Inflammatory Mediators and the Failing Heart
Past, Present, and the Foreseeable Future

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Abstract—Recent studies have identified the importance of proinflammatory mediators in the development and progression of heart failure. The growing appreciation of the pathophysiological consequences of sustained expression of proinflammatory mediators in preclinical and clinical heart failure models culminated in a series of multicenter clinical trials that used “targeted” approaches to neutralize tumor necrosis factor in patients with moderate to advanced heart failure. However, these targeted approaches have resulted in worsening heart failure, thereby raising a number of important questions about what role, if any, proinflammatory cytokines play in the pathogenesis of heart failure. This review will summarize the tremendous growth of knowledge that has taken place in this field, with a focus on what we have learned from the negative clinical trials, as well as the potential direction of future research in this area. (Circ Res. 2002;91:988-998.)

Key Words: tumor necrosis factor ■ inflammatory mediators ■ clinical trial ■ etanercept ■ infliximab

“If at first you do not succeed, you are running about average.” —M.H. Alderson

Although clinicians have recognized the pathophysiological importance of myocardial inflammation as early as 1669,1 the formal recognition that inflammatory mediators were activated in the setting of heart failure did not occur for another three centuries. Since the sentinel description of inflammatory cytokines in patients with heart failure in 1990,2 there has been a growing interest in the role that these molecules play in regulating cardiac structure and function, particularly regarding their potential role in disease progression in heart failure. The growing appreciation of the pathophysiological consequences of sustained expression of proinflammatory mediators in preclinical and clinical heart failure models culminated in a series of multicenter clinical trials that used “targeted” approaches to neutralize tumor necrosis factor (TNF) in patients with moderate to advanced heart failure. However, as recently reported, these targeted approaches have resulted in worsening heart failure.3,4 These discouraging results have raised a number of important questions about what role, if any, proinflammatory cytokines play in the pathogenesis of heart failure. To this end, in the present review, we will summarize the tremendous growth of knowledge that has taken place in this field, with a focus on what we have learned from the negative clinical trials, as well as the potential direction of future research in this area.

Scientific Rationale for Studying Inflammatory Mediators in Heart Failure
The portfolio of cytokines that will constitute the focus of much of the present review includes TNF and the interleukin (IL)-1 family (including the recently described member IL-185) and the IL-6 family of cytokines. These molecules...
Deleterious Effects of Inflammatory Mediators in Heart Failure

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have been referred to as proinflammatory cytokines, insofar as they were traditionally thought to be derived exclusively from the immune system and were therefore considered to be primarily responsible for mediating inflammatory responses in tissues. However, these inflammatory mediators are now known to be expressed by all nucleated cell types residing in the myocardium, including the cardiac myocyte, thus suggesting that these molecules may do more than simply orchestrate inflammatory responses in the heart.6 The interest in understanding the role of inflammatory mediators in heart failure arises from the observation that many aspects of the syndrome of heart failure can be explained by the known biological effects of proinflammatory cytokines (Table). That is, when expressed at sufficiently high concentrations, such as those that are observed in heart failure, cytokines are sufficient to mimic some aspects of the so-called heart failure phenotype, including (but not limited to) progressive left ventricular (LV) dysfunction, pulmonary edema, LV remodeling, metabolic acidosis, and cachexia.6,7 Regarding the potential mechanisms for the deleterious effects of TNF on LV function, the literature suggests that TNF modulates myocardial function through at least two different pathways: (1) an immediate pathway that is manifest within minutes and is mediated by activation of the neutral sphingomyelinase pathway15 and (2) a delayed pathway that requires hours to days to develop and is mediated by NO-mediated blunting of β-adrenergic signaling.6,17 Insofar as the basic cellular and molecular mechanisms that are responsible for the immediate and delayed negative inotropic effects of TNF have been reviewed recently in considerable detail, they will not be discussed further in the present review.16,19 Although both IL-1 and IL-6 have been shown to produce negative inotropic effects in various experimental models,20–22 the signal transduction pathways that are responsible for the negative inotropic effects of IL-6 have not been clearly established. In contrast, the negative inotropic effects of IL-1 appear to be mediated, at least in part, through the production of NO (ie, the delayed pathway).23,24 Recently, it has been suggested that TNF and IL-1 may produce negative inotropic effects indirectly through activation and/or release of IL-18, which is a recently described member of the IL-1 family of cytokines.25 Relevant to the present discussion is the observation that specific blockade of IL-18 using neutralizing IL-18 binding protein leads to an improvement in myocardial contractility in atrial tissue that has been subjected ischemia/reperfusion injury.5 Although the signaling pathways that are responsible for the IL-18–induced negative inotropic effects have not been delineated thus far, it is likely that they will overlap those for IL-1, given that the IL-18 receptor complex uses components of the IL-1 signaling chain.25

