1.4 Endothelium Dysfunction in Heart Failure: A Review

TSUTOMU IMAIZUMI

Abstract. Patients with heart failure frequently complain of easy fatigability on exertion. The decreased exercise capacity is not directly related to cardiac function, which is limited by muscle blood flow. In patients with heart failure, redistribution of blood flow occurs; in order to maintain blood flow to vital organs, e.g., brain and heart, blood flow to nonvital organs, e.g., skin and muscle, is decreased. Thus, patients with heart failure have decreased exercise capacity because of decreased muscle blood flow. The decreased muscle flow is caused not only by enhanced vasoconstriction but also by impaired metabolic vasodilation during exercise. We hypothesized that the impaired vasodilation could be due to abnormal endothelium function. We found that patients with heart failure have abnormal vasodilator responses to acetylcholine, an endothelium-dependent vasodilator, with preserved vasodilator responses to nitroglycerine, an endothelium-independent vasodilator. Thus, patients with heart failure have abnormal endothelium function. We also found that patients with heart failure have abnormal metabolic vasodilation to handgrip exercise and during reactive hyperemia after arterial occlusion. L-Arginine pretreatment restored both the responses to acetylcholine and metabolic vasodilation. The degree of endothelial dysfunction was correlated with the magnitude of impairment of metabolic vasodilation. Thus, the impaired metabolic vasodilation in heart failure may be due to endothelial dysfunction to which impaired L-arginine availability may contribute. Recently, it has been demonstrated that an endogenous nitric oxide synthase inhibitor, asymmetric dimethylarginine, is present in human plasma. We found that this compound is increased in heart failure, and the increase parallels the New York Heart Association functional status of heart failure. Our results suggest that the restoration of endothelium function by L-arginine in heart failure is caused by the competitive inhibition of asymmetric dimethylarginine.

Key words. Asymmetric dimethylarginine, L-arginine, Metabolic vasodilation, Nitric oxide

Third Department of Internal Medicine, Kurume University School of Medicine, 67 Asahimachi, Kurume 830-0011, Japan
Exercise Capacity and Cardiac Function

Patients with heart failure frequently complain of easy fatigability on exertion. The decreased exercise capacity is not directly related to cardiac function (ejection fraction) (Fig. 1), which is limited by muscle blood flow. In patients with heart failure, the control of regional blood flow is markedly altered, i.e., redistribution of blood flow occurs. In order to maintain blood flow to vital organs such as the brain and heart, blood flow to nonvital organs such as the skin and muscle is decreased. Thus, patients with heart failure have decreased exercise capacity because of decreased muscle blood flow.

Enhanced Vasoconstriction

We examined forearm muscle blood flow by plethysmography. As shown in Fig. 2, patients with heart failure are characterized by heightened vasoconstriction, which decreases muscle blood flow. It is well known that the augmented sympathetic nervous system and the renin-angiotensin system are responsible for enhanced vasoconstriction in heart failure (Fig. 3). We demonstrated in the pacing induced rabbit heart failure model that impaired vagal function may cause sympathetic overactivity [1]. However, this issue is beyond the scope of this review.

Impaired Vasodilation

Patients with heart failure have not only enhanced vasoconstriction but also impaired vasodilation. For instance, they have elevated plasma levels of atrial natriuretic peptide, and the vasodilator responses to human atrial natriuretic peptide are impaired compared with those in healthy subjects [2]. As shown in Fig. 4, metabolic vasodilation just after exercise is impaired in heart failure [3].