Proinflammatory Cytokines
Predictors of a Failing Heart?

David R. Murray, MD; Gregory L. Freeman, MD

Congestive heart failure (CHF) is a complex clinical syndrome characterized by exercise intolerance, fatigue, dyspnea, and volume retention occurring as a consequence of myocardial injury and subsequent dysfunction. Progression of this disease is thought to be mediated by neurohormones, such as norepinephrine and angiotensin II, by virtue of the toxic effects that they exert on the heart and the peripheral vasculature.1 These mediators are capable of altering the function and structure of the left ventricle (LV), ie, remodeling, via direct effects on cardiomyocyte biology and extracellular matrix composition and via indirect effects on the loading conditions under which the heart must function.1 Indeed, antagonizing the activation of the renin angiotensin system and the adrenergic system has become the mainstay of contemporary pharmacologic management of patients with this disease.1,2 β-blockers and angiotensin converting enzyme inhibitors have been shown to improve ventricular performance and clinical outcomes in patients with symptomatic heart failure due to LV systolic dysfunction, thus supporting the “neurohormonal hypothesis”.1,2

See p 1486

Another group of peptides, the proinflammatory cytokines, are upregulated in patients with CHF and have been implicated in the pathophysiology of this disease. The most well studied of these cytokines is tumor necrosis factor (TNF).3 Comparatively less is known about interleukin (IL)-1, IL-2, IL-6, and interferon-γ in the setting of heart failure. Cardiomyocytes as well as other nucleated cell types within the myocardium are capable of synthesizing TNF in response to various forms of cardiac stress such as myocardial infarction4 and LV pressure or volume overload.5 Neither TNF mRNA nor TNF protein appear to be constitutively expressed in the nonfailing heart; in contrast, TNF mRNA and protein appear to be uniformly expressed in failing human hearts.6 Both types of TNF receptors have been identified in human myocardium and are dynamically regulated.6 When given exogenously7,8 or expressed in transgenic models9 at sufficiently high concentrations, TNF recapitulates several aspects of the heart failure phenotype. TNF provokes cardiomyocyte hypertrophy and sarcomeric protein synthesis,10 triggers apoptosis in isolated cardiomyocytes through activation of the neutral sphingomyelinase pathway,11 promotes fetal gene expression,9 blunts adrenergic responsiveness,12 and impairs contractile function.7,8 Without altering preload or afterload, TNF induces LV dilation, perhaps as a result of extracellular matrix degradation, allowing for rearrangement (“slippage”) of bundles or groups of cardiac myocytes.7,8 These alterations in LV geometry are accompanied by systolic and diastolic dysfunction.8 Thus, excessive activation of TNF, and possibly of other proinflammatory cytokines, may contribute to the LV remodeling observed in CHF via mechanisms that involve both myocyte and nonmyocyte elements of the myocardium.

Circulating levels of TNF and IL-6 are elevated in patients with heart failure, particularly those with cardiac cachexia13 and edematous decompensation.14 Studies have consistently shown a direct relationship between levels of these cytokines and deteriorating functional classes of heart failure.15,16 Circulating TNF and its soluble receptors (sTNFR1 and sTNFR2) as well as IL-6 (but not its soluble receptor) predict mortality independent of age, gender, etiology of heart failure, NYHA Class, ejection fraction and serum sodium.17 Of interest, the circulating level of sTNFR2, a biologically “inert” protein cleaved from the cell surface membrane by TNF-α-converting enzyme (TACE), appears to be the most accurate predictor of mortality.17 Although these clinical studies cannot address whether the findings represent an epiphenomenon that is associated with, but not causally related to worsening disease severity and outcomes, the preponderance of data suggests that TNF and IL-6 (a promoter of cardiomyocyte hypertrophy and a negative inotrope)18 exert direct toxic effects on the heart and peripheral circulation. Conceivably, even sTNFR2 may be a surrogate marker for worsening LV function and/or LV remodeling: TACE levels correlate with the degree of LV systolic dysfunction in patients with dilated cardiomyopathy.19

Until now, clinical studies evaluating cytokines and heart failure have been limited to patients with symptomatic disease in the setting of documented systolic dysfunction. In the current issue of Circulation,20 Vasan and colleagues sought to determine whether elevated levels of inflammatory markers antedate the development of CHF in individuals free of the condition. A subgroup of 732 elderly Framingham study subjects (mean age 78 years, 67% women) without prior myocardial infarction (MI) and CHF participated in this study. Blood was obtained to determine baseline levels of IL-6, C-reactive protein (CRP, low sensitivity immunoprecipitation assay), and spontaneous production of TNF by
Peripheral blood mononuclear cells (PBMC). Subjects with a history of MI were excluded because prior MI is a known powerful trigger for cytokine activation, progressive LV remodeling and CHF.\(^4\) Over a mean follow-up of 5.2 years, 56 subjects (35 women) developed CHF as defined by Framingham criteria. After adjustments for established risk factors, including the occurrence of MI during follow-up, the investigators found that the risk of developing CHF increased \(\sim 1.6\)-fold to 1.7-fold per tertile increment in PBMC TNF and IL-6 levels, respectively. Participants with serum CRP levels \(\geq 5\) mg/dL (only 9\% of subjects) experienced a 2.2-fold increased risk of CHF. Subjects with elevated serum IL-6 and PBMC TNF \(>\) median values as well as CRP \(\geq 5\) mg/dL had a 4.1-fold risk for developing CHF.

