Endothelin and Endothelin Antagonists: Treatment of CHF

**Introduction**

The endothelium, only recognized in the 1970s to have a place in vascular physiology, is now increasingly attributed roles in vascular pathophysiology. The nitric oxide pathway is the best studied and most widely investigated pathway of endothelial origin, and is believed to be important in terms of maintaining both normal vascular function and normal vascular structure. Nitric oxide released by endothelial type III or constitutive nitric oxide synthase is an important regulator of resting vascular tone and shear stress, at both conduit and resistance level vessels. Nitric oxide also inhibits numerous processes that are plausibly participative in atherogenesis – processes such as monocyte adhesion, platelet aggregation and adhesion, and smooth muscle proliferation. Deficient vascular nitric oxide activity is believed to contribute to several disease states including pulmonary hypertension, variant angina, acute coronary syndromes, and has been observed in many other disease states. As a general statement, nitric oxide is a beneficial substance that preserves vascular function and structure, and loss of nitric oxide production may be associated with earlier, abnormal and pathologic vascular states. Production of nitric oxide is one of the most important functions of the endothelium.

Although the above principals appear generally valid, the exact role(s) that nitric oxide plays within different pathophysiologic states are probably more undefined than defined at this point. In some situations, it appears that nitric oxide may actually be a harmful substance – such as situations of oxidative stress. Superoxide free radicals can combine with nitric oxide to produce the highly reactive free radical peroxynitrite which is known to oxidize LDL cholesterol, to cause membrane damage and apoptosis. Thus, by what is known to date, the endothelial production of nitric oxide appears largely beneficial, but the whole story is not known, and some aspects of nitric oxide are not favorable.

Other aspects of endothelial metabolic activity, such as angiotensin II and endothelin production, appear to largely contribute to disease processes, and to have few favorable effects. Again, the roles of these substances are incompletely understood, but they underscore the point that dysfunctional endothelium has potential to contribute to disease processes.

**Endothelin antagonists in management of CHF**

Dr. Duncan Stewart (Chief, Division of Cardiology, St. Michael's Hospital).

Endothelin is a 21 amino acid peptide which is produced by endothelial cells. It is an extremely potent vasoconstrictor and inducer of cell proliferation, and its role in vascular physiology and pathophysiology is only partially understood. Circulating endothelin levels are increased in a variety of conditions characterized by vasoconstriction including congestive heart failure, pulmonary hypertension and cardiogenic shock.
Plasma endothelin levels correlate with the severity of pulmonary hypertension in chronic congestive heart failure. There is evidence that the normal pulmonary circulation clears endothelin, and that the hypertensive pulmonary circulation fails to clear endothelin, and may actually release it into the circulation. This observation is in keeping with a pathologic study that demonstrated increased staining of immunoreactive endothelin confirmed with in situ hybridization studies in the medium and small pulmonary arteries of patients with primary pulmonary hypertension. These observations confirm that the endothelium of the severely hypertensive pulmonary circulation produces increased endothelin, and this results in a net release of endothelin into the circulation.

**Endothelin receptors**

Endothelin acts by coupling to two types of receptors – ET<sub>A</sub> and ET<sub>B</sub> receptors. ET<sub>A</sub> receptors are found on smooth muscle cells of blood vessels and cardiomyocytes. Stimulation of the ET<sub>A</sub> receptor results in constriction of vascular smooth muscle, and increased cardiomyocyte contraction, as well as in smooth muscle cell hypertrophy. Endothelin receptors are found on widespread vascular beds, but appear particularly important on pulmonary, renal and coronary vascular beds. Endothelin is a known vasoconstrictor of the above vascular beds. Stimulation of the ET<sub>B</sub> receptor which is found on the vascular smooth muscle cell as well as on the endothelial cell, results in smooth muscle contraction but also in stimulation of endothelial nitric oxide synthase. Therefore, ET<sub>B</sub> stimulation causes vasoconstriction and also vasodilation, resulting in a net vasoconstriction.

