Allopurinol and Endothelial Function in Heart Failure
Future or Fantasy?

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The endothelium plays an important role in the control of vascular tone by releasing both vasodilating and vasoconstricting substances. These mechanisms are important for the regulation of both microvascular and larger conduit arteries. Chronic heart failure (CHF) is characterized by increased vasoconstriction and a reduced vasodilator response during exercise. These abnormalities seem to be caused by a number of compensatory mechanisms, and some neurohumoral factors involved in this impaired vasodilator response have been studied extensively in the past. There is now growing evidence to suggest that the endothelium makes an important contribution to the abnormal vasodilator response in CHF. In particular, the role of endothelium-derived nitric oxide (NO) has received considerable attention.

Pathophysiological Implications of Endothelial Dysfunction in CHF

Because endothelial vasodilator function is involved in control of tissue perfusion, impaired exercise-induced release of NO may contribute to reduced exercise capacity in CHF. Recent experimental studies have demonstrated that impaired endothelium-dependent vasodilation after NO synthase inhibition was associated with an early reduction of exercise capacity. Conversely, the improvement of endothelium-dependent vasodilation in patients with CHF after exercise training was closely correlated with the achieved increase in peak oxygen uptake, suggesting that improved endothelial function contributed to increased exercise capacity after physical training in patients with CHF.

Reduced endothelium-dependent, NO-mediated vasodilation may also contribute to myocardial perfusion abnormalities in patients with CHF and further augment myocardial damage. Inhibition of the NO synthase resulted in impaired myocardial perfusion during adenosine-induced hyperemia measured with positron emission tomography, suggesting that endothelium-derived NO plays a significant role in the regulation of myocardial perfusion. In patients with dilated cardiomyopathy, an impaired myocardial blood flow response to pacing tachycardia or dipyridamol infusion was observed. Furthermore, the degree of myocardial blood flow reduction (in response to dipyridamol) was an independent predictor of subsequent cardiac events in patients with idiopathic left ventricular dysfunction. In addition, recent experimental studies suggest that endothelial NO synthase (eNOS)-derived NO production lowers myocardial oxygen consumption and limits left ventricular remodeling. Ventricular dysfunction, remodeling, and mortality were markedly greater in eNOS-deficient mice as compared with wild-type mice after myocardial infarction, even after correction for differences in blood pressure. The potential pathophysiological implications of endothelial dysfunction in CHF are summarized in the Figure.

Endothelial Dysfunction in CHF: Role of Oxidant Stress

Given the above observations, there has been an intense interest in understanding the mechanisms that cause endothelial dysfunction in CHF. A concept that has received substantial attention is increased production of reactive oxygen species within the vessel. In particular, superoxide (O$_2^-$) reacts rapidly with NO, resulting in formation of the peroxynitrite anion and loss of bioactivity by NO. Recently, it has been recognized that reactive oxygen species, and especially peroxynitrite, can oxidize tetrahydrobiopterin, a critical co-factor for NO synthase.

Oxygen radical formation is increased in patients with CHF, as is indicated by elevated plasma levels of malondialdehyde. Furthermore, short and long-term administration of the antioxidant vitamin C reverses the impairment of endothelium-dependent, NO-mediated vasodilation in patients with CHF. In addition, in experimental models of heart failure, endothelium-dependent vasodilation is improved by several structurally unrelated antioxidants, including superoxide dismutase, tiron, and mercaptopropionylglycine, which supports the idea that increased oxygen radical formation contributes to endothelial dysfunction in heart failure. These observations, however, raise the question of what mechanisms lead to increased vascular oxygen radical formation in patients with CHF.
Potential pathophysiological implications of endothelial dysfunction in CHF. An impaired endothelium-dependent vasodilation and consecutively reduced tissue perfusion during exercise likely contributes to impaired exercise capacity and increased “afterload” in CHF. Recent experimental studies suggest that eNOS-derived NO also regulates myocardial oxygen consumption (ie, increases myocardial efficiency) and limits left ventricular remodeling.

In the current issue of Circulation, Farquharson et al21 tested the hypothesis that xanthine oxidase-mediated superoxide formation is important for endothelial dysfunction in patients with CHF. In a small but well designed double-blind, crossover study, the authors demonstrate that oral treatment with allopurinol (300 mg/d), an inhibitor of xanthine oxidase, for 1 month improves endothelium-dependent vasodilation in the forearm circulation of patients with CHF. Treatment with allopurinol was associated with reduced oxidant stress, as suggested by a decrease of plasma levels of malondialdehyde. These observations add a novel aspect to our understanding of endothelial dysfunction in CHF and suggest that xanthine oxidase is involved in endothelial dysfunction in patients with CHF. It remains to be demonstrated, however, whether vascular activity of xanthine oxidase is indeed increased in patients with CHF.

Xanthine oxidase has been shown to be a relevant source of $O_2^-$ in human arteries,22 and immunohistochemical studies have confirmed the presence of xanthine oxidase in vascular endothelial and smooth muscle cells of human vessels.23 This enzyme is synthesized as xanthine dehydrogenase that uses an electron acceptor to become a source of $O_2^-$ and hydrogen peroxide.24 A mechanism that causes conversion of xanthine dehydrogenase to xanthine oxidase in endothelial cells is exposure to tumor necrosis factor-$\alpha$, which could play a role in patients with CHF.25 In addition, peroxynitrite, the reaction product of NO and $O_2^-$, converts xanthine dehydrogenase to oxidase likely by oxidizing cysteines in the enzyme.26 Recent experimental studies have demonstrated that xanthine oxidase binds to endothelial cells and thereby impairs nitric oxide bioactivity.27 The question arises whether allopurinol could represent a novel addition to the treatment of patients with CHF. In this respect, several recent studies have evaluated the effect of xanthine oxidase inhibition by allopurinol on myocardial oxygen consumption in experimental models of heart failure and in patients with CHF. Myocardial xanthine oxidase levels were found to be increased in patients with CHF and in those with experimental heart failure.28–31 Both in patients with CHF and in experimental heart failure, xanthine oxidase inhibition lowered myocardial oxygen consumption and improved myocardial efficiency.28–30 The ability of xanthine oxidase inhibition to improve myocardial efficiency was dependent on NO synthase activity, ie, the beneficial effect of allopurinol was not observed after inhibition of the NO synthase,30 suggesting that allopurinol may improve myocardial efficiency by preserving NO bioactivity. It should be noted, however, that some of the beneficial effects of allopurinol and its metabolite oxypurinol may be related to their hydroxyl radical scavenging capacity32 in addition to their effect on xanthine oxidase.

In summary, the observations by Farquharson et al21 are intriguing. If this concept holds true and can be confirmed in a larger patient population, it could pave the way to an inexpensive and possibly effective addition to the treatment of patients with CHF. Allopurinol has a well-established safety profile and is used widely for the treatment of gout. It has, therefore, the potential to be tested as a novel therapeutic strategy for the treatment of CHF.

References


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