Endothelial dysfunction and heart failure

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Congestive heart failure (CHF) is a complex syndrome in which abnormalities of cardiac, hemodynamic, neurohumoral, immunologic, and peripheral functions take place. Endothelial dysfunction is a newly discovered hallmark of CHF. It contributes to increased baseline peripheral vascular tone and accounts for impaired vasodilation during exercise in patients with CHF. In turn, high peripheral vascular resistance increases cardiac afterload and further impairs cardiac function.

Focus on nitric oxide

Endothelial dysfunction has been demonstrated in patients with CHF as reduced vasodilation in response to acetylcholine infusion and reactive hyperemia[1,2]. Both these effects are mediated by endothelium-derived nitric oxide (NO).

Among vasodilator factors, NO is undoubtedly the most important. This gas radical, which is synthesized from the amino acid L-arginine by the enzyme NO synthase (NOS), causes vasodilation by activating soluble guanylate cyclase which leads to reduced intracellular calcium concentration in smooth muscle cells.

The reduced NO availability may be due to reduced production or increased degradation of NO. Both these events are likely to occur in CHF. A marked reduction in endothelial NOS (eNOS) was observed in the thoracic aorta and in the skeletal muscle microvasculature of rats and dogs with CHF[3-5]. A specific decrease in synthetic activity of the L-arginine-NO metabolic pathway has been demonstrated in patients with CHF, NYHA class II-III[6]. Moreover, we have recently reported a reduction in eNOS protein in human endothelial cells cultured with the serum of patients with CHF, NYHA class IV[7].

The reduced peripheral endothelial shear stress, secondary to impairment of left ventricular function, and the activated immune system are likely to be involved in the down-regulation of eNOS in CHF. Indeed, laminar shear stress is a mechanical stimulus able to turn on eNOS while the cytokine tumor necrosis factor (TNF)-α turns it off[7-9]. We observed in fact that incubation of human endothelial cells with TNF-α resulted in a time-dependent down-regulation of eNOS. However, the reduction of eNOS in endothelial cells cultured with the serum of CHF patients is not exclusively due to their increased circulating levels of TNF-α, as addition to the serum of a neutralizing TNF-α antibody partially counteracted this effect. Therefore, reduced endothelial eNOS in CHF is likely a result of the activation of a complex cytokine network.

CHF is indeed associated with elevated circulatory levels of pro-inflammatory cytokines such as interleukin-1, interleukin-6, C-C chemokines and TNF-α[10-13]. All these cytokines can induce endothelial and left ventricular dysfunction and remodeling either directly or via the production of reactive oxygen species[14].

Focus on oxygen free radicals

The production of reactive oxygen free radicals is increased in patients with CHF, and this results in oxidative stress, i.e. an imbalance between the production of oxygen free radicals and the antioxidant defence mechanism[15]. The oxidative stress activates a family of transcription factors that are involved in cardiac and vascular re-

modeling. In addition, oxygen free radicals are implicated in the process of apoptosis, i.e. a programmed cell death, which may be responsible for a continuous loss of myocardial and endothelial cells. This phenomenon may result in progressive decrease of myocardial and endothelial function which occurs over time in CHF patients.

Data from a limited number of clinical studies also provide evidence for an increase in oxidative stress in patients with CHF: 1) plasma levels of malondialdehyde (MDA), a marker of lipid peroxidation, are significantly higher in CHF patients than in controls, both at rest and during exercise[16]; 2) there is an inverse correlation between exercise-induced changes in MDA levels and erythrocyte superoxide dismutase activity[17]; 3) plasma levels of MDA are significantly associated with the severity of CHF[18].

The increased oxygen free radical formation in CHF may lead to increased NO degradation. The radicals NO and superoxide actually react to form peroxynitrite, a strong oxidant with only minimal vasodilator activity.

Focus on apoptosis

Apoptosis is a newly discovered determinant of endothelial dysfunction in CHF, whereas apoptosis in the myocytes of the failing heart has been an extensively studied topic[19]. Despite the fact that inflammatory cytokines, angiotensin II, catecholamines, bacterial lipopolysaccharides and oxidative stress, all factors activated in CHF[20,21], have adverse effects on both endothelial function and integrity[22-26], only few reports in CHF have been released up to date. Apoptotic endothelial cell damage is evident in leg skeletal muscle interstitial capillaries of rats with CHF[27]. We have demonstrated that, in cultured human endothelial cells, the serum of patients with CHF favors apoptosis[7]. Blood levels of the cytokine TNF-α partially accounted for such an effect, once again highlighting the close link between inflammation and endothelial dysfunction in CHF[7]. In support of this hypothesis, we found a positive correlation between TNF-α levels and the degree of apoptosis.

The incubation of endothelial cells with the serum from NYHA class IV CHF patients also resulted in a severe reduction of both protein and non-protein SH groups, suggesting the occurrence of an oxidative stress within the endothelial cell which could be the trigger for the increased rate of apoptosis. The addition of the anti-human TNF-α antibody resulted in a significant reduction of SH groups depletion, suggesting a possible link between TNF-α oxidative stress and apoptosis. Moreover, carvedilol time-dependently reduced the rate of apoptosis induced by the CHF serum. The beneficial effects of carvedilol were accompanied by maintenance of near normal levels of the protein and non-protein SH groups of the endothelial cells, suggesting that the reduction of the oxidative stress resulted in a reduction of the rate of apoptosis.

Conclusions

Endothelial dysfunction is likely to play a role in the pathophysiology of CHF and, in the near future, we will see therapeutic treatment targeted to this end.

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