The role of the cardiac endothelin system in heart failure

Oliver Zolk and Michael Böhm

Klinik III für Innere Medizin, Universität zu Köln, Köln, Germany

Introduction

Since the isolation and identification of endothelins as very important vasoconstrictor peptides in 1988, clinical and experimental evidence suggests that endothelins play an important role in cardiac and vascular pathology associated with heart failure. Because of the frequency of heart failure in end-stage renal disease, this issue is definitely also of interest to the clinical nephrologist.

Though secreted predominantly abluminally by endothelial cells, plasma concentrations of endothelin-1 ET-1 are increased two to threefold in patients with heart failure irrespective of aetiology [1]. As with noradrenaline, plasma levels of ET-1 and big endothelin-1, the inactive precursor of ET-1, are of prognostic significance, predicting worsening heart failure, need for hospitalization, and death [2]. Plasma endothelin is correlated closely to the degree of heart failure in patients categorized according to the classification of the New York Heart Association. These observations strongly suggest a pathophysiological role for endothelin in chronic heart failure. From in vitro and in vivo studies studies endothelin is considered to function more as a local regulator than as a systemic hormone [3]. Indeed, local endothelin synthesis has been observed, confirming the hypothesis of an autocrine/paracrine endothelin system in the heart. Neonatal rat cardiac myocytes express preproET-1 mRNA and synthesize and secrete mature endothelin-1 [4].

ET-1 is produced from the 38 residue inactive intermediate big ET-1 via specific cleavage. The protease that catalyses the conversion, endothelin-converting enzyme (ECE), is expressed in the endocardium and myocardium, and constitutes a potential regulatory site for the production of the peptide [5]. The diverse biological activities of ET-1 are mediated mainly through two receptor subtypes, the ET\textsubscript{A} and ET\textsubscript{B} receptors. Both receptor subtypes are expressed in cardiac myocytes and coronary vessels. Thus the molecular basis for an autocrine/paracrine action of endothelin in the myocardial tissue is present.

Action of endothelin in the heart

Soon after discovery of ET-1, this vasoactive substance was reported to have several biological actions on cardiac tissue. In human myocardium in vitro endothelin has been shown to exert a positive inotropic effect via sensitization of cardiac myofilaments to calcium and activation of the sodium proton exchanger [6]. The positive inotropic effect is accompanied by prolongation of the duration of the action potential [7]. This pharmacological action of ET-1 may contribute to the pro-arythmogenic property of the peptide when it is endogenously released or exogenously applied [8,9].

Endothelins also affect heart function indirectly via profound coronary vasoconstriction. In contrast to the positive inotropic and chronotropic effects seen in isolated heart studies, a decrease in cardiac output is seen when endothelin is infused into the intact animal [10]. This may be the consequence of the vasoconstrictor action of endothelin and the resulting decline in myocardial perfusion as well as increase in afterload. In accordance with this suggestion, inhibition of coronary constriction by adenosine unmasked the positive inotropic effect of ET-1 [11]. Finally, cell culture studies demonstrate that endothelin is a potent growth factor for cardiomyocytes [12].

Recent in vitro and in vivo studies suggest that ET-1 is involved in the mechanism by which angiotensin induces cardiac hypertrophy. The cardiac endothelin

Correspondence and offprint requests to: Michael Böhm, Klinik III für Innere Medizin, Joseph-Stelzmann-Str. 9, D-50924 Köln, Germany. Email: michael.boehm@medizin.uni-koeln.de

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atria and right ventricles of patients with congestive heart failure compared to non-failing control myocardium [16].

The source of elevated tissue ET-1 in congestive heart failure is unclear. Several mechanisms have been discussed. One possibility is an increased production of ET-1 via enhanced synthesis of preproendothelin-1 (ppET-1). Ventricular hypertrophy and congestive heart failure have been associated with increased myocardial expression of ppET-1 mRNA in experimental animal models [13,15,16]. However, over time a normalization of ET-1 mRNA expression is observed in some animal models of heart failure, although cardiac dysfunction persists [17]. In human left ventricular myocardium, ppET-1 mRNA-expression is unchanged in hearts from patients with dilated cardiomyopathy compared to non-failing donor hearts. Taken together, these results suggest that induction of ET-1 mRNA expression is an early, but transient response to alterations of heart function. Besides ppET-1 expression, enhanced conversion of endothelin precursor peptides may result in increased tissue ET-1. Among the ECE identified, the membrane-bound metalloprotease ECE-1 is the major ET-1-forming enzyme in the cardiovascular system. ECE-activity in left ventricular membrane preparations did not significantly differ between failing hearts and non-failing donor hearts. These data correlate with findings on mRNA concentrations, indicating unchanged ECE-1 mRNA-expression.

Apart from altered ET-1 production, decreased clearance of ET-1 within the myocardium may also occur. Several in vivo and in vitro data raise the possibility of a local clearance mechanism mediated by ETB receptors [18]. Since ETB receptors are downregulated in left ventricular myocardium from patients with end-stage heart failure, this mechanism may contribute to the elevated tissue ET-1 levels observed in these patients [15]. In contrast to the decreased ETB receptor expression, increased ETA receptor density has been reported in end-stage heart failure due to dilated cardiomyopathy [6,15,19]. Thus a relative shift in endothelin receptor expression in favour of the ETA subtype occurs. Although the number of ETA receptor, is increased, ET-1 induced inositol phosphate formation is unchanged in the failing left ventricular myocardium [19]. These findings indicate that the ETA receptor signalling pathway is desensitized in end-stage heart failure. A candidate mechanism may be the agonist-induced phosphorylation of the ETA-receptor protein by G-protein-coupled receptor kinases.

Conclusions and perspectives

In chronic human heart failure, alterations of the tissue endothelin system occur. Elevated endogenous ET-1 concentrations due to decreased cardiac clearance and changes in the ET receptor expression pattern in favour of the ETA receptor may have important implications.
for the pathophysiology of heart failure. Antagonists of endothelin receptors are available and have been used to demonstrate the pathophysiological effects of endothelin. Long-term treatment with an ET<sub>A</sub> receptor antagonist greatly improved the survival rate of animals with congestive heart failure. This beneficial effect was accompanied by amelioration of left ventricular dysfunction. In cultured cardiac myocytes, endothelin induces cellular hypertrophy associated with the induction of fetal genes. In experimental animal models of pressure overload administration of an ET<sub>A</sub> receptor antagonist transiently inhibited myocyte hypertrophy and prevented fetal gene induction. These data are in line with the interpretation that ET-1 plays an important role in the progression of left ventricular dysfunction. Moreover, these observations suggest that endothelin receptor antagonists, most probably ET<sub>A</sub>-antagonists, could be of value in the treatment of patients with heart failure.

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References

18. Brunner F, Doherty AM. Role of ET(B) receptors in local clearance of endothelin-1 in rat heart: studies with the antagonists PD 155080 and BQ-788. FEBS Lett 1996; 396: 238–242

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