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ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO
Scientific Update™

Endothelin-1:
A Prognostic Indicator in Patients with Heart Failure?

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Endothelin-1 (ET-1) is the most potent vasoconstrictor peptide known. It was first identified in 1988 in endothelial cell-conditioned media.[1] ET-1 is a 21 residue peptide which is produced from a larger, inactive precursor, big ET-1, by the action of endothelin-converting enzymes (ECE). Soon after its discovery, it was recognized that circulating levels of ET-1 were markedly elevated in a variety of cardiovascular diseases, including congestive heart failure (CHF).[2,3] The greatest increases were observed in patients with cardiogenic shock after myocardial infarction (MI).[2] In addition to its vasoconstrictor actions, which may contribute to elevated peripheral vascular resistance, ET-1 has a variety of biological effects that may contribute to hemodynamic compensation in patients with circulatory compromise.[4] It is a potent inotropic agent and has a similar pattern of increased contractility to that observed in norepinephrine.[5] As well, it is a growth factor, stimulating proliferation or hypertrophy of a variety of vascular and nonvascular cells, which may contribute to long-term adaptations of the cardiovascular system to chronic hemodynamic stress. ET-1 also interacts with a variety of other neurohumoral mediators, stimulating the release of atrial natriuretic factor (ANF), renin, and aldosterone, as well as augmenting sympathetic neurotransmitter release. Finally, ET-1 has a variety of potent direct effects on renal function, the net result of which is a decrease in glomerular filtration rate (GFR) and salt and water retention. Although many of these effects may initially be beneficial in maintaining circulatory function in the face of short-term hemodynamic stress, they may be counterproductive over the long-term and may in fact contribute importantly to morbidity and mortality in patients with CHF.

Myocardial infarction

After acute MI, circulating ET-1 levels rise rapidly, peaking at approximately 6 hours, and, in patients with uncomplicated infarctions, rapidly returning towards the

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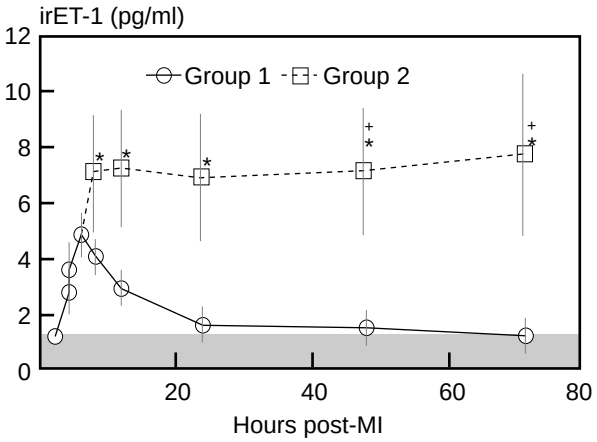
normal range by 72 hours (Figure 1).[6] In contrast, in patients with MI complicated by heart failure, ET-1 levels remain elevated over this period.[6] Based on this discriminating feature, Omland et al[7] studied the prognostic predictive value of elevated ET-1 levels in patients suffering from an acute MI. Patients with elevated ET-1 levels at 72 hours post-MI had a far higher mortality rate than patients with low ET-1 levels. In fact, in this study, multiple logistic regression analysis indicated that ET-1 was the strongest independent predictor of mortality, outperforming more traditional predictive variables, such as age, ventricular function, or infarct size. Thus, the authors speculated that activation of the ET-1 system in patients with cardiac dysfunction post-MI may be detrimental and contribute directly to a poor prognosis in these patients due to the mechanisms discussed above. If this is the case, inhibition of the ET-1 system may have beneficial effects in these patients.

Figure 1: Time course of plasma immunoreactive endothelin-1 (irET-1) (ordinate) in patients after uncomplicated (Group I) and complicated (Group II) myocardial infarction (MI). The time in hours after (post) the onset of myocardial infarction appears on the abscissa. The shaded area indicates the normal range. * = p < 0.05 compared with values in normal subjects: + = p < 0.05 compared with values in Group I.

