

REVIEW PAPER

Inflammatory Biomarkers in Heart Failure

Heart failure (HF) is a complex clinical syndrome that is the end result of a wide variety of pathophysiologic processes. Multiple pathophysiologic models have evolved as frameworks for understanding the development and progression of HF. Originally, HF was seen primarily as a hemodynamic phenomenon due to low cardiac output and elevated filling pressures. More recent understanding of HF has been dominated by a neurohormonal model, which suggests that maladaptive activation of a variety of neurohormonal pathways is a primary driver of HF progression. In the past 2 decades, evidence from both animal and human studies has suggested an important role for inflammation in the development and progression of HF. This has led to the so-called cytokine hypothesis, which states that "heart failure progresses, at least in part, as a result of the toxic effects exerted by endogenous cytokine cascades on the heart and the peripheral circulation."¹ Despite strong evidence from basic and preliminary clinical investigations, therapeutic interventions that were developed based on the cytokine hypothesis have not proven to be efficacious in HF when tested in rigorous clinical trials.^{2,3} Still, significant interest remains in the use of inflammatory markers as "biomarkers" that may aid in the diagnosis, prognosis, or treatment of patients. In this review, we summarize the available data on the clinical use of inflammatory biomarkers in HF.

Supporting Evidence for the Cytokine Hypothesis

The human immune response relies on a complex cascade of signaling

Multiple lines of evidence support the "cytokine hypothesis," which suggests that inflammation plays an important role in the development and progression of heart failure. Circulating markers of inflammation, such as tumor necrosis factor α , interleukin 6, and C-reactive protein, may be useful in establishing the diagnosis, gauging prognosis, and evaluating the response to therapy in patients with heart failure. In addition to their potential as heart failure biomarkers, inflammatory cytokines have been investigated as targets of heart failure therapy. Although results for therapies directed against specific cytokines (such as tumor necrosis factor α) have thus far been disappointing, multiple studies continue to address the therapeutic potential of modulating the immune response in heart failure. In this review, the authors analyze available data supporting the use of inflammatory markers both as biomarkers and as potential therapeutic targets. (CHF. 2006;12:324–328)

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proteins, termed cytokines. Cytokines are secreted by both inflammatory and noninflammatory cells and act as signals in the regulation of both the innate and acquired immune response. Both proinflammatory and anti-inflammatory cytokines have been characterized, resulting in a model of a carefully regulated system designed to modulate the inflammatory response. In general, the cytokine cascade is highly overlapping and redundant, and multiple molecules may serve to mediate similar biologic effects in different circumstances.

The initial observation suggesting a possible role of proinflammatory cytokines in HF was by Levine and colleagues,⁴ who demonstrated elevated circulating levels of the cytokine tumor necrosis factor α (TNF- α) in patients with chronic HF. Subsequently, data

from animal models have shown that either continuous infusion of TNF- α or overexpression in transgenic models leads to time-dependent depression in left ventricular function and left ventricular dilation consistent with the adverse remodeling seen in patients with HF.^{5–7} In addition to direct myocardial effects, inflammatory cytokines have been implicated in the pathogenesis of other aspects of the HF syndrome such as pulmonary edema, skeletal muscle atrophy, and cachexia.^{8,9}

Notably, although normal myocytes do not produce TNF- α , the failing myocardium produces this cytokine and its receptors in significant quantities.¹⁰ Given the adverse effects of TNF- α on myocardial function, the stimulus for this seemingly maladaptive inflammatory activation



remains uncertain, although a variety of hypotheses have been proposed.¹¹ The initial stimulus for the production of proinflammatory cytokines may result from increased ventricular wall stress, ischemic injury, or peripheral hypoxia.^{12,13} An alternative hypothesis is that mesenteric venous congestion in the setting of volume overload leads to increased bowel permeability and bacterial translocation with endotoxin release into the circulation.¹⁴ Regardless of the relative importance of specific triggers, the data from basic studies clearly support an important role for inflammation in the progression of HF.

Specific Inflammatory Markers

A variety of inflammatory markers have been identified as having a potential role in the progression of HF. Due to the highly redundant structure of the immune system, many of these biologically active molecules have overlapping functions as part of a complex "cytokine cascade" that regulates immune and inflammatory responses.