**Endothelin antagonists**

To this point, there is little data on the effect of endothelin antagonists in humans. In an acute study of nonselective endothelin antagonist in patients with chronic congestive heart failure, there was significant reduction of right and left heart pressures, with the magnitude of the right heart pressure reductions about twice as great as those seen in the systemic arterial circulation.

Experimental work with non-selective endothelin antagonists has suggested that it is possible to block experimentally induced pulmonary hypertension. Preliminary data on the effect of endothelin antagonism on myocardial performance in a murine myocarditis/heart failure model was presented by Stewart et al. This study was a 2 by 2 design (infection with myocarditis-inducing virus and nonselective endothelin receptor antagonism). Induction of myocarditis/heart failure was associated with a significant fall in dP/dt which appeared blocked by treatment with a nonselective endothelin antagonist.

Dr. Stewart concluded that 1) endothelin is a biologically important agent, particularly in pulmonary hypertensive states, 2) that endothelin receptor antagonism appears protective against the development of pulmonary hypertension and 3) that preliminary evidence suggests that endothelin receptor antagonism may have protective effects on the myocardium.

In patients with coronary artery disease and in patients with chronic congestive heart failure, nonselective endothelin receptor antagonism has been well tolerated, and resulted in vasodilation of both the systemic artery and pulmonary artery circulations. These preliminary studies are encouraging of chronic studies of endothelin antagonism in the setting of most probable benefit – chronic congestive heart failure with pulmonary hypertension. Should such studies yield beneficial results, and affirm acceptable safety and tolerability profiles, then it would be anticipated that endothelin antagonism would be studied in other disease states where endothelin production is believed to play an important role.

**ACE Inhibitors: Treatment of CHF**

**Dr. Carl Leir**

ACE-inhibitors confer symptomatic benefit and hemodynamic benefit and reduce mortality in patients with symptomatic heart failure. In the post-infarct setting, ACE-inhibitors reduce mortality, hospitalizations, and development of CHF in patients with impaired or preserved left ventricular function.

The mechanisms by which ACE-inhibitors effect these beneficial results are multiple and are incompletely understood. The hemodynamic benefits of ACE-inhibitors are numerous and include reducing salt-water retention, reducing afterload, and decreasing diastolic and systolic wall stress. ACE-inhibitors reduce angiotensin II and aldosterone levels. Angiotensin II and aldosterone stimulate myocardial and vascular hypertrophy and fibrosis. Some of the observed benefits of ACE-inhibitors are likely mediated through blocking of these processes.

ACE-inhibitor therapy is a pillar in the treatment of chronic congestive heart failure, and has proven to consistently be associated with improved functional capacity and with reduced mortality. The virtual serendipitous observation that patients with coronary artery disease/ventricular dysfunction who receive ACE-inhibitor therapy have reduced coronary mortality has incited a proliferation of basic research that has attempted to define specific ways by which ACE-inhibitors could stabilize atherosclerotic coronary artery disease at the tissue level, leading to improved clinical outcomes.

**ACE Inhibition in Prevention of Atherosclerosis**

There is evidence that ACE-inhibitors favorably influence vascular endothelial function through mechanisms other than angiotensin II antagonism. ACE is structurally related to the kininase 2 enzyme responsible for the degradation of kinins, and ACE-inhibitors may cause vasorelaxation by facilitating the accumulation of vasorelaxing kinins in the vessel wall.
such as bradykinin. In both experimental and in human studies, it appears that ACE-inhibition normalizes reduced endothelial release of nitric oxide, partially by potentiation of bradykinin activity. Intact porcine coronary circulation studies suggest that ACE-inhibitors have differential effects on coronary conductance and resistance vessels. Epicardial vasodilation induced by the ACE-inhibitor ramiprilat is partially blocked by the nitric oxide synthase antagonist L-NAME, but not by the selective bradykinin antagonist HOE 140; whereas, resistance vessel vasodilation was blocked by both L-NAME and HOE 140. In hypercholesterolemic rabbits, ramipril preserves endothelial function. In an isolated pig heart ischemia-reperfusion model, ACE-inhibitors preserve endothelium-dependent microvascular responses. In the recently published TREND study, ACE-inhibitor therapy in patients post-infarction reduced coronary endothelial dysfunction (as assessed by intracoronary acetylcholine injection to stimulate endothelial nitric oxide production) over 6 months post-infarction. Thus, ACE-inhibitors may favorably modulate nitric oxide activity and endothelial function, possibly through preservation of kinin-mediated vasodilation.