Effects of Cytokines on LV Function

The observation that proinflammatory cytokines are capable of modulating LV function was first reported in a series of important experimental studies showing that direct injections of TNF would produce hypotension, metabolic acidosis, hemoco­centration, and death within minutes, thus mimicking the cardio­chronicodynamic response seen during endotoxin-induced septic shock.11 Furthermore, injections of antibodies raised against TNF were subsequently shown to attenuate the hemodynamic collapse seen in endotoxin shock. Studies in dogs have shown that a single infusion of TNF results in abnormalities of systolic function within the first 24 hours of infusion.12,13 Experimental studies in rats have shown that circulating concentrations of TNF that overlap those observed in patients with heart failure are sufficient to produce persistent negative inotropic effects that are detectable at the level of the cardiac myocyte; moreover, the negative inotropic effects of TNF are completely reversible when the TNF infusion is stopped.7 Subsequent studies in transgenic mice with targeted overexpression of TNF in the cardiac compartment have shown that forced overexpression of TNF results in depressed LV ejection performance and that the depressed LV ejection performance was dependent on TNF "gene dosage."9,14

Effects of Proinflammatory Cytokines on LV Remodeling

The term LV remodeling has been used to describe the multitude of changes that occur in cardiac shape, size, and composition in response to myocardial injury. Inflammatory mediators have a number of important effects that may play an important role in the process of LV remodeling, including myocyte hypertrophy,26 alterations in fetal gene expression,9...
and progressive myocyte loss through apoptosis. In addition to the above effects, there are several lines of evidence suggesting that TNF may promote LV remodeling through alterations in the extracellular matrix. First, when concentrations of TNF that overlap those observed in patients with heart failure are infused continuously in rats, there is a time-dependent change in LV dimension that is accompanied by progressive degradation of the extracellular matrix. Moreover, similar findings have been reported after a single infusion of TNF in dogs. Second, recent studies in transgenic mice with targeted overexpression of TNF have shown that these mice develop progressive LV dilation. For example, Kubota et al showed that a transgenic mouse line that overexpressed TNF in the cardiac compartment developed progressive LV dilation over a 24-week period of observation (Figure 1). Similar findings have also been reported by Bryant et al and Sivasubramanian et al, who observed identical findings with respect to LV dysfunction and LV dilation in transgenic mice with targeted overexpression of tumor necrosis factor-α. Circ Res. 1997;81:627–635, by permission of the American Heart Association ©1997.}

### Figure 1
LV remodeling in a transgenic (TG) mouse model of TNF overexpression. Magnetic resonance images of the heart were obtained from 24-week-old TG mice with targeted TNF overexpression (A, B, and C) and an age-matched control (WT) mouse (D, E, and F). As shown, there was significant LV dilation in the animal harboring the TNF transgene in the cardiac compartment. Reproduced from Kubota T, McTiernan CF, Frye CS, Slawson SE, Lemster BH, Koretsky AP, Demetris AJ, Feldman AM. Dilated cardiomyopathy in transgenic mice with cardiac specific overexpression of tumor necrosis factor-α. Circ Res. 1997;81:627–635, by permission of the American Heart Association ©1997.