TNF- α was first described in 1975, and subsequently termed cachectin due to its putative role in the development of cachexia. TNF- α is secreted in response to a wide variety of inflammatory stimuli and is involved in multiple cell signaling pathways related to regulation of the immune response. TNF- α exerts its biologic activity through 2 TNF- α receptors, TNFR1 and TNFR2, which are expressed by almost all nucleated cells. These receptors are inserted into the cell membrane and may also be cleaved and released into the circulation. Low levels of these soluble TNF- α receptors may stabilize and prolong the biologic activity of circulating TNF- α , whereas high levels of receptors may "buffer" the biologic effects of excess circulating TNF- α .¹⁵

Although TNF- α is the best-studied inflammatory marker in HF, other cytokines may play a role as well. Interleukin 6 (IL-6) is a proinflammatory cytokine that has a complex

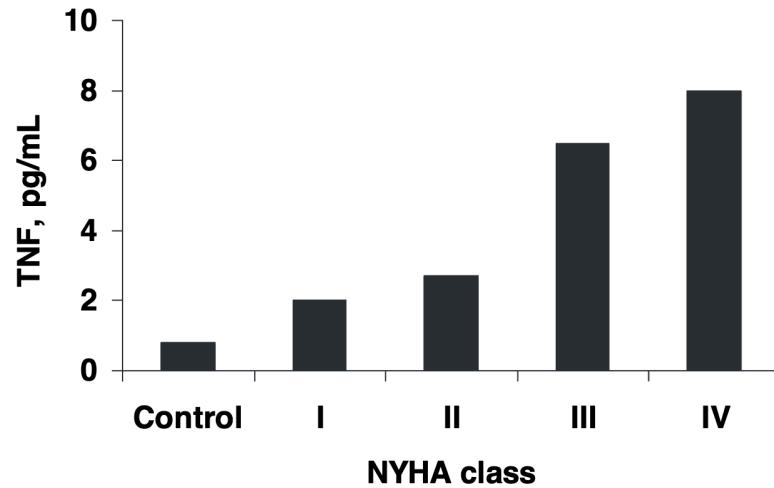


Figure 1. Levels of tumor necrosis factor (TNF) α by New York Heart Association (NYHA) functional class. Adapted from Seta et al.¹

role in the regulation and propagation of the immune response and, like TNF- α , can recapitulate some aspects of the HF phenotype in animal models.⁸ In general, IL-6 appears to induce a hypertrophic response in myocytes, potentially contributing to adverse remodeling. Other cytokines such as IL-1, IL-18, cardiotrophin-1, and Fas ligand may also play a role in the development of HF, but their precise roles are not well understood.

C-reactive protein (CRP) was first discovered in 1930 and named from its reaction with the C-polysaccharide of *Streptococcus pneumoniae*. CRP is not a cytokine, but it is produced from the liver in response to inflammatory stimuli (in particular, IL-6), and it activates the classical complement cascade. As a biologic marker of inflammation, it is widely available in clinical laboratories due to its role in the risk stratification of patients at risk for ischemic heart disease.¹⁶

Inflammatory Markers and Prognosis

Accurate estimation of prognosis is critical in HF to appropriately triage patients among invasive and costly therapies such as cardiac resynchronization therapy, cardiac transplantation, and ventricular assist devices. A variety of studies have demonstrated that

inflammatory cytokines are elevated in patients with HF in concordance with disease severity (Figure 1).¹⁷ Importantly, inflammatory markers appear to be elevated relatively early in the disease process (New York Heart Association [NYHA] class I or II), in contrast to classical neurohormones such as catecholamines, which are generally elevated only in more advanced disease (NYHA class III or IV).¹⁸ Several studies have shown inflammatory markers to be powerful predictors of long-term outcomes in patients with chronic HF. In a substudy of the Valsartan Trial (VEST),¹⁹ Deswal and colleagues demonstrated that TNF- α , IL-6, TNFR1, and TNFR2 were all significant independent predictors of long-term mortality. In this analysis, the soluble TNF- α receptors TNFR1 and TNFR2 were the most powerful predictors of long-term mortality, a finding that has been replicated in other studies.²⁰ The strong performance of the TNF- α receptors as prognostic biomarkers may be due in part to the fact that they reflect the degree of TNF- α elevation over time and are therefore less subject to short-term variability than TNF- α itself.