There is also evidence that ACE-inhibitors favorably influence vascular structure. In animal studies, ACE-inhibitors and angiotensin II receptor antagonists have been observed to have anti-atherogenic effects. In the Watanabe heritable hyperlipidemic rabbit, trandolapril was reported to reduce atherosclerosis. Numerous studies have observed cell and molecular effects of angiotensin II, such as induction of growth, cell migration, and mitosis of vascular smooth muscle cells, increased synthesis of fibronectin, collagen type I and III in fibroblasts, leading to thickening of the vascular wall and myocardium, and fibrosis that would appear consistent with processes involved in atherosclerosis. Blocking the production of angiotensin II with ACE-inhibitors, or potentially as with angiotensin II receptor antagonists, would then, as current wisdom would have it, have beneficial tissue effects such as reducing intimal thickening in response to vascular injury. In a rat model, it has been observed that kinins mediate the antiproliferative effects of ramipril. The combination of inhibiting angiotensin II-induced cellular and molecular effects of preserving kinins, and of increasing nitric oxide production, which appears to have anti-atherogenic effects, may underlie these observations. The clinical relevance of these observations is being tested in the long-term large scale clinical trials (HOPE, PEACE).

**Summary**

If it is possible to favorably alter vascular structure and function with ACE-inhibitors and gain clinical benefit, then perhaps it may be possible to inhibit other pathways of endothelial origin, such as endothelin, and to gain clinical benefit. In normal subjects, and in patients with coronary artery disease and in patients with chronic congestive heart failure, nonselective endothelin receptor antagonism has been well tolerated in acute studies, and resulted in demonstrable vasodilation of both the systemic and pulmonary arterial circulations. Patients with chronic congestive heart failure exhibited nearly twice the reduction in pulmonary as in systemic vascular beds. The observation that endothelin antagonists appear to preferentially vasodilate the constricted pulmonary circulation would put such compounds in a highly sought after class of agents that are potentially of great clinical interest. It is conceivable that more complex pharmacotherapy may be entertained in patients with hemodynamically important heart failure – such as combined ACE-inhibition and endothelin antagonism. In a rat heart failure study, Teerlink et al observed that the effect of the endothelin antagonist bosentan was additive to that of ACE-inhibitors. This is unproved in humans.

However, numerous important questions pertaining to the pharmacology and clinical acceptability of endothelin receptor antagonism are unanswered at this point in time, and can only be answered through carefully controlled studies, which may or may not set the stage for clinical use of agents of this class. Acute tolerability has been demonstrated in normal and in heart failure patients, but chronic tolerability and safety are unknown. Animal models have not suggested chronic toxicity, but human safety in the chronic setting is unknown. The optimal formulation of an endothelin antagonist is unknown – should it be selective ETA or non-selective ETA and ETB? Precisely how endothelin antagonists work is still unclear – does the elevation of serum endothelin after receptor antagonism reflect displacement from competition at the receptor binding site, or does it reflect an alternate cause such as altered clearance? Furthermore, is the fundamental nature of the effect of endothelin paracine/autocrine or is it endocrine? Are circulating levels of endothelin a marker of local cellular physiology/pathophysiology (spillover), or a mediator (messenger) of physiology/pathophysiology?

**Conclusion**

The endothelium is a key modulator of coronary physiology and a participant in certain pathophysiologic states. Endothelial dysfunction, including impaired nitric oxide activity, and greater secretion of endothelin, has been identified as a potential target in treatment of coronary atherosclerotic disease, myocardial dysfunction, and pulmonary hypertension. Addition of endothelin receptor antagonists may expand our therapeutic armamentarium. ACE Inhibitors have already become a household name in the management of CHF and LV dysfunction. Recently recognized importance of ACE inhibition with regard to endothelial dysfunction offers a promising future for this class of drugs.
References


