The Cytokines and Heart Failure-A Review

A Jahan[1], M Ullah[2]

[1]Department of Cardiology, Z.H. Sikder Womens Medical College and Hospital, Dhaka. [2]Department of Cardiology, NICVD, Dhaka.

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Abstract:

Heart Failure (HF) develops in several stages - the first stage is some disorder that places a hemodynamic burden on the myocardium or causes myocardial injury. The second stage is that of cardiac compensation, which involves neurohormonal activation to preserve cardiac output and tissue perfusion. And the final stage is the progression of HF, which is complex and is the result of the harmful effects of the compensatory mechanisms of the second stage; an immune-system activation manifested by increases in inflammatory cytokines, including tissue necrosis factor–alpha (TNF-á), soluble receptors of TNF-á (sTNFR1 and 2), interleukin (IL)-1, IL-6 and IL-10, and C-reactive protein (CRP). It has recently been recognized that elevated circulating levels of various proinflammatory cytokines (TNF- á, IL-1, IL-6) leading to free radical overproduction, as well as to cardiac myocyte and endothelial cell apoptosis, play a significant role in the pathophysiology of CHF. The extracellular domains of proinflammatory cytokine receptors (sTNFR1, sTNFR2 and sIL-6R) are also elevated in CHF and provide more complete information on cytokine activation in this syndrome. This article reviews the contribution of inflammatory cytokines in the disease progression in patients with heart failure, their diagnostic as well as prognostic values and possibly therapeutic interventions on these biologic active molecules.

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Introduction:

Congestive HF and its sequelae is a terminal pathway of myocardial injury from different causes sustained by multiple mediators.[1-5] Despite repeated attempts to develop a unifying hypothesis that explains the clinical syndrome of heart failure, no single conceptual paradigm has withstood the test of time. Clinicians viewed HF initially as a problem of excessive salt and water retention that was caused by abnormalities of renal blood flow called the cardiorenal model for HF. As physicians began to perform careful haemodynamic measurements, it became apparent that HF was associated with a reduced cardiac output and excessive peripheral vasoconstriction that led to the development of the cardiocirculatory or hemodynamic model for heart failure, wherein heart failure was thought as a result of abnormalities of the pumping capacity of the heart. Although both of these models for heart failure explained the excessive salt and water retention that HF patients experience, neither of these explained the relentless disease progression that occurs in this syndrome. The important insight that HF was also a progressive disorder and not simply a disorder of excessive salt and water retention led to the development of the neurohormonal model for HF, in which the elaboration of neurohormones was considered to lead not only to salt and water retention, but also to disease progression through progressive left ventricular remodeling and dysfunction.[6]

Later it has become evident that another class of biologically active molecules, generically referred to as cytokines, are also overexpressed in HF.[1,7,8,9] Over the past several years, there has been an increasing appreciation that overexpression of proinflammatory cytokines play an important role in the pathogenesis of heart failure and cytokines such as TNF-α , IL-1, IL-6, IL-10 represent another class of biologically active molecules that are responsible for the development and progression of heart failure.[2,10,11] Proinflammatory cytokines, such as TNF- α and IL-6 are capable of modulating cardiac and peripheral vascular functions by a variety of mechanisms including abnormal regulation of nitric oxide synthase expression,

Address for correspondence: Dr Afreed Jahan, Department of Cardiology, Z.H. Sikder Womens Medical College and Hospital, Gulshan branch, Dhaka, Bangladesh. e-mail: afreedjahan@gmail.com

overproduction of oxygen free radicals, and induction of cardiac myocyte and endothelial cell apoptosis.[12,13, 14] It has also been reported that circulating apoptosis mediators, such as soluble Fas (sFas) and soluble Fas ligand (sFasL), are elevated in CHF and correlated well with the severity of symptoms and prognosis of patients with heart failure.[15,16,17] Recent interest has arisen in the prognostic capability of the novel interleukin-1 receptor family member ST2 in patients suspected of having heart failure.[18,19,20] Immune activation is well established in patients with chronic heart failure and reduced ejection fraction and is associated with an impaired prognosis. Patients with HF and preserved ejection fraction have an impaired prognosis as well.[11] Therapy blocking some of these cytokines in patients with HF may achive improvement in disease progression and prognosis.

