Focused Perspective

Endothelin Expression and the Progression of Heart Failure
Exemplifying the Vagaries of Therapeutic Development

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Increased expression of endothelin (ET)-1 has been well described in heart failure and has been thought to potentiate the progression of this disorder through hemodynamic effects as well as vascular and cardiac remodeling.\(^1,2\) Investigations of heart failure animal models\(^3,4\) as well as early clinical studies\(^5-7\) supported a potential beneficial effect of ET-1 blockade in heart failure. On the basis of these observations, it is surprising that larger-scale clinical trials failed to support the value of chronic endothelin receptor blockade in reducing symptoms or adverse clinical outcomes for patients with heart failure.\(^8,9\) In fact, there was evidence for harm, in part mediated through increased fluid retention. The study by Schirger et al\(^10\) in this issue provides us with important new insights into the role of ET-1 in the progression of cardiovascular remodeling to clinical heart failure. This study also reminds us of the caution required in navigating the complex road from a partial understanding of pathophysiology to achieving clinical benefit through pharmacological intervention.

See p 249

Schirger et al\(^10\) observe, first, that during a phase of “transition” from experimental ventricular remodeling and dysfunction to the earliest signs of sodium retention, ET-1 expression is upregulated, without evidence of either systemic or tissue activation of the renin-angiotensin system (RAS). Second, they find that blockade of the ETA receptor in the presence of experimental heart failure produced no improvement in sodium excretion but increased plasma renin activity (PRA) and further increased plasma ET-1. In adding to our understanding of the complexity of interactions between endothelin and other neurohormonal systems in mediating structural and functional manifestations of progressive heart failure, the authors demonstrate the difficulty in applying our always-limited understanding of pathophysiological mechanisms to anticipating the clinical impact of a particular drug. Critical differences between early and late stages of disease, the multiplicity of effects of a particular agent, and the presence of concomitant treatments all can impact importantly on the physiological and clinical consequences of a particular treatment.

Based on existing data, there has been little justification for differential drug therapy during different phases in the progression of cardiac dysfunction and clinical heart failure. Data regarding the RAS, from this perspective, are mixed. The absence of RAS activation early in the expression of clinical heart failure is consistent with observations from the Studies of Left Ventricular Dysfunction (SOLVD) that minimally symptomatic patients within the Prevention trial manifest minimal elevations in PRA, and the degree of PRA expression that was observed might be explainable on the basis of diuretic administration.\(^11\) Schirger et al\(^10\) cite the absence of significant survival benefit among patients randomized to enalapril within SOLVD Prevention as further evidence for the relative unimportance of RAS activation early in the course of heart failure.\(^12\) However, enalapril induced a significant reduction in the frequency of heart failure hospitalizations within this study. Furthermore, we observed a significant beneficial effect of enalapril on ventricular remodeling within a substudy of SOLVD Prevention.\(^13\) It is therefore likely that the positive survival trend observed in this trial would have reached statistical significance with a larger number of events.

In contrast to the RAS, sympathetic activation more clearly occurs early in the course of ventricular remodeling and clinical heart failure.\(^13\) Clinical trial data support a role for β-blockers across the spectrum of disease from asymptomatic ventricular dilatation and dysfunction, to patients with symptoms at rest.\(^14-16\) More recently, aldosterone antagonists have been shown to improve survival in the following 2 distinct populations of patients: those with current or recent symptoms at rest and those with low ejection fraction and symptoms of heart failure after acute myocardial infarction.\(^17,18\) The consistency of findings across these 2 populations suggests (although it does not prove) that aldosterone antagonism will be beneficial across a broad spectrum of patients with ventricular remodeling and clinical heart failure. Thus, the aggregate data across trials involving angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and aldosterone blockers fail to support variability in clinical benefit across various stages of disease.

However, these findings do not dispel the possibility that drugs that have failed to improve clinical outcomes for patients with heart failure—inotropic agents and tumor necrosis factor-α antagonists, for example—might have fared better if they had been studied within a more circumscribed population. The findings of Schirger et al\(^10\) support such a possibility with regard to ET-1 blockers. The Figure presents a mechanistic hypothesis, suggested by these findings, by

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which ET-1 expression might drive different responses through alternate hemodynamic effects at different stages of disease. During a stage of early cardiac remodeling, before substantial hemodynamic derangement, ET-1-induced vasoconstriction might be expected to raise blood pressure and downregulate both sympathetic tone and the RAS, in part via baroreceptor mechanisms. Under these conditions, ET-1 receptor antagonism might activate the RAS, as was observed by Schirger et al. In contrast, during more advanced stages of heart failure, ET-1 contribution to increased vascular tone would tend to depress cardiac output and contribute to a vicious cycle of events, including further activation of the adrenergic nervous system and RAS. ET-1 blockade might then be expected to mitigate against these events and dampen adrenergic and RAS activation.

A detailed understanding of the impact of ET-1 expression at various stages of heart failure, as Schirger et al. have begun to elucidate, does not assure accurate prediction of the clinical effects of ET-1 blockade, in part because of the potential impact of concomitant medications. The authors propose that combining ET-1 blockade with ACE inhibition might improve clinical responses by mitigating against an RAS potentiating effect of ET-1 blockade during early stages of the transition to heart failure. However, in trials already performed, effects of ET-1 blocking agents were examined in the presence of ACE inhibitors. The confounding influence of concomitant therapy on a drug’s effect is multifactorial and difficult to anticipate. It is possible, for example, that in later stages of disease, when ET-1 blockade might be expected to exert a salutary effect, there might tend to be overlap between effects of an ACE inhibitor and those of an ET-1 blocker, the effects of which are in part mediated through RAS downregulation. The overlapping mechanisms of action might mitigate against added benefit from added therapy, and “side” effects such as fluid retention might assume a more prominent role in driving the observed net clinical effects.

Each of these factors—variability of action at various stages of disease, the role of concomitant medications, and collateral actions of the proposed therapeutic agent—render projection of an agent’s clinical actions exceedingly difficult. Examination of the effects of an agent on the process of ventricular remodeling remains an attractive tool for predicting the agent’s impact on clinical outcomes. However, animal investigations of remodeling effects may be of limited value, because the model used may not accurately represent the spectrum of disease that exists within the target human population. Furthermore, the clinical use of concomitant medications renders extrapolation from animal to human investigation even more difficult. Animal investigations had demonstrated prevention or reversal of ventricular remodeling by ET-1 blockade within heart failure models. In contrast, we have recently shown absence of a significant benefit by ET-1 blockade on the remodeling process, using MRI in patients with clinical heart failure and ventricular dilatation (I.S. Anand, MD, et al, unpublished data, 2002).

The work of Schirger et al further confirms a role for ET-1 in the pathogenesis of heart failure and, at the same time, provides important insight into the complexity of this role—including interaction with other neurohormonal systems—during various stages of the disease. Findings to date with ET-1 blockers represent a prime example of how challenging it is to translate basic observations from animal models into anticipated clinical benefit. The increasingly complex medical regimens used in patients with heart failure will mandate development of more sophisticated approaches to developing new therapeutic modalities in this condition.

References


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