Together, these observations suggest that sustained myocardial inflammation provokes time-dependent changes in the balance between MMP activity and TIMP activity. That is, during the early stages of inflammation, there is an increase in the ratio of MMP activity to TIMP levels that fosters LV dilation. However, with chronic inflammatory signaling, there is a time-dependent increase in TIMP levels, with a resultant decrease in the ratio of MMP activity to TIMP activity and a subsequent increase in myocardial fibrillar collagen content. Although the molecular mechanisms that are responsible for the transition between excessive degradation and excessive synthesis of the extracellular matrix are not known, studies have been performed in experimental models of chronic injury/inflammation in an array of different organs, including liver, lung, and kidney, wherein an initial increase in MMP expression is superseded by increased TIMP expression and increased expression of a number of fibrogenic cytokines, most notably transforming growth factor-β. Thus, excessive activation of proinflammatory cytokines may contribute to LV remodeling through a variety of mechanisms, including increased MMP activity and decreased TIMP activity.
of different mechanisms that involve both the myocyte and nonmyocyte components of the myocardium.

**Effects of Proinflammatory Mediators on Endothelial Function**

In addition to the effects of inflammatory mediators on cardiac structure and function, there is growing evidence that the concentrations of inflammatory mediators that exist in heart failure are sufficient to contribute to endothelial dysfunction. The functional role of TNF in modulating endothelial function has been suggested in studies by Agnoletti et al., who have demonstrated that the serum of patients with heart failure induces apoptosis and downregulates endothelial constitutive NO synthase in human umbilical vein endothelial cells. The importance of TNF in their studies was suggested by experiments in which an anti-TNF antibody partially antagonized the effects of heart failure sera on endothelial cell apoptosis.

The role of TNF-induced endothelial dysfunction is further supported by studies by Anker et al., who have shown that circulating TNF levels are correlated significantly with the extent of peripheral skeletal muscle weakness/fatigue in patients with heart failure.

Finally, in a recent clinical study that used a soluble TNF antagonist (etanercept) to neutralize TNF, there was a short-term improvement in forearm mediated blood flow that was fully reversible after the cessation of therapy.

**Clinical Rationale for Studying Inflammatory Mediators in Heart Failure**

As noted at the outset, the interest in understanding the role of inflammatory mediators in heart failure arises from the observation that many aspects of the syndrome of heart failure can be explained by the known biological effects of proinflammatory cytokines (Table). A second rationale for studying inflammatory mediators in heart failure is that the pattern of expression of cytokines is very similar to that observed with the classic neurohormones (eg, angiotensin II and norepinephrine) that are believed to play an important role in disease progression in heart failure (see review).

That is, proinflammatory cytokines, including TNF, IL-1β, and IL-6, are expressed in direct relation to worsening NYHA functional classification. Moreover, the observation that a variety of redundant inflammatory mediators are activated in heart failure also has potential therapeutic implications for the types of antiinflammatory strategies that should be used in clinical trials. Insofar as proinflammatory cytokines were initially identified in patients with cardiac cachexia, there is a common misperception that these molecules are elaborated only in patients with end-stage heart failure. However, as reported in a number of studies and as shown in Figure 4, proinflammatory molecules are activated earlier in heart failure (ie, NYHA class II) than are the classic neurohormones, which tend to be activated in the latter stages of heart failure (ie, NYHA classes III and IV).

Another clinical similarity between both inflammatory mediators and classic neurohormones is that circulating levels of both families of molecules have prognostic importance in the setting of heart failure. As shown in Figure 5A, data from the multicenter Vesanarione Trial (VEST) have shown that there is a significant overall difference in survival as a function of increasing TNF levels, with the worst survival in patients with TNF levels >75th percentile. Similar findings have been observed with respect to the Kaplan-Meier analysis of circulating levels of IL-6 (Figure 5B). This analysis further showed that levels of soluble TNF receptor type 1 (sTNFR1) and soluble TNF receptor type 2 (sTNFR2) are highly predictive of adverse outcomes, consistent with prior reports...
5C and 5D). Indeed, a univariate Cox analysis of the VEST cytokine database has shown that TNF (P=0.01), IL-6 (P=0.0003), sTNFR1 (P=0.0001), and sTNFR2 (P=0.0001) are significant univariate predictors of mortality. Moreover, when the cytokine and/or cytokine receptor was separately entered into a multivariate Cox proportional hazards model that included age, sex, etiology of heart failure, NYHA class, ejection fraction, and serum sodium, TNF, IL-6, sTNFR1, and sTNFR2 remained significant independent predictors of mortality, along with NYHA class and ejection fraction.

