Inflammatory cytokines in heart failure: roles in aetiology and utility as biomarkers

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This editorial refers to ‘Relationship of interleukin-6 with regional and global left-ventricular function in asymptomatic individuals without clinical cardiovascular disease: insights from the Multi-Ethnic Study of Atherosclerosis’, by A.T. Yan et al. on page 875

The pathogenesis of left ventricular (LV) failure and cardiomyopathy, especially in the absence of ischaemic injury, remains incompletely understood. Among the key pathways implicated in the evolution of myocardial failure are neurohormonal activation, oxidative stress/nitroso–redox imbalance, and immune activation. Support for immune activation in heart failure comes from studies showing increased levels of inflammatory cytokines in patients with heart failure and increased expression of immunological antigens within the heart. With regard to the former, levels of inflammatory cytokines correlate with both severity of heart failure and the development of heart failure in asymptomatic patients, and as such these mediators may have both pathophysiological importance and utility as clinically predictive biomarkers.

A key issue arising from these associations is whether the cytokines are causally or non-causally correlated with disease pathophysiology. This is addressed by studies in which a cytokine is experimentally overexpressed. Indeed, in the case of tumour necrosis factor-α (TNF-α), classically shown to be associated with heart failure severity, it is shown that direct animal injections mimicked endotoxin-induced septic shock. Furthermore, injections of antibodies against TNF-α attenuated the haemodynamic collapse seen in those animals. Other studies in rats have shown that circulating concentrations of TNF-α similar to those seen in patients with heart failure are sufficient to produce persistent negative inotropic effects that are detectable at the level of the cardiac myocyte and are completely reversible after TNF-α is stopped. Similar findings have been reported in cardiac restricted transgenic overexpression of TNF-α; however, recent experimental data suggest that only ablation of the gene for TNF receptor 1 blunts heart failure, whereas ablation of the gene for TNF receptor 2 exacerbates heart failure. These data could explain the failure of anti-TNF therapy and suggest that the benefit in anticytokine therapy lays in the balance between receptor activity rather than the antagonistic effect on one specific receptor.

The effects of interleukin 6 (IL-6) on myocardial function are also well documented in vivo and in vitro. In vivo, subcutaneous administration of IL-6 to rats leads to a dose-dependent myocardial contractile function deterioration. In vitro, IL-6 has a direct negative inotropic effect on isolated papillary muscle, probably related to up-regulation of myocardial nitric oxide synthase. In addition, IL-6 down-regulates the sarcoplasmic reticulum Ca²⁺ ATPase (SERCA2) in isolated cardiac myocytes. Finally, administration of IL-6 to rat cardiac myocyte cultures results in reduced expression of α-myosin heavy chain, β-myosin heavy chain, and cardiac actin. Together these findings support the notion that both TNF-α and IL-6 have a specific direct role in the development of heart failure. Thus, it is in the context of these insights into both disease causality and predictive power that it is valuable to ask whether these inflammatory cytokines can be predictive of the development of heart failure in asymptomatic individuals.

Several novel opportunities have arisen from the ground-breaking Multiethnic Study of Atherosclerosis (MESA) to address this key question. MESA is a prospective study designed to evaluate the development and progression of subclinical cardiovascular disease in asymptomatic individuals in whom there was no evidence of cardiovascular outcomes and a low burden of cardiovascular risk factors. Thus, this study offers a unique opportunity to examine the actual development of LV dysfunction over time as a function of levels of various inflammatory markers.

Yan et al. have reported a cross-sectional analysis of 894 participants in the MESA study correlating regional LV systolic function using the highly sophisticated technique of magnetic resonance imaging (MRI) with inflammatory markers. The study found that asymptomatic MESA participants without known cardiovascular disease but with elevated IL-6 had depressed regional LV systolic function independent of known cardiovascular risk factors or...
proxy markers of coronary artery disease. Interestingly, because of the ability of MRI to provide accurate measures of regional contraction, it could be determined that this association was strongest in the septum and the inferior wall.

To gain more insights into the IL-6 association, the investigators also incorporated measures of C-reactive protein in their predictive model and found that when C-reactive protein was introduced into the statistical model the statistical significance of IL-6 did not change. This interesting and important finding could further indicate the possibility of IL-6 being a better predictor of the inflammatory effects in the myocardium.

