

Tumor Necrosis Factor-Alpha in Heart Failure: More Questions Than Answers

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Heart failure (HF) as a clinical syndrome is posing an increasing social and economic burden, particularly in developed countries with their ageing populations.¹ No single pathophysiological mechanism can explain the clinical manifestations of HF, which presents as the unfavourable endpoint of a many cardiac diseases; most commonly ischaemic heart disease, hypertension, idiopathic dilated cardiomyopathy (IDC), and advanced valvular disease. Our emerging understanding of the pathophysiologic mechanisms that underpin HF implicates inflammatory processes and the vascular endothelium in the progression of this disease.

Heart failure is characterised by immune activation. Specific and non-specific inflammatory markers are elevated in patients with HF regardless of aetiology, and have been associated with the severity and progression of disease.^{2,3} Indeed, tumor necrosis factor alpha (TNF- α) levels, in particular, appear to provide incremental prognostic information in heart failure patients (reviewed by Baumgarten et al).⁴ Levine et al in 1990 were the first to demonstrate that TNF- α levels were significantly increased in patients with HF compared to controls and that increased TNF- α levels were associated with increased severity of disease.⁵ Other studies have consistently confirmed elevated levels of this cytokine in HF patients,⁴ indeed, pathophysiologically relevant concentrations seem to mimic aspects of the syndrome.⁴ Thus, in experimental stu-

dies introduction of TNF- α produces left ventricular dysfunction and cardiomyopathy, promotes left ventricular remodelling and promotes apoptosis and cachexia.⁴ The receptors for TNF- α (TNFR-1 and -2) have also been characterized and their soluble forms can be detected in circulation. Furthermore, these soluble receptors appear to be important regulators of TNF- α activity in HF patients, and elevation in circulating levels are associated with an adverse outcome.⁶

Many investigators have also documented the presence of endothelial dysfunction in patients with HF. However, it remains unknown whether abnormal endothelial function is a primary event or arises as a consequence of the syndrome.⁷ The typical constellation of biochemical abnormalities that characterise HF—enhanced angiotensin-converting enzyme activity, increased oxidative stress and raised endothelin-1 levels—leads to a reduction in endothelium-derived nitric oxide (NO) bioavailability and increased vasoconstrictor tone. In addition, the increase in circulating pro-inflammatory cytokines in HF patients, notably TNF- α , may also reduce synthesis of NO by down-regulating expression of endothelial nitric oxide synthase, the key enzyme involved in NO production.⁸ Activation of the NF-kappa B pathway in dysfunctional endothelial cells may initiate or further enhance production of adhesion molecules and cytokines, thereby promoting this process.⁹

Endothelial activation and dysregulation of endothelium-dependent vasodilation may have peripheral and central effects. A reduction in arterial compliance (increased stiffness) may lead to augmentation of aortic systolic pressure and reduction in diastolic pressure. These changes result in increased left ventricular afterload and end systolic pressure increasing myocardial work, in addition to reduced coronary perfusion pressure potentially exacerbating myocardial ischemia which together may facilitate the progression of HF. Furthermore, evidence of a strong relationship linking the severity of heart failure and endothelial dysfunc-

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tion and that treatment regimens prescribed in heart failure patients exert at least part of their beneficial effect through the vascular endothelium suggest that interventions targeting factors which interact with the vascular endothelium may be of potential value in HF.^{10,11}

In this issue Sitges et al report their observations of the effect of neurohormonal activation and the severity of heart disease on endothelium-dependent peripheral vascular reactivity in patients with IDC and matched healthy control subjects.¹² The authors demonstrate the presence of endothelial dysfunction and increased levels of pro-inflammatory cytokines, in particular TNF- α , in patients with IDC. These disturbances were dependent, at least in part, on the severity of the disease. Whilst other groups have previously demonstrated disturbed endothelial function and up regulated inflammatory processes in heart failure patients, this study is the first to demonstrate an association between endothelial dysfunction and TNF- α levels in a "pure" cohort of patients with HF due to IDC.^{13,14} This observation is of particular value, as it confirms the relationship between endothelial dysfunction and TNF- α in heart failure independent of the inflammation and endothelial dysfunction that accompany the atherosclerotic process, which may have potentially confounded results from previous cohorts which included patients with coronary artery disease.^{13,14}

Despite this interesting information, it remains difficult to decipher whether TNF- α is causally involved in HF, a picture that is becoming progressively more complicated following results from other studies investigating the effects of TNF- α antagonism. Although preliminary clinical trials have shown that TNF- α receptor blockade improves cardiac performance and endothelium dependent dilatation in HF patients,^{15,16} the value of these observations is called into question by the results of large randomised clinical trials. Both trials investigating the value of etanercept, a recombinant chimeric soluble TNF receptor 2 in CHF—The Research into Etanercept Cytokine Antagonism in Ventricular Function (RECOVER) and Randomised Etanercept North American Strategy to Study Antagonism of Cytokine (RENAISSANCE)—had to be discontinued prematurely because of failure to demonstrate any additional clinical benefit from the use this regimen.^{17,18} Furthermore, TNF- α antagonism with infliximab, a chimeric monoclonal antibody to TNF- α , not only did not improve the clinical condition of patients with moderate to severe chronic heart failure, but also had an adverse effect at high doses.¹⁹

What do these controversies tell us about the role of TNF- α in HF? It is always possible that these clinical trial "failures" simply reflect inappropriate study population selection and/or wrong treatment choices e.g. drug used, or dose and frequency of administration. Alternatively, targeting TNF- α may be effective in

restoring only certain aspects of HF pathophysiology that are insufficient to overcome other more significant mediators of disease progression. Finally, it may be that although TNF- α levels have value as independent prognostic markers in HF this molecule may not be an important causal mediator of the initiation and progression of clinical HF.

Therefore, the clinical significance of a relationship between endothelial dysfunction and inflammatory process in patients with ICD requires further examination. A more thorough understanding of the role of inflammation including TNF- α the various clinical manifestations of HF has great therapeutic potential, but it is certainly too early to consider treating HF patients with expensive specific anti-TNF- α antagonists in the absence of data to suggest a beneficial effect on disease outcome. However, further detailed mechanistic studies investigating the effect of longer-term administration of TNF- α antagonists in patients with HF using endothelial function as an outcome measure may help determine the most appropriate treatment regimes and which patient groups, if any, are most likely to benefit.

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