A third rationale for studying the role of proinflammatory mediators in the setting of heart failure stems from the growing evidence that there are critical interactions between inflammatory mediators and the mediators of the classic neurohormonal systems. Indeed, over the past two decades, our perception of the role of angiotensin II in the cardiovascular system has changed dramatically. Whereas angiotensin II has been traditionally viewed as a circulating neurohormone that stimulated the constriction of vascular smooth muscle cells, aldosterone release from the adrenal gland, sodium reabsorption in the renal tubule, and/or as a stimulus for growth of cardiac myocytes or fibroblasts, it is becoming increasing apparent that angiotensin II provokes inflammatory responses in a variety of different tissues and cell and tissue types. Mechanistically, angiotensin II activates a redox-sensitive transcription factor, termed nuclear factor-κB, that is critical for initiating the coordinated expression of classic components of the myocardial inflammatory response, including increased expression of proinflammatory cytokines, NO, chemokines, and cell adhesion molecules. Moreover, recent experimental studies have shown that pathophysiologically relevant concentrations of angiotensin II are sufficient to provoke TNF mRNA and protein synthesis in the adult heart through a nuclear factor-κB–dependent pathway and that ACE inhibitors decrease the short-term expression of inflammatory mediators in the heart in a chronic infarct model. Finally, clinical studies that have examined long-term administration of ACE inhibitors or angiotensin receptor blockers have shown that whereas ACE inhibitors have mixed results in terms of inhibiting proinflammatory cytokines, angiotensin type 1 receptor antagonists have consistently led to significant decreases in circulating levels of inflammatory mediators (TNF) and cell adhesion molecules (intercellular adhesion molecule-1 and vascular adhesion molecule-1) in patients with heart failure. Similarly, findings have recently been reported for the use of β-adrenergic–blocking agents in experimental and clinical heart failure studies. That is, β-adrenergic blockade with a β₁-selective adrenergic antagonist has been shown to prevent the expression of proinflammatory mediators in an experimental model of postinfarct LV remodeling. In a subset analysis of the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), treatment with metoprolol did not lead to a decrease in the level of proinflammatory mediators, whereas in a different study, the use of a nonselective β₁,₂-adrenergic antagonist with ancillary antioxidant properties (carvedilol) resulted in a significant reduction in the transcadiac production of TNF in a small number of patients. It remains unclear whether the differences in these two studies are related to the differences in selective versus nonselective β-adrenergic blockade, differences in ancillary properties between metoprolol and carvedilol, differences in the degree of ACE inhibition in the two studies, or a sample bias. Nonetheless, the aggregate data suggest that there are important interactions between the renin-angiotensin/angiotensin II and proinflammatory cytokines; moreover, there is increasing evidence that many of the conventional therapies for heart failure may work, at least in part, through the modulation of proinflammatory cytokines.

Inflammatory Mediators as Therapeutic Targets in Heart Failure

The rationale for using antiinflammatory strategies in patients with heart failure is 3-fold: first, as noted above, the excessive elaboration of proinflammatory cytokines appears to mimic many aspects of the heart failure phenotype; second, many of
the deleterious effects of inflammatory mediators are potentially reversible once inflammation subsides; and third, heart failure remains a progressive disease process despite optimal therapy with ACE inhibitors and β-blockers. As shown in Figure 6, the biological effects of proinflammatory mediators can be antagonized through transcriptional or translational approaches or by so-called biological response modifiers, which bind and/or neutralize soluble mediators (eg, TNF or IL-1β). In addition, there are several novel “immunomodulatory strategies” that alter the levels of inflammatory mediators through multiple mechanisms. The clinical studies that have attempted to suppress proinflammatory cytokine production in patients with heart failure using transcriptional and/or translational approaches have been discussed in detail in several recent reviews and will be discussed only briefly in the present review. Accordingly, the remaining part of the present review will focus on the recent series of clinical trials that have used targeted approaches that antagonize TNF as well as the studies that have used immunomodulatory therapies that decrease the levels of inflammatory mediators.

Transcriptional and/or Translational Approaches

Both pentoxifylline and thalidomide have been used successfully in small studies involving patients with moderate to advanced heart failure. As shown in Figure 6, both of these agents are believed to affect the synthesis of inflammatory mediators by blocking their transcriptional activation. Sliwa et al studied the effects of pentoxifylline in patients with dilated cardiomyopathy and NYHA class II and III heart failure.

