Increased peripheral vascular resistance is a hallmark of advanced chronic congestive heart failure (CHF) and contributes to the phenomenon of “increased afterload” that complicates this condition. Multiple factors probably underlie this phenomenon, including increased water and sodium content of the vasculature, increased neurohormonal activation, and intrinsic abnormalities of the vasculature. During the past decade, it has also been shown that endothelium-dependent vasodilation is strikingly abnormal in both experimental animals and humans with compromised cardiac function. Given that endothelial regulation of vasomotion plays a major role in the control of systemic hemodynamics, this phenomenon is probably a major cause of increased systemic vascular resistance and afterload in heart failure. Because endothelial regulation of vascular tone is mediated predominantly by endothelium-derived nitric oxide (NO), numerous studies have examined abnormalities of the L-arginine/NO pathway in heart failure. Two major abnormalities have surfaced as important.

Several studies have suggested that CHF leads to a decline in expression of endothelial cell NO synthase (eNOS), which is ultimately responsible for endothelial production of NO. Wang et al produced heart failure in dogs by cardiac pacing at a rapid rate for 4 weeks. Microvascular endothelial cells released markedly less nitrite (the stable degradation product of NO) than cells from hearts of normal animals. Using the same heart failure model, Smith and colleagues observed a decrease in the expression of both eNOS and cyclooxygenase 1, the enzyme responsible for production of prostacyclin. CHF is also associated with increased circulating levels of the cytokine TNF-α. In vitro, TNF-α increases degradation of eNOS mRNA, most likely via stimulation interaction of RNA-desstabilizing proteins with a specific portion of the 3′-untranslated region of the eNOS message. Moreover, both the activity and expression of eNOS are regulated by endothelial shear stress. Thus, chronic reductions in blood flow and the resultant decrease in shear stress may decrease endothelial NO production and contribute to endothelial dysfunction in patients with CHF.

A second mechanism responsible for impaired endothelial function in heart failure is enhanced biodegradation of NO by the superoxide anion. Both NO and superoxide are radicals and when exposed to one another undergo a diffusion-limited radical-radical reaction to form the peroxynitrite anion. The latter is a strong oxidant with only minimal vasodilator activity. Ultimately, peroxynitrite degrades to nitrate and nitrite. Recent clinical and experimental studies provide indirect evidence that in chronic CHF, the production of oxygen-derived free radicals is increased. Prasad et al showed that polymorphonuclear leukocyte production of oxygen-derived free radicals is increased 4-fold in patients with heart failure compared with controls. Dhalla and Singal showed that production of superoxide in cardiac tissue is increased as a consequence of reduced antioxidant reserve in heart failure. In patients with CHF, levels of malondialdehyde are increased, compatible with increased lipid peroxidation by oxygen-derived free radicals. Pericardial levels of 8-iso-PGFα correlate with the functional severity of heart failure. There is also a correlation between plasma lipid peroxide and malondialdehyde levels and the clinical class of heart failure. In addition, there seems to be a close relationship between exercise-induced malondialdehyde, superoxide dismutase (SOD) activity, and exercise capacity in heart failure, suggesting that exercise intolerance may be related to oxidative stress in this condition.

Indirect evidence for increased oxidative stress as a determinant of endothelial dysfunction in CHF was provided by Hornig et al. In these studies, treatment with vitamin C improved endothelial dysfunction both short- and long-term in patients with CHF. Interestingly, Winlaw et al showed that plasma nitrate, the stable metabolite of NO, is paradoxically increased in patients with CHF, suggesting that NO production may be preserved or even increased in a compensatory fashion in heart failure.

In this issue of Circulation, Bauersachs et al have added to our understanding of interactions between superoxide and NO in heart failure. These authors induced heart failure in rats by producing myocardial infarction. These animals had a marked degree of endothelial dysfunction despite increased expression of both eNOS and soluble guanylyl cyclase (the downstream target of NO in vascular smooth muscle). Incubation of aortas from these animals with radical scavengers normalized cGMP responses to sodium nitroprusside and
improved vascular relaxations. These investigators also identified vascular NADH oxidase as the likely source of vascular superoxide in this model.

The findings of Bauersachs et al are extremely important and provide further insight into the pathophysiology of heart failure. In retrospect, one might have predicted that vascular NADH oxidase would be activated in heart failure. This enzyme system is the major source of reactive oxygen species in both the endothelium and vascular smooth muscle. Previous in vitro and in vivo studies have shown that angiotensin II and cytokines such as TNF-α can stimulate activity and/or expression of this oxidase. As noted above, circulating levels of TNF-α are increased in heart failure, and activation of the renin/angiotensin system is a consistent finding in this condition. It is interesting to speculate that the now well-established benefit of ACE inhibitors in heart failure may be in part related to suppression of the activity of this oxidase and a concomitant decrease in vascular oxidative stress. Indeed, recent studies have shown that treatment with either ACE inhibitors or angiotensin-receptor antagonists decrease vascular superoxide production in models of angiotensin II–driven hypertension. Finally, hydralazine has been used for many years as a treatment for heart failure. Interestingly, this drug is a potent inhibitor of NADH oxidase. It is unclear why some laboratories find that eNOS is reduced but others find that eNOS expression is not altered and in fact may be increased (as shown by Bauersachs et al) in heart failure. One explanation may be related to the type of heart failure examined. Bauersachs et al used a model resembling ischemic cardiomyopathy, whereas investigators studying pacing-induced heart failure have found a decrease in eNOS expression in the aorta and coronary microvessels. The latter model resembles an idiopathic cardiomyopathy in many respects. Vitamin C has not been found to improve endothelium-dependent vasodilation in patients with idiopathic dilated cardiomyopathy, which suggests that superoxide may not play a role in this condition. There may also be differences in the effect of heart failure on different vascular beds and perhaps in animal species used in various experiments.

Interestingly, daily exercise has been shown to enhance expression of eNOS in normal animals and to improve endothelium-dependent vasodilation in patients with CHF. The increase in cardiac output that occurs during exercise increases endothelial shear stress, which, as noted above, stimulates eNOS expression. In addition, shear stress has been shown to augment Cu/Zn SOD expression in human aortic endothelial cells. Taken together with the results of Bauersachs et al, these findings suggest that exercise may improve endothelium-dependent vasodilation by reducing local levels of superoxide by increasing endothelial Cu/Zn SOD content. CHF is generally considered to be caused by myocardial dysfunction. The present study and other recent studies suggest that heart failure also involves perturbations of vascular function and that reactive oxygen species most likely contribute to this process. Under normal circumstances, production of reactive oxygen species by mammalian cells almost certainly has important roles in modulating cell growth and development, gene expression, and inflammation. The acute production of superoxide may limit the biological effect of NO at times when vasoconstriction is needed. An example may be a “biochemical baroreflex” during prolonged activation of the renin/angiotensin system, for instance, during dehydration or hemorrhage. Unfortunately, in certain disease states, including hypertension, atherosclerosis, and now heart failure, this biochemical baroreflex goes awry, leading to increased vascular oxidant stress. Therapeutic strategies to modulate this maladaptive response should become a target of future research. Finally, studies like those of Bauersachs et al shed light on mechanisms whereby proven therapies benefit heart failure and other vascular diseases.

References


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