Introduction

Our modern understanding of the pathogenesis of heart failure has revealed a cruel irony, wherein the underlying theme of the neurohormonal hypothesis of heart failure is a perverse twist of one of Friedrich Nietzsche's more well-known, and misused, aphorisms: "What does not destroy me, makes me stronger." It appears that in the setting of heart failure, that which helps you live and survive cardiovascular stress, will ultimately be the arbiter of progressive deterioration and finally death. To the list of these double-edged neurohormones, including mediating pathologic hypertrophy and fibrosis of both ventricular and vascular tissues, acting as a proarrhythmic, and potentiating the effects of other neurohormones. Endothelin receptor antagonists were developed to investigate the hypothesis that these adverse effects could be prevented and experimental studies showed promise in this regard. Clinical studies to date have not fulfilled this promise. Further analysis of these trials will hopefully provide insight into these disparate findings and guidance for future investigations.

Nature Reveals a New Pathway: Endothelin

In the 1970s, analysis of the snake venom from Bothrops jararaca, the Brazilian pit viper, revealed a peptide that caused profound hypotension; this compound led to an understanding of the renin-angiotensin pathway and development of angiotensin-converting enzyme (ACE) inhibitors. In a similar fashion, the discovery of the sarafotoxins, extraordinarily potent vasoconstrictor peptides from the venom of Atractaspis engadensis, or Israeli burrowing asp, and their homology to endothelin, a 21-amino acid peptide, synthesized by cardiovascular and other tissues, has revealed another important cardiovascular pathway. The initial discovery that endothelial cells produced vasoconstricting compounds [1•] prepared the foundation for the identification of endothelin during a methodic search in conditioned media of cultured porcine endothelial cells [2•]. Like the snake venom to which it is related, endothelin-1 (ET-1) was found to be the most potent vasoconstrictor.

Endothelin-1 is a member of the endothelin family of gene products, which includes three isopeptides encoded from separate genes known as ET-1, ET-2, and ET-3. ET-1 is the focus of the remainder of this discussion (for an excellent review of the following material, see Miyauchi and Masaki [3]), because ET-2 and ET-3 do not appear to play a major role in human cardiovascular pathophysiology. Although the brain and kidney also produce significant amounts of this peptide, ET-1 is synthesized predominantly by cardiovascular tissues in response to cardiovascular stress. Multiple signals increase the synthesis of ET-1 (Fig. 1), including other neurohormones (angiotensin II, epinephrine/norepinephrine, and even endothelin itself), cytokines (interleukin-1, transforming growth factor-β), and other stimuli (acidosis, thrombin, hypoxia, and shear stress). The initial gene product is a 212-amino acid peptide, preproendothelin-1, which is serially cleaved to the 38-amino acid precursor, big ET-1. Big ET-1 is found in the peripheral circulation, where it is cleaved by a family of metalloproteinases, endothelin-converting enzymes (ECEs). In humans, the predominant ECE is the membrane-bound ECE-1 [4], which exists as four isoforms (ECE-1a, ECE-1b, ECE-1c, and ECE-1d). ECE-1 is widely distributed through the cardiovascular system, constitutively expressed in endothelial cells, and expressed in myocytes in pathologic conditions [5]. These enzymes cleave big ET-1 into the 21-amino acid end product, ET-1.

In fewer than 15 years since its discovery, endothelin is now recognized as playing a central role in the pathogenesis of chronic heart failure. This review examines the signaling pathways and mechanism of action of endothelin in relation to the studies that have elucidated this role. Early investigations observed that the endothelin system is markedly upregulated in heart failure, whereas others demonstrated that endothelin is the most potent vasoconstrictor. However, it has multiple other actions, including mediating pathologic hypertrophy and fibrosis of both ventricular and vascular tissues, acting as a proarrhythmic, and potentiating the effects of other neurohormones. Endothelin receptor antagonists were developed to investigate the hypothesis that these adverse effects could be prevented and experimental studies showed promise in this regard. Clinical studies to date have not fulfilled this promise. Further analysis of these trials will hopefully provide insight into these disparate findings and guidance for future investigations.
Endothelin signals via two main types of receptors, known as ETA and ETB on the basis of their relative affinities for the endothelin isopeptides (Table 1). ETA receptors bind ET-1 and ET-2 with much higher affinity than ET-3, whereas ETB receptors bind all three isopeptides with relatively equal affinities. ET receptors are members of the family of seven transmembrane-spanning G-protein coupled receptors with cell-specific signaling pathways. Although endothelin is essential for normal embryonic development, it plays a minor role in normal cardiovascular function [6]. However, in heart failure and other pathophysiologic states, the endothelin system is markedly altered, and ET-1 assumes a larger role in the regulation of hemodynamics, as well as vascular and myocardial function and remodeling.

Alterations in the Endothelin Pathway in Heart Failure

Both animal models and human studies have demonstrated that the endothelin system is dramatically affected by cardiovascular pathology. Plasma ET-1 levels were first shown to be increased in patients with cardiogenic shock [7•], but subsequent studies have found increases in acute and chronic heart failure (CHF), pulmonary hypertension, systemic hypertension, and all forms of acute coronary syndromes, as well as many other conditions. Margulies et al. [8] provided the first evidence of elevated endothelin concentrations in an experimental setting using the rapid ventricular pacing canine heart failure model, and these findings were subsequently confirmed in the rat coronary artery ligation heart failure model (Teerlink et al. [9•]). In patients with CHF, endothelin concentrations were found to be markedly elevated in a number of studies [10–12], and correlated with the extent of pulmonary hypertension [10], the severity of symptoms and ventricular dysfunction [13], and to be predictive of mortality [14••]. Other studies have shown increased local synthesis of endothelin in the noninfarcted remote myocardium in rats with chronic heart failure, establishing that increased concentrations of endothelin are indeed present in the heart at the time of progressive ventricular remodeling. Thus, it has been well established that there are both elevated circulating and local myocardial concentrations of endothelin in heart failure.

The membrane-bound ET receptors are also significantly increased in multiple heart failure studies. In the rat model of CHF, there is evidence of an increase in myocardial ETA and ETB receptor density, with a proportionately greater increase in the ETB receptor population [15]. Similar changes have been observed in the cerebral arteries in the rat CHF model, with a proportionately greater increase in the vasoconstricting smooth muscle ETB receptors [16], suggesting that upregulation of ET receptors with an increased proportion of ETB receptors is widespread. Therefore, the endothelin receptor system appears to be upregulated in the setting of heart failure. More importantly, there is substantial evidence demonstrating that these alterations have important sequelae for the vasculature and myocardium.

Effects of Endothelin on the Vasculature

Although the powerful vasoconstricting effects of ET-1 on the systemic, pulmonary, coronary, cerebral, and renal circulations are well known, we [6] and others [17] have demonstrated that endothelin appears to have a minimal to moderate role in the homeostasis of blood pressure in the system.