A total of 14 patients received pentoxifylline three times daily at a dose of 400 mg, and an equal number received placebo. The primary end points of the 6-month study were NYHA functional class and LV function. Four patients died as a result of progressive pump dysfunction during the 6-month study period, all in the placebo group. At the end of 6 months, there was an improvement in functional class in the pentoxifylline group, whereas there was functional deterioration in the placebo group. In addition, there was a significant increase in the ejection fraction in the pentoxifylline group, whereas there was no significant change in the placebo group. An important observation was that TNF levels fell significantly in the pentoxifylline group, whereas there was no significant change in the TNF levels in the placebo group. Preliminary reports from an open-label study in a small number of patients have also shown that treatment with thalidomide leads to a significant improvement in 6-minute walking distance and a trend toward a significant improvement in the quality of life and LV ejection performance. The effects of thalidomide are currently being tested in a larger ongoing clinical trial in Europe.

Targeted Anticytokine Approaches Using Biological Response Modifiers

Two different targeted approaches have been taken to selectively antagonize proinflammatory cytokines in heart failure patients. In the first approach, investigators have used recombinant human TNF receptors that act as “decays” to bind TNF, thereby preventing TNF from binding to TNF receptors on cell surface membranes of target cells. The second approach is to use monoclonal antibodies to bind and neutralize circulating cytokines.

Soluble TNF Receptors

Etanercept (Enbrel) is a genetically engineered, dimerized, fusion protein composed of two TNF p75 receptors and an IgG1:Fc portion. On the basis of early preclinical studies showing that etanercept was sufficient to reverse the deleterious negative inotropic effects of TNF in vitro and in vivo, a series of phase I clinical studies was performed in patients with moderate to advanced heart failure. These early short-term studies in small numbers of patients showed improvements in quality of life, 6-minute walking distance, and LV ejection performance after treatment with etanercept for up to 3 months. After this, two multicenter clinical trials using
etanercept were initiated in patients with NYHA class II to IV heart failure. The trial in North America, entitled Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE, n=900), and the trial in Europe and Australia, entitled Research into Etanercept Cytokine Antagonism in Ventricular Dysfunction (RECOVER, n=900), were both quality-of-life trials that used a clinical composite as the primary end point. The clinical composite score classifies patients as better, worse, or the same after a clinical intervention, on the basis of the patient’s and the physician’s assessment at the end of the study.64 Both trials had parallel study designs but differed in the doses of etanercept that were used in the two studies: RENAISSANCE used doses of 25 mg twice a week (biw) and 25 mg three times a week (tiw), whereas RECOVER used doses of 25 mg once a week (qw) and 25 mg biw. A third trial that used the pooled data from the RENAISSANCE (biw and tiw dosing) and RECOVER (biw dosing only), termed Randomized Etanercept Worldwide Evaluation (RENEWAL, n=1500), had a primary end point of all-cause mortality and hospitalization for heart failure as the a primary end point. On the basis of prespecified stopping rules, the trials were stopped early after the Data Monitoring Safety Board deemed that it was unlikely that the trials would show benefit on the primary end points if the two trials were allowed to go to completion.65 Preliminary analysis of the data showed no benefit for etanercept on the clinical composite end point in RENAISSANCE and RECOVER nor a benefit for etanercept on all-cause mortality and heart failure hospitalization in RENEWAL.66a However, in a post hoc analysis of hazard ratios for death/worsening heart failure, patients taking the biw dose of etanercept appeared to fare slightly better than patients taking the qw dose of etanercept in RECOVER, with hazard ratios for death/heart failure hospitalization of 0.87 and 1.01, respectively. In contrast, RENAISSANCE patients receiving biw etanercept experienced a 1.21 risk of death/heart failure hospitalization compared with the risk in patients receiving placebo, whereas patients receiving the tiw dose had a slightly worse hazard ratio of 1.23. These disparities in trial findings are likely related to the different length of follow-up in the two trials. Patients in RECOVER received etanercept for a median time of 5.7 months, whereas patients in RENAISSANCE received etanercept for 12.7 months. It bears emphasis that these studies were stopped prematurely; had they been allowed to continue to completion, the hazard ratios may have been worse. 