This new study adds to the growing body of knowledge regarding the role of inflammatory markers including C-reactive protein, TNF-α, and IL-6 in the identification of patients at high risk of developing heart failure in addition to their role in predicting adverse events in patients with already established heart failure. The source of the immune dysfunction characterized by elevated inflammatory cytokines is the result of an imbalance between T-helper (Th) 1 and Th2 immune systems. While it is known that Th2 cells mediate the humoral production of IL-6, it remains unclear if this is an antigen-mediated mechanism leading to the inflammatory response, and if so the exact antigens stimulating the reaction remain to be fully characterized.

With regard to the inciting stimuli of the immune system in heart failure, both the milieu of cardiac dysfunction and the mechanical stresses seem to participate. Hypoxia and cardiac ischaemia lead to significant acute elevation of inflammatory markers, and minor/chronic elevations and expression of inflammatory cytokines are also seen with mechanical overload and shear stress. Therefore, in patients without a diagnosis of heart failure, chronic insults arising from uncontrolled cardiovascular risk factors such as hypertension, hypercholesterolaemia, and diabetes could mediate expression of inflammatory markers that can perpetuate persistent inflammation, contributing to the development of future heart failure.

The study of Yan et al. raises fascinating issues regarding the mechanisms for the development and progression of heart failure and could have therapeutic implications. IL-6 mediates its effects in the myocyte through the gp130 signaling pathway (Figure 1), which in turn can lead to apoptosis and hypertrophy. The observation that IL-6 up-regulates nitric oxide (NO) production warrants further mention, as this pathway can lead to nitrosative stress and/or nitroso–redox imbalance, both of which

Figure 1. Effects of the interleukin-6 cytokine family on myocardial fibroblasts and myocytes. The figure shows the potential cellular mechanisms of interleukin-6 signalling within myocardial fibroblasts (A) and myocytes (B). Within the fibroblast, IL-6 facilitates the migration and proliferation of fibroblasts and increases the production of collagen and IL-6 receptors leading to remodelling. Within myocytes, the IL-6 receptor is linked to GP130, and the downstream signalling cascade can promote myocyte hypertrophy (via JAK), apoptosis (via MAPK), and up-regulation of inducible nitric oxide synthase (via PI3K). IL-6 also increases the expression of xanthine oxidase and NADPH oxidase mRNA. The production of superoxide and nitric oxide can increase the production of peroxynitrite (ONOO−), which in turn can lead to depressed contractility by adversely influencing excitation–contraction coupling through effects on SERCA2a and possibly the ryanodine receptor (Ryr). Peroxynitrite also causes DNA damage and increases the expression of IL-6 receptors. MAPK, mitogen activated protein kinase; JAK, Janus Kinase; PI3K, Phosphoinositide 3 kinase; SERCA, Sarcoplasmic reticulum calcium ATPase; XO, xanthine oxidase; PLB, phospholamban; iNOS, inducible nitric oxide synthase; Ryr, ryanodine receptor.
can impair LV function. Nitric oxide and superoxide are physiologically produced reactive molecules with free radicals. Nitric oxide is involved in the post-translational modification of effector molecules with cysteine residues (S-nitrosylation). Superoxide at physiological levels facilitates S-nitrosylation of proteins, but at higher levels disrupts the process by competing with NO for cysteine-rich molecules. The excess of superoxide can have two deleterious effects on heart muscle cells. First, excess free radicals can lead to overactivity of the ryanodine receptor (RYR), resulting in calcium leak from the sarcoplasmic reticulum, which in turn disrupts the process by competing with NO for NO stress and inflammation in the pathophysiology of heart failure. Intermediate depression of energy consumption. This nitroso–redox imbalance leading to mechnoenergetic uncoupling is a potential explanation for the regional wall motion abnormalities reported by Yan et al. and the incident of heart failure in prospective studies.

Interestingly, a major potential source of intracellular free radicals is the enzyme xanthine oxidase (XO), which is up-regulated in the human failing myocardium and produces uric acid as its end product. In this regard, uric acid is another marker of severity and a predictor of adverse events in patients with heart failure. Uric acid, in patients with heart failure, has been shown to be the strongest predictor of several pro-inflammatory molecules including IL-6. This finding supports the link between oxidative stress and inflammation in the pathophysiology of heart failure.

Indeed, the findings of Yan et al. support the notion that IL-6 not only is a biomarker predicting the onset of heart failure but also is potentially linked in the pathophysiological cascade, possibly through nitroso–redox imbalance and other direct mechanisms. This study sets the stage for the development of potential heart failure animal models to evaluate the effects of IL-6 receptor blockers on myocardial contractility. Importantly, based upon the study of Yan et al., IL-6 may have utility in the early prediction of later heart failure events in asymptomatic patients, and future studies designed to test this hypothesis are clearly warranted.

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References


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