A Potential Role for Endothelin in Congestive Heart Failure

The endothelin family of peptides has recently been characterized. Endothelin-1 and endothelin-3 are released by endothelial cells. Infusion of either of these endothelins in animals causes pronounced vasoconstriction, decreased cardiac output, and increased blood pressure. Whether endothelin acts solely as a local mediator of vasoconstriction or also as a circulating hormone has been controversial. Recent data also support a role for endothelin in mitogenesis in vascular smooth muscle. The main stimuli for release of endothelin are beginning to be elucidated. The study by Rodeheffer and associates reported in this issue of the Mayo Clinic Proceedings (pages 719 to 724) demonstrates that circulating levels of endothelin are increased in patients with congestive heart failure and also that circulating levels of endothelin are higher in patients with severe congestive heart failure than in those with mild congestive heart failure. This study poses several interesting questions about the role of endothelin in heart failure and the potential mechanisms of release of endothelin.

Relationship With Hypotension.—Preliminary studies have demonstrated that hemorrhage-related hypotension, infusion of endotoxin, cardiogenic shock, myocardial infarction, orthostatic hypotension, and hypoxia—like congestive heart failure—are associated with increased circulating levels of endothelin. This observed association between hypotensive states and increased circulating levels of endothelin may suggest that baroreceptor unloading in hypotension enhances release of endothelin. Alternatively, tissue hypoxia caused by hypotension or congestive heart failure may stimulate release of endothelin. Indeed, Oparil and colleagues demonstrated that hypoxia can stimulate release of endothelin. Therefore, hypoxia may be one of the physiologic links that result in release of endothelin in all these conditions.

Relationship With Coronary Artery Disease.—A recent study by Lerman and co-workers demonstrated that endothelin is also increased in patients with atherosclerosis—perhaps because of injury of endothelial cells. This effect may, in part, be responsible for the increase in endothelin observed in the current cohort of patients, inasmuch as 55% of these patients had coronary artery disease. Because 45% of patients had no evidence of coronary artery disease, however, the current study indicates that congestive heart failure may independently be responsible for the increase in endothelin. It would be interesting to know whether levels of endothelin are significantly different in patients who have heart failure with and without associated coronary artery disease. Another comparative study that would help segregate the effect of atherosclerosis from the effect of heart failure would be an assessment of patients without coronary artery disease who have heart failure in comparison with control subjects.

Effects on Cardiac Output.—The role of endothelin in heart failure is complex; endothelin has effects on each component of cardiac output, including blood volume, venous capacitance, cardiac contractility, coronary artery tone, and cardiac afterload. The effects of endothelin on these components of cardiac output are dependent on the dose and may often influence cardiac output in opposing ways. In addition to understanding the role of endothelin on components of cardiac output, examining the role of endothelin on the sequelae of heart failure, including peripheral edema and pulmonary edema, would be of interest. Finally, understanding endothelin in the context of other factors and hormones released during heart failure is important.

Endothelin affects cardiac preload in opposing ways by decreasing blood volume and by decreasing venous capacitance. Studies in our laboratory have evaluated the effects of infusion of endothelin on vascular volume and escape of albumin in the nephrectomized rat. These studies demonstrated that endothelin causes a profound loss of plasma volume, independent of renal excretion, by enhancing transudation of fluid into the extrapulmonary interstitial space presumably by increasing hydrostatic pressure. This effect decreases preload, enhances formation of peripheral edema, and protects the lung from volume overload. Endothelin also affects cardiac preload by causing vasoconstriction, which produces increased venous return by decreasing venous capacitance. The ultimate effect of endothelin on preload is based on the additive effects of these two opposing actions.

Endothelin enhances cardiac contractility in isolated cardiac atrial and ventricular tissue in vivo and in vitro. Furthermore, removal of endocardium in isolated papillary muscles in the rat depresses contractility. Thus, perhaps local or systemic release of endothelin can help cardiac output by enhancing contractility. Because high doses of endothelin can also cause coronary vasoconstriction and
myocardial infarction, endothelin-1 can cause decreased contractility at high doses.

Infusion of endothelin substantially increases cardiac afterload by causing profound arterial vasoconstriction, and the result is increased systemic vascular resistance. Although systemic vascular resistance was not measured in the current study by Rodeheffer and associates reported in this issue of the Proceedings, numerous studies have substantiated an increase in systemic vascular resistance in heart failure. Increased systemic vascular resistance during heart failure may be caused by increased sympathetic outflow, increased catecholamines, angiotensin, or vasopressin, or increased endothelin. Furthermore, infusion studies in rats and dogs have demonstrated that minimal changes in circulating levels of endothelin, such as those found in the current study, can be associated with increased blood pressure and increased systemic vascular resistance. Thus, on the basis of these observations, release of endothelin during congestive heart failure may, in part, be responsible for the increased systemic vascular resistance. Nevertheless, previous studies have been unable to show a significant correlation between systemic vascular resistance and circulating levels of endothelin in a dog model of congestive heart failure produced by rapid ventricular pacing.

Effects on Blood Pressure and the Lungs.—Burnett and colleagues have identified two peptides—atrial natriuretic factor and endothelin—that are increased in congestive heart failure. This finding may seem perplexing because these peptides have vastly different physiologic actions. Indeed, atrial natriuretic factor decreases blood pressure by decreasing venous return, whereas endothelin substantially increases blood pressure by causing vasoconstriction. Perhaps the release of endothelin-1 during heart failure may enhance atrial stretch-induced release of atrial natriuretic factor because endothelin-1 has been shown to be one factor that causes release of atrial natriuretic factor. Although the systemic effects of these peptides on blood pressure differ, their pulmonary protective effects may be similar. Both agents decrease the escape of albumin in the lungs. Atrial natriuretic factor increases the peripheral escape of albumin, most likely by increasing the permeability of peripheral capillaries, whereas endothelin increases transudation of blood out of the nonpulmonary circulation by increasing capillary hydrostatic pressure in peripheral areas. Both effects may increase peripheral edema but protect the lungs from pulmonary edema.

Future Issues.—With the current study by Rodeheffer and colleagues as a foundation, future studies should address several questions prompted by this investigation. First, what effect do medications for heart failure have on release of endothelin? Many patients were taking several drugs that may have affected release of endothelin, and studies of the effects of such drugs on release of endothelin have not been published. Second, measurement of circulating levels of endothelin does not distinguish between enhanced release of endothelin and diminished clearance of endothelin. The latter is particularly likely in the setting of congestive heart failure because it is commonly associated with a decreased glomerular filtration rate. A study in which the effects of decreased glomerular filtration rates on circulating levels of endothelin are measured would help distinguish between enhanced release and diminished clearance as a cause of increased circulating levels of endothelin in heart failure. Third, the assay used to measure endothelin cross-reacts with proendothelin. Therefore, the measured endothelin may be inactive proendothelin, which would have no effect on systemic vascular resistance. This issue could be addressed by using an assay that does not cross-react with proendothelin for investigating the effects of heart failure on levels of endothelin. Finally, a study in which systemic vascular resistance is measured in patients with heart failure and in control subjects would help determine whether changes in endothelin correlate with changes in systemic vascular resistance. The current study by Rodeheffer and co-workers adds a new dimension to our understanding of the pathophysiologic changes in heart failure and provides useful information for future studies of the role of endothelin in heart failure.

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REFERENCES