁻²; P<0.05). In patients with HF, sitaxsentan caused an infusion rate–dependent decrease in local PVR (P<0.05 versus baseline; P<0.05 versus controls). In contrast, sitaxsentan infusion had no effect on local PVR in controls. Heart rate, mean arterial pressure, cardiac index, and MPAP were not affected by sitaxsentan in either group.

**Conclusion**—Selective ET_A receptor blockade caused local pulmonary vasodilation in patients with HF, but not in control subjects with normal LV function. These data indicate that ET contributes to the secondary pulmonary hypertension associated with HF. *(Circulation. 2002;106:1618-1621.)*

**Key Words:** endothelin | heart failure | hypertension, pulmonary

Secondary reactive pulmonary hypertension is frequent in patients with left ventricular systolic failure. In such patients, plasma endothelin-1 (ET) is elevated and correlates with survival. The pulmonary circulation is a major source of ET in heart failure (HF), and pulmonary ET spillover correlates strongly with pulmonary vascular resistance (PVR), leading to the suggestion that ET contributes to secondary pulmonary hypertension in patients with chronic HF. In vitro, ET is a potent constrictor in pulmonary resistance vessels. Stimulation of ET_A receptors uniformly causes constriction, whereas stimulation of ET_B receptors may cause either constriction or dilation, the latter reflecting the release of nitric oxide. The contribution of ET to secondary pulmonary hypertension in patients with HF is not known, in part because of the difficulty of assessing pulmonary vascular reactivity in the presence of confounding changes in systemic hemodynamics.

Sitaxsentan is a nonpeptide, high-affinity competitive antagonist that is 6000-fold selective for the human ET_A (versus ET_B) receptor. We previously found that short-term systemic administration of sitaxsentan caused a greater decrease in pulmonary versus systemic vascular tone in patients with moderate to severe HF, suggesting that ET plays a role in mediating pulmonary hypertension in such patients. To directly test this hypothesis, sitaxsentan was infused into a segmental pulmonary artery, and the effect on pulmonary arterial tone was assessed by measuring the change in local blood flow velocity using a Doppler-tipped wire in patients with left ventricular (LV) systolic failure and control subjects with normal LV function.

**Study Population**
The study population consisted of 12 adults, aged 21 to 90 years, undergoing diagnostic cardiac catheterization. Patients in the HF group (n=8) had a history of chronic heart failure and an LV ejection fraction <45%. The control group (n=4) consisted of patients who had no history of heart failure, a normal LV ejection fraction (LVEF), and normal resting LV hemodynamics. Control patients...
were being catheterized to define coronary artery anatomy. Exclusion criteria included valvular disease or myocarditis, acute coronary syndrome, symptomatic ventricular arrhythmias, significant pulmonary disease, primary pulmonary hypertension or pulmonary hypertension due to causes other than HF, current smoking, and systolic blood pressure <90 mm Hg or >200 mm Hg. All vasoactive medications were held on the day of study. The study protocol was approved by the institutional review committee and followed institutional guidelines, and all patients gave informed consent.

Study Protocol
Diagnostic cardiac catheterization was performed via a percutaneous femoral approach. After completion of the diagnostic procedure, heparin 5000 IU was administered intravenously, and research catheters were placed as previously described. An 8F multipurpose guiding catheter (Cordis) was positioned in a left lower-lobe pulmonary artery over a 0.035-inch guidewire. A 1.0-mm infusion catheter (Cook) was advanced through the guiding catheter and positioned in the straight portion of a segmental pulmonary artery. A 0.014-inch Doppler-tip wire (Jomed) was advanced just distal to the tip of the infusion catheter until a stable flow velocity signal with minimal noise was obtained. Doppler velocity was continuously monitored on a FloMap system (Jomed).

Resting measurements of heart rate (HR), mean arterial pressure (MAP), right atrial pressure (RAP), pulmonary artery systolic pressure (PASP), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI) by Fick, pulmonary vascular resistance (PVR), and systemic vascular resistance (SVR) were taken. A baseline infusion of 5% dextrose was administered through the infusion catheter into the segmental pulmonary artery. Next, sitaxsentan (Texas Biotechnology Corporation) was infused at increasing rates of 0.3125, 0.625, 1.25, 2.5, 5.0, and 10.0 mg/min for 3 minutes each by increasing the drug concentration in the infusate. Systemic and pulmonary arterial pressures, ECG, and pulmonary blood flow velocity were continuously monitored. At the end of each experimental condition, the following measurements were taken: HR, MAP, PASP, MPAP, CI, and the time-averaged instantaneous peak velocity (APV) in the segmental pulmonary artery during the entire cardiac cycle. Because diameter measurements were not made at the level of the Doppler wire, we calculated the local pulmonary vascular resistance index (PVRi, mm Hg · cm⁻¹ · s⁻¹) as the MPAP divided by APV. ET levels were measured by ELISA (R&D) in a sample obtained during the baseline period.

Statistical Analysis
Data are expressed as mean±SEM. APV and PVRI are expressed as percent change from baseline. Background characteristics were compared by 2-sided t test, Fisher’s exact test, or Kruskal-Wallis test. Comparison of means within each patient group was by repeated measures ANOVA, with Schef’s F test used for multiple post-hoc comparisons. Differences between treatment groups at each post-baseline dose were determined via 1-way ANOVA with effect for treatment. Statistical significance was defined as a P<0.05.