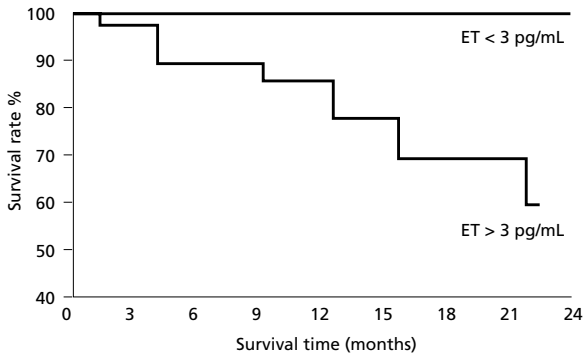


Congestive heart failure

In patients with CHF, there are marked increases in circulating levels of nearly all vasoactive agents. This probably reflects an activation of compensatory mechanisms that are thought to be crucial for the maintenance of circulatory function in heart failure.

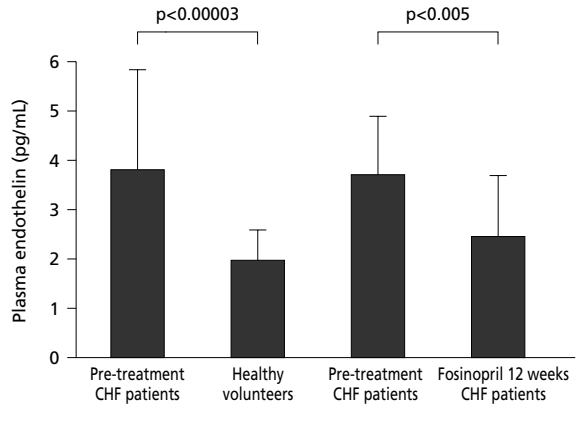
In chronic heart failure, increases in ET-1 levels are related to the functional class[8] and the degree of pulmonary hypertension,[9] both of which correlate with severity of heart failure and prognosis. Not surprisingly, plasma levels of ET-1[10] as well as the inactive precursor, big ET-1,[11] were strong predictors of cardiac mortality (Figure 2), performing better in multivariate models than the more classical hemodynamic variables or even levels of ANF.[11] However, at this time, it is unknown whether this association represents a direct causal link. Of possible relevance is a report that an angiotensin-converting enzyme (ACE) inhibitor, fosinopril, reduced circulating

Figure 2: Plasma endothelin (ET) levels and time to cardiac death



ET-1 levels in patients with heart failure (Figure 3).[12] Since it is well known that this class of drugs reduces mortality in CHF, these data may be interpreted as being consistent with a role for ET-1 in contributing to the poor prognosis of these patients. However, against this interpretation are the results of other studies in which other ACE inhibitors such as captopril, enalapril and quinapril have failed to reduce circulating ET-1 levels.[13,14] The reason for the apparent selective effect of fosinopril on inhibiting the ET-1 system in heart failure is unknown but may be related to the unique chemical structure of this compound, which contains a phosphorous atom, much like the inhibitor of endothelin-converting enzyme, phosphoramidon. Thus, it is intriguing to speculate that fosinopril may uniquely inhibit the ECE in addition to its well-known ACE-inhibiting activity.

Figure 3: Effect of fosinopril on endothelin levels



Direct confirmation of a role of ET-1 in adverse cardiac events in these patients may come from studies with new agents that inhibit the ET-1 system. Potent antagonists of the endothelial receptors have been developed and are in various phases of clinical trials. Unfortunately, at this time, there are no human data addressing the possible impact of this class of drugs on prognosis in heart failure. However, in animal studies, the selective inhibition of the ET_A-receptor resulted in a dramatic almost 50% reduction in mortaltiy at 12 weeks in the rat myocardial-infarction model of heart failure,[15] associated with improved hemodynamics and a marked improvement in ventricular remodeling.

Conclusion

Inhibition of the ET-1 system in CHF represents an exciting target in the search for new therapeutic strategies. Of current therapeutic options, early results suggest that fosinopril may reduce ET-1 levels in patients with congestive heart failure. However, at this time, one must be cautious in interpreting the scarce and still preliminary data available. The study of ET-1 antagonists in patients with CHF has only just begun. At present, data are available only for short-term hemodynamic effects of the intravenous infusion of a nonselective antagonist of ET_A and ET_B receptors, bosentan.[16] In this study, the ET antagonist had a very favourable effect on pulmonary and systemic hemodynamics, supporting the view that this novel class of therapeutic agents will be a welcome addition in the treatment of CHF.

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