Endothelin Receptor Blockade and Exacerbation of Heart Failure

To the Editor:

We have read with interest the report by Lüscher et al. on the Heart Failure Endothelin A Receptor Blockade Trial (HEAT). Administration of an endothelin A receptor antagonist, darusentan (30, 100, or 300 mg/d), for 3 weeks significantly decreased systemic vascular resistance with concomitant increase in cardiac index in patients with chronic heart failure (HF). However, early exacerbation of HF was observed in 36.7% of the patients receiving 300 mg darusentan, in contrast to 12.1% in the placebo group. Similarly, treatment with nonselective endothelin A/B receptor antagonist, bosentan, was accompanied by worsening HF in the Research on Endothelin Antagonism in Chronic Heart Failure (REACH-1) and the Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure (ENABLE) trials (preliminary results presented by M. Packer, MD, at the 51st Annual Scientific Sessions of the American College of Cardiology, 2002, Atlanta, Ga). It has been proposed that development of sustained fluid retention may account for the adverse prognosis in patients receiving endothelin receptor antagonists.

Among the major mechanisms regulating cardiac contractile force, the β-adrenoceptor system and the force-frequency relationship are impaired, while the Frank-Starling mechanism—ie, increased contractile force in response to elevated end diastolic volume—is preserved in hypertrophied and even in failing hearts. Therefore, in these pathological conditions, the adaptation of the heart to varying levels of load is more dependent on the Frank-Starling mechanism.

We have recently studied the contribution of endogenous endothelin to the Frank-Starling response in Langendorff-perfused normal and hypertrophied rat hearts. Mixed endothelin A/B receptor antagonist, bosentan, attenuated the preload-induced maximal increase in cardiac contractility by more than 50% in the hypertrophied hearts but not in normal rat hearts. Of note, bosentan had no effect on contractility under baseline conditions. Our findings imply that endogenous endothelin plays a significant role in the maintenance of cardiac function during acute increases in hemodynamic load in severely hypertrophied hearts.

We propose that treatment with endothelin receptor antagonists can either improve or worsen cardiac function depending on the loading conditions of the heart. Endothelin receptor blockade is likely to increase cardiac performance at rest by decreasing peripheral resistance. However, blockade of the myocardial endothelin system may impair the adaptation of the heart to increased load by interfering with the Frank-Starling response. This mechanism may explain the observed fatal adverse events and early exacerbation of HF (eg, fluid retention) in the study of Lüscher et al.

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