On the basis of these findings, the prescribing information for infliximab in rheumatoid arthritis and Crohn’s disease now cautions against its use in patients with heart failure.

**Monoclonal Antibodies**

A second targeted approach that has been tried in clinical heart failure trials is the use monoclonal antibodies directed against a particular cytokine. Infliximab (Remicade) is a chimeric monoclonal antibody consisting of a genetically engineered murine Fab fragment (that binds human TNF) fused to a human FC portion of human IgG1. Although infliximab had been shown to be effective in Crohn’s disease and rheumatoid arthritis, there are no published preclinical nor phase I safety studies to support the use of this specific agent in heart failure. The Anti-TNFα Therapy Against CHF (ATTACH) was a phase II study in 150 patients with moderate to advanced heart failure. The primary end point of the ATTACH trial was the clinical composite score described above.64 Patients were randomized to receive three separate intravenous infusions of infliximab (5 or 10 mg/kg) at baseline and at 2 and 4 weeks, followed by an assessment of the clinical composite at 14 and 28 weeks. Analysis of the completed trial data showed that there was a dose-related increase in death and heart failure hospitalizations with infliximab compared with placebo at 14 weeks (21% increase) and at 28 weeks (26% increase). By 38 weeks of follow-up, 9 infliximab patients had died (2 in the 5 mg/kg group and 7 in the 10 mg/kg group) compared with just one death in the placebo group.64b On the basis of these findings, the prescribing information for infliximab in rheumatoid arthritis and Crohn’s disease now cautions against its use in patients with heart failure.

**Why Have Targeted Anti-TNF Therapies Failed in Heart Failure Trials?**

Given the wealth of preclinical data and early clinical studies that have suggested a role for TNF antagonism in heart failure, the negative results of the clinical trials have been discouraging. This statement notwithstanding, analysis of the aggregate clinical trial data permits some insight into why these studies have been negative. It is important to recognize that neither the trials with etanercept nor the trial with infliximab was neutral (ie, no effect). Instead what was consistently observed in both trials was a dose- and time-dependent worsening of heart failure and/or worsening outcomes. Although one can never exclude “play of chance” as a plausible explanation for the worsening clinical outcomes in both trials, the dose- and time-dependent effects that were observed in both trials argue against this possibility. However, there are two explanations that warrant further discussion. The first is that the biological agents that were used in the trials had intrinsic toxicity, and the second is that TNF antagonism has untoward effects in the setting of heart failure. Regarding the first explanation, it bears emphasis that infliximab exerts its effects, at least in part, by fixing complement in cells that express TNF on the membrane. As shown in Figure 7A, infliximab is directly cytotoxic to cells expressing TNF on the membrane. Whereas this type of biological action is beneficial in eliminating activated T cells that have invaded the gastrointestinal mucosa of patients with Crohn’s disease, it is likely to be overtly deleterious in the setting of heart failure. Regarding the second explanation, it bears emphasis that infliximab exerts its effects, at least in part, by fixing complement in cells that express TNF on the membrane. As shown in Figure 7A, infliximab is directly cytotoxic to cells expressing TNF on the membrane. Whereas this type of biological action is beneficial in eliminating