Cytokines, cytokine receptors and the heart

Cytokines are a group of small proteins and polypeptides produced and secreted throughout the body. They are involved in immune function, inflammation, tissue repair, cell growth, and normal physiologic processes such as sleep regulation. Altered cytokine expression often signifies emergence of a symptom or disease. Although cytokines usually act locally in a paracrine manner, affecting adjacent cells, they may also act intracellularly, travel distally through circulation in an endocrine fashion, or act within the same cell after release. As a common rule, cytokines have either proinflammatory or antiinflammatory properties. However, they cannot be clearly divided into distinct categories because their effects often overlap.[21]

The cytokines interleukin (IL)-1, IL-2, IL-12; tumor-necrosis factor (TNF)-α and interferon (IFN)-α are generally considered proinflammatory, whereas IL-4 and IL-10 are typically antiinflammatory. Transforming growth factor (TGF)-β is unique because when secreted early in immune response, it appears to evoke anti-inflammatory characteristics, but once disease is established, it leads to progressive organ fibrosis.[21,22] Transforming growth factor-β is implicated as an important proinflammatory mediator in cardiac remodeling and heart failure after myocardial infarct.[23] Another marker of inflammation is C-reactive protein, a major component of the acute-phase response. The cytokine IL-6 seems to be involved in regulating this acute-phase process and has numerous functions in the body, many of which are proinflammatory.[23] In addition, the chemokines and cell adhesion molecules—such as monocyte chemotactic protein-1, vascular cell adhesion molecule, endothelial leukocyte adhesion molecule, intracellular adhesion molecule, and the selectins—represent other relevant indicators of inflammation. These molecules are critical in attracting and adhering circulating leukocytes to the inflammation site, and they may play a pivotal role in starting the inflammatory process.[23,24]

Many aspects of congestive heart failure can be explained by the known biologic effects of the pro-inflammatory cytokines. When expressed at sufficiently high concentrations, cytokines mimic some aspects of the so-called heart failure phenotype. Data from experimental and clinical investigations suggested that the potential untoward effects of proinflammatory cytokines in heart failure include the following:[7,25,26,27]

- Left ventricular dysfunction.
- Pulmonary edema.
- Cardiomyopathy.
- Reduced leg blood flow.
- Abnormalities in myocardial metabolism.
- Anorexia and cachexia.
- Beta-receptor uncoupling from adenylate cyclase.
- Abnormalities of mitochondrial energetics
- Activation of the fetal gene program.

Thus the elaboration of cytokines, similar to the elaboration of neurohormones, may represent a biochemical mechanism that is responsible for producing symptoms in patients with heart failure.

To understand how cytokines play a role in HF, it is important to delineate the concept of cytokine bioactivity. When interpreting the biologic activity of any cytokine, it is critically important to know the concentration of the cytokine that one is measuring, the concentration of the receptors on which the cytokine is acting as well as the presence or absence of any circulating antagonists for the particular cytokine of interest.

The effects of cytokines are initiated by the binding of these low-molecular weight proteins to specific receptors that exist on the membranes of most mammalian cell types, including the adult cardiac myocyte. For TNF-α, there are two subtypes of TNF receptors : type I or a lower-affinity receptor (TNFR1 or TNF-β) and type 2 or higher-affinity (TNFR2 or TNF-α) receptor, which have been immunolocalized to the adult human cardiac myocyte, thus providing a potent signaling pathway for the negative inotropic effects of TNF- α.[28]

