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Endothelial Function in Patients with Chronic Heart Failure

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Summary: Congestive heart failure is characteristically associated with systemic vasoconstriction and impaired vasodilatory capacity, leading to decreased peripheral perfusion. Factors identified as possible causes of reduced vasodilatory capacity include activation of the sympathetic nervous system and the renin–angiotensin system, vascular stiffness due to increased sodium and fluid retention, and structural vascular changes. More recently, the role of the endothelium as a mediator of vasoregulation and tissue perfusion has been recognized. **Key Words:** Endothelium—Heart Failure.

EVIDENCE FOR IMPAIRED ENDOTHELIUM-MEDIATED VASODILATION IN HEART FAILURE

In the last decade, several studies investigating endothelial function have provided strong evidence for the role of endothelial dysfunction of both large conduit, as well as small resistance vessels in patients with heart failure (1). Endothelium-dependent vasodilation has been studied by different methods and has been reported to be reduced in various circulatory beds (2–6). Kubo et al. (2) measured forearm blood flow response to the intra-arterial administration of metacholine in patients with chronic congestive heart failure (CHF) and showed an attenuated response. Similar findings were described by Katz et al. (4), who studied the effect of acetylcholine on femoral artery flow measured by the Doppler technique and showed a marked attenuation in endothelium-mediated vasodilation. These findings of impaired vasodilation were not related to the aetiology of CHF and were found in patients with both ischaemic and non-ischaemic cardiomyopathy. Ramsey et al. (5) measured conduit artery distensibility in patients with CHF caused by dilated cardiomyopathy. These investigators evaluated common iliac artery pulse-wave velocity and brachial artery diameter and blood flow by high-resolution ultrasound and continuous-wave Doppler, and found a decreased response to acetylcholine and reactive hyperaemia indicating decreased distensibility of peripheral, conduit arteries in patients with heart failure.

Impaired endothelium-dependent vasodilation has also been found in the coronary circulation in heart failure patients. Treasure et al. (6) studied the effect of acetylcholine infusion into the left anterior descending coronary artery in eight patients with heart failure secondary to idiopathic dilated cardiomyopathy (DCM). While control patients increased coronary blood flow after acetylcholine infusion (232 ± 40%), no significant change was noted in cardiomyopathy patients (41 ± 24%). More recently, Mathier et al. (7) extended these observations to patients with acute-onset idiopathic dilated cardiomyopathy and demonstrated the existence of coronary endothelial dysfunction at both the microvascular and the epicardial level in patients with acute-onset idiopathic DCM.

Vasodilatory capacity of the pulmonary arterial vasculature in response to endothelial stimulation has recently been studied by Elkayam et al. (8). In spite of a comparable reduction in pulmonary resistance with adenosine in patients with and without CHF, the response to endothelial stimulation with acetylcholine was markedly attenuated in patients with heart failure.

The same group of investigators also studied the renal vasodilatory effect of endothelial stimulation in patients

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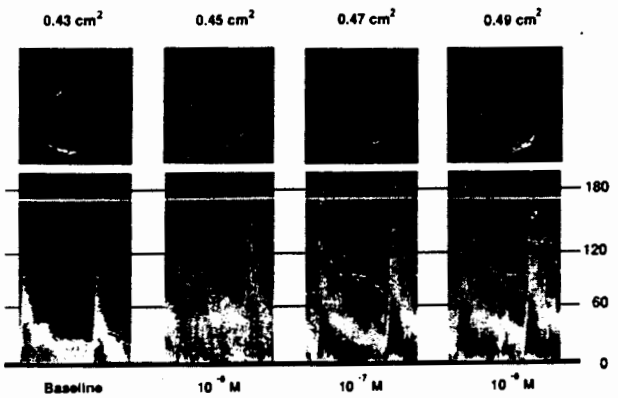

FIG. 1. Renal artery cross-sectional area (top) and Doppler flow velocity (m/s) (bottom) at baseline and during infusion of graded doses of acetylcholine into the renal artery in one of the study patients. Reported values of cross-sectional area are averages of 15 to 30 beats.

with CHF (9). This study established the effects of acetylcholine infusion directly into the renal artery on the main renal artery diameter measured by intravascular ultrasound and renal artery flow measured by intravascular Doppler. The study showed a significant change in renal artery diameter, with an approximately 160% increase in renal blood flow in response to endothelium stimulation with acetylcholine (Fig. 1). The strong endothelial response demonstrated in this study may suggest that, unlike in other circulatory beds, there is a preserved endothelial function in the renal circulation in patients with heart failure. It might also raise the possibility of renal endothelial stimulation and endogenous nitric oxide (NO) production as a potential therapeutic target for enhancement of renal blood flow in patients with heart failure.

Although the pathogenesis of endothelial dysfunction in patients with heart failure is unknown, impairment of endothelium-dependent relaxation seems to be related to a loss of bioactive endothelial NO due to either reduced synthesis or increased oxidative inactivation (10). Because endothelium-derived NO has been shown to be vasoprotective by a variety of mechanisms, preservation or restoration of NO availability appears to be an important therapeutic target. Improvement of endothelium-mediated vasodilation in the peripheral and coronary circulation has been demonstrated with interventions that either increase NO production (such as supplementation of L-arginine, administration of angiotensin-converting enzyme inhibitors, spironolactone and dobutamine, or exercise) or decrease NO degradation (such as the antioxidant, vitamin C). In addition, the use of exogenous NO donors, such as the organic nitrates, seem to restore the ability of the endocardium to release endogenous NO.

SUMMARY

In summary, numerous studies published in the last decade have clearly demonstrated an attenuated endothelium-dependent vasodilation in patients with chronic heart failure. This abnormality has been demonstrated in the peripheral and coronary circulation, in patients with both ischaemic and non-ischaemic cardiomyopathy, and its magnitude correlates with the severity of symptoms. The presence of endothelial dysfunction in patients with cardiomyopathy and new onset symptoms suggests that change in endothelial function occurs early in the course of the disease. Relative responsiveness of the renal circulation to endothelial stimulation suggests that the development of endothelial dysfunction may not be homogenous, and its magnitude may differ among different circulatory systems.

Although the clinical implications of the attenuated endothelium-dependent vasodilation in heart failure is not entirely clear, it may be contributing to decreased organ perfusion, impaired exercise tolerance and progression of disease due to vascular and ventricular remodelling. Improvement of endothelial function with a number of therapeutic interventions that have also proven effective in improving exercise tolerance, symptoms and survival in patients with heart failure, may suggest a therapeutic role for improved endothelial function in patients with chronic heart failure.

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