The result of this study must be interpreted with caution. The study population consisted of predominantly elderly, white subjects (67\% female) with a high prevalence of hypertension (\(\sim 70\%\)), atrial fibrillation (\(\sim 7\%\)), and preexisting cardiovascular disease (\(\sim 25\%\) with history of angina, cerebrovascular or peripheral vascular disease without prior documented MI). As pointed out by the authors, the results cannot be generalized to include other ethnicities, younger age groups, and patients with different co-existing conditions.

A more important limitation of this study is the lack of data related to the status of ventricular function at the time of baseline assessment. Although patients with confirmed prior MI (presumably diagnosed on the basis of history, cardiac enzymes and/or Q-waves on ECG) were excluded, subjects with preexistent cardiovascular disease, LV hypertrophy, left bundle branch block, atrial fibrillation, valvular disease, and hypertension were included. Surely some of these patients must have had subclinical LV systolic and/or diastolic dysfunction at the time of cytokine assessment, related to occult MI, myocardial hibernation, pressure or volume overload, or other forms of injury. Elevated inflammatory markers in this study may have identified patients with vascular disease at risk for myocardial infarction\(^{21,22}\) or patients with preexisting subclinical LV dysfunction.\(^{23}\) Without a baseline assessment of ventricular structure and function, the study cannot address whether IL-6, TNF, and CRP predicts the de novo development of cardiomyopathy versus foreshadowing the transition between subclinical LV dysfunction and overt congestion.

The study does, however, offer some clues suggesting that inflammatory mediators can predict a transition toward a congested state. Determination of whether the patient had CHF was based on Framingham criteria.\(^{20}\) These criteria rely heavily on the presence of signs (eg, rales, jugular venous distension, hepatojugular reflux, peripheral edema, hepatomegaly) and symptoms (eg, paroxysmal nocturnal dyspnea, orthopnea, dyspnea on exertion) related to volume overload characterizing the congestive state. Lacking in these criteria are measures of exercise intolerance (unrelated to dyspnea), fatigability, generalized weakness, and energy depletion—symptoms that are more subtle and less specific in an elderly population vulnerable to the confounding factors of orthopedic and neurologic injury as well as the debilitating effects of aging. This study does not define whether inflammatory markers predict the development of “noncongestive” heart failure. Of interest, limited follow-up echocardiographic data showed that 6 of the 14 CHF patients (43\%) with serum IL-6 levels in the top tertile had preserved systolic function, suggesting that IL-6 might interact with the vasculature and/or with other neurohormonal systems to promote congestion. The influence of IL-6 on ventricular systolic performance may actually be less important.

Although this study suggests that TNF, CRP, and especially IL-6 levels are predictors for the development of CHF, several limitations preclude the routine use of these markers for risk stratification in clinical practice. First, many neurohormonal and clinical markers have been linked to outcomes in patients with CHF but comparative data regarding which ones are redundant and which ones are incremental in an asymptomatic patient population are limited. As a case in point, Vasan and colleagues found that serum IL-6 levels were related to CRP levels.\(^{20}\) This result was not as surprising as IL-6 is a central mediator of the acute-phase response and a primary determinant of the hepatic production of C-reactive protein.\(^{24}\) Furthermore, the authors did not provide hazard ratios for the other known predictors of CHF such as LV hypertrophy, hypertension, coronary artery disease, valvular disease, diabetes, and obesity.\(^{20}\) As such, side-by-side comparison of the value of elevated cytokines and these known predictors is not possible. Whether any of the inflammatory markers provide meaningful information over and above established variables remains to be proven. Secondly, to be useful for a large, general population, a screening test should be sensitive, accurate, reliable, easily standardized and inexpensive. Whether these features apply to tests used to detect this set of biochemical parameters is not clear. The sensitivity, specificity, negative and positive predictive values of IL-6, TNF, and CRP were not analyzed. Moreover, elevated levels of all three inflammatory markers were present in only 12 out of the 56 patients diagnosed with CHF, suggesting limited clinical utility. Finally, identification of risk should ideally lead to a treatment intervention that modifies that risk. Treatment of hypertension, coronary artery disease, and valvular disease can prevent the development of CHF. Whether the same can be said for neutralizing the biologic activity of proinflammatory cytokines remains unclear, and early interventional trials in patients with established CHF have not been encouraging.\(^{25}\)

Notwithstanding these limitations, Vasan and colleagues have provided data implicating inflammatory mediators as independent predictors of the onset of congestion in an elderly cohort. This study provides further support for the hypothesis that cytokines, namely, IL-6 and TNF, are maladaptive proteins that participate in the development and progression of heart failure by virtue of their toxic effects on the heart and peripheral vasculature. As with other neurohormonal markers which predict adverse outcomes in patients with heart failure, the ultimate distinction between whether the elevated level of a cytokine is a parallel phenomenon or a true causal mediator of disease rests on the demonstration that antagonizing or suppressing the cytokine results in beneficial effects. For the proinflammatory cytokines, illumination of this important point will require further investigation.
References


Key Words: Editorials ■ heart failure ■ cytokines ■ tumor necrosis factor ■ interleukins
Proinflammatory Cytokines: Predictors of a Failing Heart?
David R. Murray and Gregory L. Freeman

Circulation. 2003;107:1460-1462
doi: 10.1161/01.CIR.0000060808.79274.0C

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/107/11/1460

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/