In the Valsartan Heart Failure Trial (Val-HeFT),²¹ CRP was shown to be a powerful predictor of morbid events and all-cause mortality, with increasing

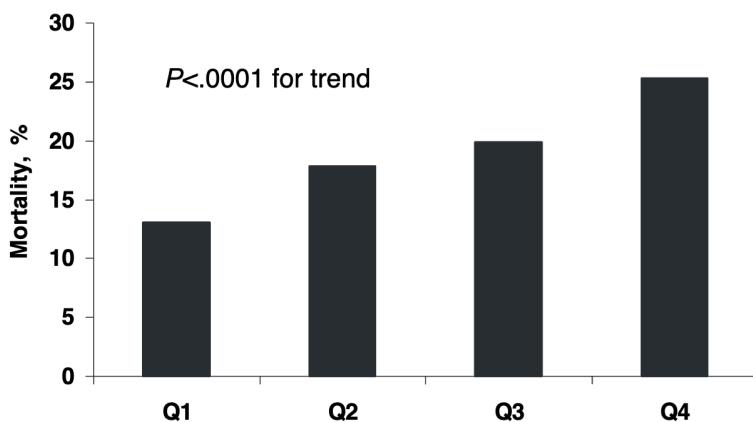


Figure 2. Long-term mortality by quartile (Q) of baseline C-reactive protein in the Valsartan in Heart Failure (Val-HeFT) study.²¹

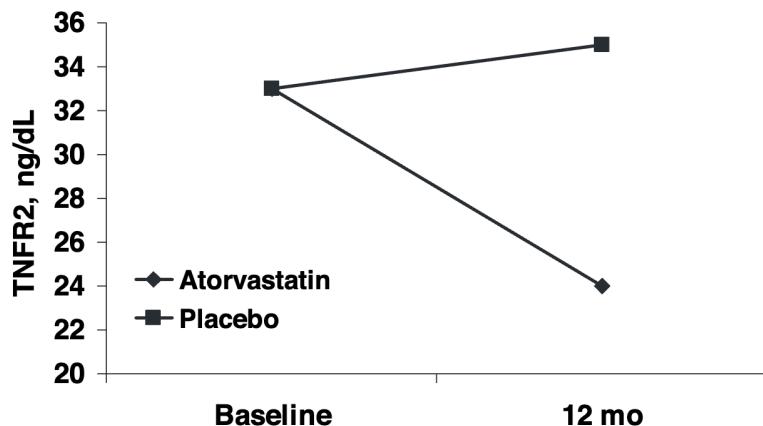


Figure 3. Decrease in circulating tumor necrosis factor (TNF) R2 in patients with nonischemic cardiomyopathy treated with 20 mg/d of atorvastatin.²⁷

event rates with increasing quartiles of baseline CRP (Figure 2). CRP added prognostic information to that provided by standard clinical variables as well as B-type natriuretic peptide (BNP). The combination of a CRP level above the median (3.23 mg/L) and BNP above the median (96 pg/mL) identified patients at particularly high risk (hazard ratio=2.1; $P<.001$). As a practical matter, CRP may be a particularly useful biomarker in the clinical care of HF patients due to its wide availability in clinical laboratories.

Given the observation that inflammatory markers may be elevated early in the course of HF, there is significant interest in the use of such markers

to predict new-onset HF. In 2 large observational cohorts, both CRP²² and IL-6²³ have been shown to predict the development of HF during long-term follow-up in elderly patients without evidence of preexisting HF. In the Framingham Heart Study,²³ patients with no prior history of myocardial infarction or HF with elevated levels of IL-6, TNF- α , and CRP had a markedly increased risk (hazard ratio=4.1; $P=.01$) of developing incident HF compared with the remainder of the cohort. After adjustment for established risk factors, there was a 60% and 68% increase in risk of incident HF per tertile increment in TNF- α and IL-6, respectively.²³ While unable

to establish cause and effect, these data suggest that inflammatory cytokines are elevated early in the disease process and may substantially predate the development of clinically apparent HF.

Modulation of Inflammation in HF

Based on the evidence supporting a role of inflammation in the pathophysiology of HF, there has been significant interest in pharmacologic manipulation of the immune response as HF therapy. Data suggest that current pharmacotherapies for HF may have effects on the immune system that account for some of their therapeutic benefits. Data on the response of inflammatory markers to β -blocker therapy have been variable, with some studies suggesting that β -blockers may reduce circulating inflammatory markers,²⁴ where others have not shown a significant impact of β -blocker therapy.²⁵ High doses of angiotensin-converting enzyme inhibitors appear to favorably affect inflammatory cytokines, with high doses (40 mg/d) of enalapril leading to decreases in circulating IL-6, whereas lower doses (5 mg/d) did not.²⁶

The 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors or statins have anti-inflammatory effects, and recent data suggest they may have clinically relevant anti-inflammatory effects in HF. Small preliminary studies with both simvastatin and atorvastatin in patients with idiopathic cardiomyopathy have demonstrated improvement in both inflammatory markers and ejection fraction compared with placebo^{27,28} (Figure 3). These data suggest that statins may have a role in the treatment of idiopathic cardiomyopathy, potentially mediated by their favorable effects on inflammatory markers. This concept is being tested in larger clinical trials.