activated T cells that have invaded the gastrointestinal mucosa of patients with Crohn’s disease, it is likely to be overtly deleterious in the setting of heart failure. Regarding the first explanation, it bears emphasis that infliximab exerts its effects, at least in part, by fixing complement in cells that express TNF on the membrane. As shown in Figure 7A, infliximab is directly cytotoxic to cells expressing TNF on the membrane. Whereas this type of biological action is beneficial in eliminating activated T cells that have invaded the gastrointestinal mucosa of patients with Crohn’s disease, it is likely to be overtly deleterious in the setting of heart failure. Regarding the second explanation, it bears emphasis that infliximab exerts its effects, at least in part, by fixing complement in cells that express TNF on the membrane. As shown in Figure 7A, infliximab is directly cytotoxic to cells expressing TNF on the membrane. Whereas this type of biological action is beneficial in eliminating activated T cells that have invaded the gastrointestinal mucosa of patients with Crohn’s disease, it is likely to be overtly deleterious in the setting of heart failure.
complexe d’anti-TNF-α monoclonal antibody cA2 binds recombinant transmembrane TNF-α and activates immune effector functions. Cytokine. 1995;7:251–259, by permission of the International Cytokine Society ©1995. B, Etanercept increases the levels of immunoreactive TNF in the peripheral circulation of human subjects after intravenous endotoxin administration. As shown, high-dose etanercept (60 mg/m²) increased immunoreactive TNF levels more than low-dose etanercept (10 mg/m²). Modified from Suffredini AF, Reda D, Banks SM, Tropea M, Agosti JM, Miller R. Effects of recombinant dimeric etanercept on human inflammatory responses following intravenous endotoxin administration. J Immunol. 1995;155:5038–5045, by permission of the American Association of Immunologists ©1995. C, Kinetic analysis of TNF binding to etanercept using surface plasmon resonance biosensor technology (BIAcore assay)69 is shown. Etanercept was exposed to 1000, 500, 250, 125, 62.5, 31.25, 16.63, 3.90, and 1.95 nmol/L TNF, and the kinetics of TNF binding were determined by the decay of the light signal after peak binding to etanercept. The off rate of TNF from etanercept was determined to be 620 ms. Reproduced from Frishman JI, Edwards CK III, Sonnenberg MG, Kohno T, Cohen AM, Dinarello CA. Tumor necrosis factor (TNF)-α-induced interleukin-8 in human blood cultures discriminates neutralization by the p55 and p75 TNF soluble receptors. J Infect Dis. 2000;182:1722–1730, by permission of the Infectious Diseases Society of America ©2000. D, Etanercept increases TNF bioactivity. Animals were inoculated with bacteria, and levels of TNF bioactivity were measured at the indicated time points. TNF bioactivity peaked at 90 minutes after bacterial inoculation but was undetectable at later time points. Mice treated with etanercept after bacterial inoculation showed a significant reduction in the level of peak TNF bioactivity; however, as shown, TNF bioactivity was significantly prolonged by etanercept. Mice that received etanercept after bacterial inoculation followed by an anti-TNF neutralizing antibody (TN3) had a shorter duration of TNF bioactivity. The arrow indicates the timing of the administration of the neutralizing anti-TNF antibody.65 Modified from Evans TJ, Moyes D, Carpenter A, Martin R, Loetscher H, Lesslauer W, Cohen J. Protective effect of 55- but not 75-kD soluble tumor necrosis factor receptor-immunoglobulin G fusion proteins in an animal model of gram-negative sepsis. J Exp Med. 1994;180:2173–2179, by permission of the Rockefeller University Press ©1994.