Results
Baseline Characteristics
The HF and control groups were similar with regard to age and sex (Table 1). Most HF patients were in New York Heart Association class I or II and were receiving angiotensin-converting enzyme inhibitors and diuretics. Compared with controls, HF patients had reduced LVEF (mean, 24±4%), elevated PVR (mean, 177±23 dyne · s⁻¹ · cm⁻²), and increased plasma ET levels (mean, 1.9±0.3 pg/mL). Right and left heart filling pressures and pulmonary artery pressures tended to be higher in the HF group.

| TABLE 1. Baseline Characteristics |
|------------------|------------------|------------------|
|                  | Control          | Heart Failure    |
| Patients, n      | 4                | 8                |
| Age, y           | 57±7             | 53±3             |
| Sex, male/female | 4/0              | 7/1              |
| LVEF, %          | 68±2             | 24±4             |
| NYHA class, I/II/III, n | 4/0/0          | 2/5/1            |
| Coronary artery disease, present/absent | 1/3             | 1/7              |
| Hypertension, present/absent | 1/3             | 4/4              |
| Medications      |                  |                  |
| ACE inhibitor    | 2                | 8                |
| Diuretic         | 1                | 7                |
| β-Blocker        | 2                | 4                |
| Nitrate          | 2                | 3                |
| HR, bpm          | 70±5             | 76±6             |
| RAP, mm Hg       | 4±1              | 7±1              |
| MAP, mm Hg       | 28±1             | 42±4             |
| MPAP, mm Hg      | 16±1             | 26±3             |
| PCWP, mm Hg      | 8±1              | 13±2             |
| PVR, dyne · s · cm⁻³ | 89±20           | 177±23           |
| MAP, mm Hg       | 91±5             | 106±6            |
| CI, L · min⁻¹ · m⁻² | 3.1±0.3         | 2.9±0.3          |
| SVR, dyne · s · cm⁻³ | 1239±122        | 1452±132         |
| ET levels, pg/mL | 0.8±0.2          | 1.9±0.3          |

NYHA indicates New York Heart Association.

Hemodynamics
In the control group, sitaxsentan had no effect on local pulmonary blood flow velocity (Figure 1) or pulmonary vascular resistance (Figure 2) at any infusion rate. In contrast, sitaxsentan caused an infusion rate–dependent increase in local pulmonary blood flow velocity in HF patients, with a maximal increase in APV of 57±16% (Figure 1). This effect was associated with an infusion rate–dependent decrease in local pulmonary vascular resistance, with a maximal decrease in PVRI of 39±7% (Figure 2). Intrapulmonary sitaxsentan infusion had no effect on HR, MAP, PASP, MPAP, or CI in either group (Table 2).

Figure 1. Effect of sitaxsentan on time-averaged peak velocity (APV) of segmental pulmonary artery blood flow in patients with heart failure (●) and control subjects with normal LV function (○). *P<0.05 versus baseline; †P<0.05 versus control at same dose.
Discussion

The present study demonstrates that ET contributes to increased pulmonary vascular tone in patients with LV systolic failure. In contrast, ET seems to have little or no role in the maintenance of basal pulmonary vascular tone in humans with normal LV function. By using intrapulmonary infusion, we were able to test the role of ET in the control of pulmonary vascular tone in humans in vivo. This approach allowed the observation of local effects of ET on pulmonary vascular tone independent of the confounding effects of changes in systemic vascular tone and myocardial function, both of which may cause secondary changes in pulmonary blood flow.

These observations indicate that ET contributes to the secondary pulmonary hypertension in patients with chronic heart failure. It is noteworthy that the patients in this study had well-compensated LV failure; 5 of 8 were in New York Heart Association class II and 2 were in class I. Consistent with this, the mean plasma ET level and PVR were only modestly elevated. These findings thus suggest that ET may play a role in the pathophysiology of patients with mild HF. A limitation of this study is that we are unable to comment on the effects of sitaxsentan in patients with more severe HF. In such patients, it is possible that the contribution of ET is reduced because of downregulation of ET receptors. On the other hand, we previously reported that the decrease in PVR with systemic sitaxsentan was greater in patients with a more elevated baseline PVR.

In vitro studies have shown that ET causes vasoconstriction of pulmonary resistance arteries from several species. This effect is mediated primarily via the ET\(_A\) receptor, whereas stimulation of the ET\(_B\) receptor may cause either relaxation or constriction. Sitaxsentan is approximately 6000-fold selective for the ET\(_A\) subtype. Therefore, it is likely that the effect of sitaxsentan, which was observed over an \(\sim\)10-fold concentration range, is due mostly, if not entirely, to inhibition of ET\(_A\) receptors. It is theoretically possible that the vasodilatory effect of sitaxsentan is due, in part, to displacement of ET from ET\(_A\) receptors resulting in ET\(_B\) receptor stimulation and nitric oxide release. Conversely, Cowburn et al. have reported that in patients with HF, ET\(_B\) receptors may mediate vasoconstriction rather than vasodilation, in which case the displacement of ET would blunt rather than augment the vasodilator effect of sitaxsentan. Furthermore, animal studies have suggested that expression of ET\(_B\) receptors in the pulmonary circulation may be reduced in heart failure.

A technical limitation of this study is that vascular diameter was not measured. Previous studies that used this technique, however, have demonstrated that subsystemic doses of vasoactive agents do not alter vessel diameter at the level of the infusion, but rather exert their major effects on distal vasculature. If there were an increase in artery diameter at the level of the Doppler-tipped catheter, we may have underestimated the magnitude of the vasodilator effect with sitaxsentan.

These observations have implications for the pathophysiology and treatment of chronic LV failure. First, they demonstrate that ET contributes to secondary pulmonary hypertension through its effect on vascular tone. In addition, they raise the possibility that on a chronic basis, ET may contribute to pulmonary hypertension by causing vascular hypertrophy and fibrosis. Secondary pulmonary hypertension may lead to right heart failure, which is an important determinant of functional capacity and survival in patients with chronic left heart failure and after cardiac transplantation. The clinical impact of ET blockers remains to be determined.

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References


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