has led to an appreciation of the clinical importance of achieving regression of cardiac hypertrophy, as well as control of blood pressure, in patients receiving antihypertensive therapy. The superiority of converting enzyme inhibitors compared to other antihypertensive agents in effecting regression of cardiac hypertrophy could be attributable to their characteristic profile of actions. By inhibiting the production of A II, they not only decrease afterload through blood pressure reduction, but also ameliorate myocardial ischemia through improvement in myocardial blood flow resulting from increased myocardial and arteriolar compliance due to reduction in the size of individual myocardial cells and regression of interstitial and perivascular tissue fibrosis. Recent findings that converting enzyme inhibitors improve the prognosis for patients with heart failure can be readily understood based on the underlying pathological events leading to a hypertrophic heart.

2. Roles of Neurohumoral Factors in the Progression of Heart Failure

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Key words: atrial natriuretic peptide, heart failure, tissue renin-angiotensin

Introduction

Congestive heart failure is characterized by the activation of several neuroendocrine systems. The increased activity of the sympathetic nervous system has already been well documented as helping to maintain systemic perfusion in the setting of ventricular dysfunction, along with the renin-angiotensin system, arginine vasopressin and endothelin (1). To counterbalance the intense vasoconstriction and sodium retention that are associated with these systems secretions of various vasodilator hormones, such as atrial and brain natriuretic peptides, prostaglandins and dopamine, are increased. Recent data have demonstrated that atrial natriuretic peptide suppresses the renin-angiotensin system, as well as norepinephrine and endothelin, which are all associated with myocyte growth and cardiac interstitial proliferation. However, there have been no previous reports on the mechanism by which endogenous atrial natriuretic peptide regulates these vasoconstrictor hormones in the clinical setting of heart failure.

Atrial and brain natriuretic peptides in heart failure

In congestive heart failure the plasma concentration of atrial natriuretic peptide (ANP) increases, due to enhanced atrial and ventricular synthesis. Circulating brain natriuretic peptide (BNP) also increases as a result of enhanced ventricular production. Although ANP increases more as the severity of heart failure progresses, BNP is more markedly elevated than ANP in severe heart failure, indicating that BNP reflects myocardial damage in addition to hemodynamic disorder (2). Gottlieb has demonstrated that the measurement of ANP is an important prognostic factor in patients with chronic heart failure (3). The present study shows that while both ANP and BNP are significant predictors of survival in heart failure (Fig. 1), only BNP is found to be an independent predictor of mortality by the Cox proportional hazard model (ANP: ns, BNP: p=0.0015). These findings may be due to the fact that the plasma levels of BNP increase more sensitively than ANP in response to the severity of heart failure.

The compensatory effects of ANP appear to be attenuated in severe congestive heart failure despite increased secretion of ANP and BNP. Plasma levels of ANP and cGMP, an intracellular second messenger of ANP, become elevated with the progression of heart failure, however in severe heart failure the plasma cGMP level has been observed to reach a plateau despite an increased level of ANP (4, 5). Furthermore, we have demonstrated that HS-142-1, a specific antagonist of guanylate cyclase-coupled ANP receptors, does not change the pulmonary capillary pressure and cardiac output in severe heart failure, although it did worsen hemodynamics in mild heart failure (6, 7). This evidence may account for the depressed ANP receptor in severe heart failure.

Tissue renin-angiotensin system in aorto-caval shunt rat heart

Although circulating renin-angiotensin is not always elevated in heart failure, large-scale studies of heart failure have demonstrated that the early administration of angiotensin converting enzyme inhibitor prevents morbidity and mortality in patients with heart failure. Recently, as a result of major...
advances in molecular biology, local synthesis of renin-angiotensin has been confirmed. Moreover, the tissue renin-angiotensin system has been shown to be distinct from the circulating renin angiotensin system (8).

We produced the aorto-caval shunt in rats in which circulating renin did not increase despite the elevation of plasma ANP. The expression levels of renin, angiotensinogen, angiotensin-converting enzyme, and angiotensin II types 1a and 1b receptor mRNA were determined by the reverse transcription polymerase chain reaction (RT-PCR). The expression levels of renin or angiotensinogen and AT1 receptors in the left ventricle were very low compared to angiotensin-converting enzyme mRNA in the ventricle which was found to be quite abundant. The administration of lisinopril attenuated the development of ventricular hypertrophy in this model. These results indicate the importance of converting enzyme in the formation of angiotensin II in the aorto-caval rat.

Conclusion

The main event which leads to heart failure is the loss of a critical quantity of functional myocardial cells after an injury to the heart. Heart failure does not develop when the heart is injured but rather when the compensatory hemodynamic and neurohumoral mechanisms are overwhelmed or exhausted. Prolonged activation of the sympathetic nervous and renin-angiotensin systems may exert adverse effects on the heart independent of their hemodynamic action. Endogenous ANP plays a role in counteracting norepinephrine and angiotensin II in heart failure although this action is markedly attenuated in severe heart failure. The administration of angiotensin-converting enzyme or angiotensin II antagonist may reverse the down-regulated ANP receptor.

Acknowledgments: The authors wish to express their appreciation to the following researchers: Naoharu Iwai, Toshiyuki Kanamori, Takako Kiriyama, Hitoshi Shimoike, Tomoko Hisanaga, Daisuke Fukai, Keizo Bito, Yukiharu Maeda, Keiko Maeda, Yuzuru Matuda, Atsuyuki Wada.

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