Genetic modification of vascular endothelial function as therapeutic strategy in heart failure

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IN PATIENTS WITH CHRONIC HEART failure, endothelial dysfunction contributes to increased systemic vascular resistance, decreased exercise tolerance, and reduced tissue perfusion. One of the better-characterized mechanisms responsible for endothelial dysfunction is the increased production of superoxide anions (9). In the vascular wall, superoxide anions are generated mainly through the activation of NADPH oxidase by the univalent reduction of oxygen (4, 11). Under physiological conditions, superoxide anions are scavenged by superoxide dismutases (CuZn-SOD, extracellular SOD, and MnSOD) producing a relatively stable reactive oxygen species H₂O₂ (11). H₂O₂ has been shown to be an important endothelium-derived hyperpolarizing factor that mediates endothelium-dependent relaxation in the resistance arteries (8). High concentrations of superoxide anions chemically inactivate endothelium-derived nitric oxide (NO) to form a potent oxidant peroxynitrite (7). The NO-superoxide anion reaction rate of 6.7 × 10¹⁰ M⁻¹s⁻¹ is three times faster than the reaction between superoxide anion and SOD (4). Therefore, increased production of superoxide anions consumes NO causing endothelial dysfunction.

Bauersachs and colleagues (1) provided evidence that heart failure causes vascular endothelial dysfunction by increased superoxide anion production. Superoxide anions were mainly generated in the vascular smooth muscle, because removal of endothelium did not affect free radical production (1). Furthermore, this same group demonstrated that high levels of superoxide anions in the aortas of rats with heart failure were produced by the upregulated NADPH oxidase (12). Activation of renin-angiotensin humoral system is responsible for the induction of NADPH oxidase and the subsequent increased superoxide anion production in the vasculature (1). Vitamin C supplementation reduces vascular superoxide anion production and potentiates endothelial function of patients with chronic heart failure (3, 5). It has also been speculated that in heart failure, therapeutic effects of angiotensin-converting enzyme inhibitors, angiotensin II antagonists, spironolactone, hydralazine, and statins are mediated, in part, by a decrease in vascular oxidative stress (2, 9, 10).

In this issue of American Journal of Physiology-Heart and Circulatory Physiology, Iida and colleagues (6) report a series of elegant experiments demonstrating the vascular protective effect of extracellular SOD (ecSOD) gene transfer in a rat model of heart failure. Four days after ecSOD transfer, the generation of superoxide anions was reduced, and endothelial function in the aortas and mesenteric arteries of rats with heart failure was significantly improved. One of the most striking findings in this study is that improved endothelial function in mesenteric arteries was derived from enhanced vascular release of H₂O₂. These results point to two important molecular targets for vascular protection in heart failure: 1) ecSOD scavenges superoxide anions thereby potentiating endothelium-dependent relaxation responses by increasing bioavailability of NO, and 2) restoration of endothelium-bound ecSOD enzymatic activity enables the vasculature to release sufficient amounts of H₂O₂ that contribute to the normalization of vasodilation (Fig. 1).

Thus, in addition to scavenging of superoxide anions, optimal release of H₂O₂ in the resistant arteries may be an important mechanism responsible for maintenance of normal systemic vascular resistance. Indeed, endothelial function in small vessels is largely dependent on production and release of endothelium-derived hyperpolarizing factor. This study also provides important evidence demonstrating a critical role of ecSOD heparin-binding domain for the therapeutic effect of this antioxidant enzyme. Based on this observation it appears likely...
that mutation in the ecSOD heparin-binding domain may contribute to the pathogenesis of heart failure. This attractive hypothesis remains to be tested in future studies.

REFERENCES