A second explanation for worsening heart failure in the clinical trials is that TNF antagonism has deleterious effects in the setting of heart failure. Several experimental studies have suggested that physiological levels of TNF confer cytoprotective responses in the heart during acute ischemic injury.72–74 Moreover, low physiological levels are likely to play an important role in tissue remodeling and repair. Thus, one potential explanation for the worsening heart failure observed in the targeted anti-TNF trials (albeit speculative) is that our current targeted attempts to antagonize TNF result in the loss of one or more of the beneficial effects of TNF and that this loss of homeostasis results in worsening of heart failure. Indeed, in our overly simplistic view of heart failure, we tend to view molecules in absolute terms as having either “good” or “bad” effects, with little or no consideration given to the potential for concurrent offsetting biological effects. However, in many instances, molecules such as TNF exert a spectrum of pleiotropic effects in the failing heart: some beneficial and some potentially deleterious. Accordingly, TNF antagonism might be expected to attenuate both the deleterious and beneficial effects of TNF. The observation that TNF antagonism provides short-term beneficial effects in heart failure patients62,63 and yet results in worsening heart failure when used chronically is entirely consistent with this point of view.

**Immunomodulatory Strategies**

An alternative approach to targeting specific components of the inflammatory cascade is to use approaches that result in a decrease in the systemic inflammatory response. Thus far, two different approaches have been used in heart failure studies: intravenous immunoglobulin (IVIG) and "immune modulation therapy."
Intravenous Immunoglobulin
Therapy with IVIG has been tried in a wide range of immune-mediated disorders, such as Kawasaki’s syndrome, dermatomyositis, and multiple sclerosis. Although the exact mechanism of action of IVIG is not known, a number of different mechanisms have been proposed, including Fc receptor blockade, neutralization of autoantibodies, modulation of cytokine activity, and activation of an inhibitory Fc receptor. On the basis of an initial report that IVIG was beneficial in acute cardiomyopathy,76 Gullesstall77 conducted a double-blind trial with IVIG for 26 weeks in 47 patients with moderate heart failure who were receiving conventional therapy for heart failure, including ACE inhibitors and β-blockers. They observed that compared with placebo, IVIG induced a marked rise in plasma levels of the antiinflammatory mediators (IL-10 and IL-1 receptor antagonist) and that these changes were accompanied by a significant increase in LV ejection performance by $\approx 10\%$ and a decrease in N-terminal proatrial natriuretic peptide levels.77 Thus, in that small study, immunomodulatory therapy with IVIG was effective in patients with heart failure.

Immune Modulation Therapy
Immune modulation therapy uses a medical device (the VC7000 Blood Treatment System, Vasogen Inc) to expose a sample of blood to a combination of physiochemical stressors ex vivo. The treated blood sample is then administered intramuscularly along with local anesthetic into the same patient from whom the autologous blood sample is obtained. The physiochemical stresses to which the autologous blood sample is subjected are known to initiate or facilitate apoptotic cell death. The uptake of apoptotic cells by macrophages results in a down-regulation of proinflammatory cytokines, including TNF, IL-1β, and IL-8, and an increase in production of the antiinflammatory cytokines, including transforming growth factor-β and IL-10.78,79 Recent studies have shown that immune modulation therapy leads to a decrease in the production of proinflammatory cytokines and a corresponding increase in antiinflammatory cytokines in human subjects.80 Given that an imbalance exists between proinflammatory and antiinflammatory cytokines in patients with heart failure,89 immune modulation therapy may restore this balance more toward normal. In a recent trial using immune modulation therapy in 73 patients with moderate heart failure, the investigators noted that compared with the placebo group, the group receiving immune modulation therapy experienced significantly fewer hospitalizations (24 versus 41) and deaths (1 versus 7). The decrease in event rate in the treatment arm was also supported by improvements in quality of life and NYHA clinical classification.81,82 Based on the encouraging results of this pilot trial, a larger pivotal trial involving immune modulation therapy is being planned.

Inflammatory Mediators and the Failing Heart: Past, Present, and the Foreseeable Future
In the present review, we have focused on the recent clinical and experimental evidence suggesting that inflammatory mediators play a role in disease progression in heart failure by virtue of the direct toxic effects that these molecules exert on the heart and the peripheral circulation. Indeed, pathophysiologically relevant concentrations of these molecules mimic many aspects of the so-called heart failure phenotype in experimental animals, including LV dysfunction, LV dilation, activation of fetal gene expression, cardiac myocyte hypertrophy, and cardiac myocyte apoptosis (Table). Thus, analogous to the proposed role for neurohormones in heart failure, inflammatory mediators represent another distinct class of biologically active molecules that may contribute to the progression of heart failure. Nonetheless, the early attempts to translate this information to the bedside not only have been disappointing but also have led to worsening heart failure in many instances. Although one interpretation of these findings is that inflammatory mediators are not viable targets in heart failure, according to the arguments delineated above, the countervailing point of view is that we simply have not targeted proinflammatory mediators with agents that can be used safely in the context of heart failure or that targeting a single component of the inflammatory cascade is not sufficient in a disease as complex as heart failure. This latter statement notwithstanding, it should also be recognized that in the wake of the current success with β-blockers, no recent clinical trials have been able to improve on conventional therapy for heart failure. Accordingly, we may have reached a therapeutic ceiling for the so-called neurohormonal approaches for treating heart failure. This having been said, is there a foreseeable future for antiinflammatory strategies in heart failure? Despite the inauspicious beginning with targeted antiinflammatory approaches, strategies that use small molecules that have a broad spectrum of antiinflammatory properties (eg, pentoxifylline, thalidomide [or its analogues], and statins) and immunomodulatory strategies that activate antiinflammatory pathways (eg, immune modulation therapy) are currently being evaluated. As with all therapeutic approaches in heart failure, the only way to really answer the question of whether broader spectrum antiinflammatory strategies will have any added value in heart failure, aside from the empiric hand-waving of a few pundits and prophets, is through well-designed clinical trials.

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