Small studies have suggested that exercise training may be beneficial in patients with chronic HF, and data suggest that some of this effect may be mediated by anti-inflammatory effects of exercise. In a crossover study,

Adamopoulos and associates²⁹ showed that exercise training results in a significant decrease in circulating TNF- α and IL-6, which then revert to pretraining levels after detraining. The extent to which immunomodulatory effects may explain some of the putative benefits of exercise training is currently being tested in a substudy of the National Institutes of Health (NIH)-sponsored study, Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION).

The largest studies examining pharmacotherapy aimed at modulating inflammatory cytokines have utilized direct antagonism of TNF- α . Etanercept is a recombinant human TNF- α receptor that binds to TNF- α and functionally inactivates the cytokine. Pilot studies suggested that etanercept was safe and provided improvement in quality of life, 6-minute walk distance, and ejection fraction in patients with HF.^{30,31} Larger clinical trials, however, failed to show significant benefit of etanercept in HF. The Randomized Etanercept Worldwide Evaluation (RENEWAL) program,³ in which 2048 patients were randomized to various regimens of etanercept vs placebo, was stopped early due to lack of therapeutic benefit. Analysis of data from this program showed no significant difference between etanercept and placebo but a trend toward worsening in the active treatment arms. Similarly, the development of infliximab, a monoclonal antibody against TNF- α , was halted after the preliminary studies showed increased risk of death and HF hospitalization in the active treatment group.² Although a variety of potential explanations have been put forward for the failure of anti-TNF- α therapy in HF,

the disconnect between the underlying scientific rationale for such therapy and the failure of larger clinical trials remains incompletely understood. Specific biologic attributes of etanercept and infliximab may have increased the biologic half-life of TNF- α or resulted in the fixation of complement to cardiomyocytes. In addition, due to the redundancy of the cytokine cascade, it is possible that intervention on a single cytokine (such as TNF- α) may be insufficient to favorably impact the progression of HF. Finally, since inflammation may play a larger role in some patients than in others, it is possible that specific groups of patients with greater degrees of inflammation may receive more benefit from immune-directed therapies.³² Given these considerations, ongoing development in this area has focused on anti-inflammatory therapies that may modify immune response in a less specific fashion.

Intravenous (IV) immunoglobulin serves to modulate immune response through a variety of poorly understood mechanisms, including neutralization of microbial antigens and autoantibodies, Fc-receptor blockade, and complement inactivation. In a pilot study, Gullestad and colleagues³³ demonstrated favorable effects on ejection fraction, neurohormones, and hemodynamics with IV immunoglobulin treatment compared with placebo. Pentoxifylline, an agent known to inhibit TNF- α production, among other physiologic effects, has similarly shown favorable effects of HF symptoms and ejection fraction in preliminary studies.^{34,35} These promising data will require confirmation in larger studies.

Recently, immune modulation therapy (IMT), which involves treatment of venous blood with oxidative stress to augment intrinsic anti-inflammatory mechanisms, has been tested in HF. In a small pilot study, patients with chronic HF treated with IMT showed significant improvement in the risk of death or rehospitalization for HF.³⁶ Preliminary results of a larger clinical study, the Advanced Chronic Heart Failure Clinical Assessment of Immune Modulation Therapy (ACCLAIM) trial, did not demonstrate a benefit of IMT over placebo. Definitive evaluation of this potential efficacy of IMT in HF will require review of the totality of data from the ACCLAIM study, which have not yet been published.

Conclusions

There is a significant body of basic and clinical research to support the cytokine hypothesis that the inflammatory cascade is directly involved in the progression of HF. As biomarkers, proinflammatory markers such as TNF- α , IL-6, and CRP are clearly related to disease severity and provide significant prognostic information beyond that provided by traditional clinical variables and other markers such as BNP. Although direct inhibition of TNF- α has not proven to be a successful therapeutic intervention in HF, a variety of other less specific immunomodulatory therapies are currently being evaluated in HF patients. Moving forward, use of inflammatory biomarkers may allow identification of patients most likely to respond to therapies directed at the immune system, allowing the "personalization" of therapy to maximize efficacy and minimize harm.

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