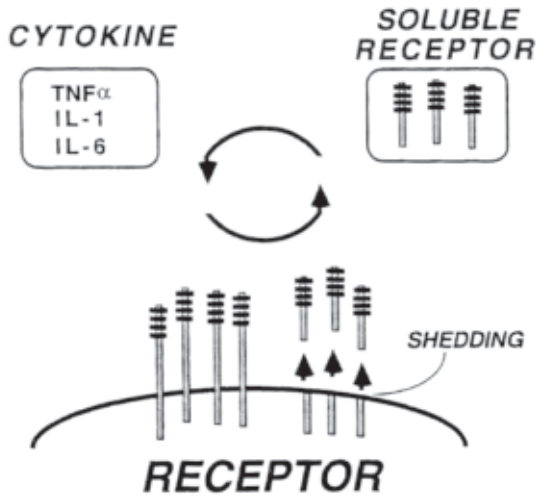

Fig.-1: *Cytokine bioactivity*[29]

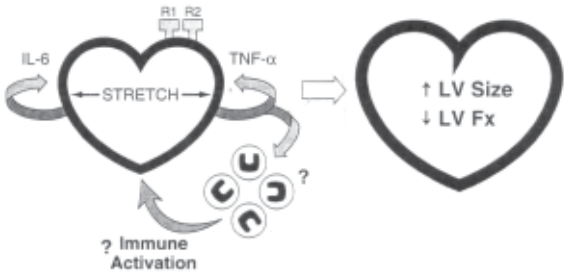

Fig.-2: *Model for cytokine overexpression in HF*[29]

The biology of TNF receptors is that mammalian cells appear to shed TNF receptors (Fig.1) after a variety of different stimuli, including exposure to TNF-α. Once the type 1 (TNFR1) and type 2 (TNFR2) TNF receptors are proteolytically cleaved from the cell membrane, they exist in the circulation as circulating soluble receptors (referred to as sTNFR1 and sTNFR2).[29] It has been suggested that they serve as biologic buffers, which are capable of rapidly neutralizing the highly cytotoxic activities of TNF-α. It has been shown that sTNFRs are sufficient both to block and to reverse the negative inotropic effects of TNF-α.[30]

Studies have shown that all mammalian species express two related Interleukin-1 genes, IL-1α and IL-1 β, which mediate systemic immune responses as well as the production of inflammatory responses via production of prostaglandins. The cross-linking studies have suggested the presence of a high-affinity and higher-affinity receptor, each coded for by a single gene product. The high affinity p80 IL-1R receptor is a surface glycoprotein, termed IL-1Rt1, and is a member of the immunoglobulin superfamily. The higher-affinity p68 IL-1R protein is termed IL-1RtII. There is a descrete inhibitor for the IL-1 receptor called IL-1 receptor antagonist (IL-1ra), which competes with IL-1 for binding to its receptor and thus can attenuate the effects of IL-1.[31,32] ST2, an interleukin-1 receptor homologue, induced by proinflammatory stimuli, is the soluble isoform of the ST2 protein, a member of the interleukin (IL)-1 receptor superfamily.[30]

Increased levels of IL-6 are expressed after acute myocardial infarction[33-35] and clinical heart failure.[36,37] The human IL-6 receptor is a glycoprotein with a molecular mass of 80 kD. In contrast to the receptors for IL-1 and TNF- á, the cytoplasmic domain of IL-6 is not necessary for intracellular signaling to occur. IL-6 receptor (IL-6R) system is composed of two functional chains: an 80-kD IL-6 binding protein, termed IL-6R and a 130-kD docking protein, termed gp130, which transmits the intracellular signal.

Site and source of Cytokines in heart failure

The heart is capable of elaborating proinflammatory cytokines such as TNF-α, IL-1, IL-6 and IL-10 in response to a variety forms of environmental injury. There are at least three hypotheses with respect to the source of production for cytokines in HF: the first hypothesis is that activation of the immune system is responsible for cytokine elaboration in response to some form of tissue injury or some stimulus to the immune system[38]; the second hypothesis is that proinflammatory cytokines are elaborated by the heart under certain forms of stress and that elevated levels of TNF-α represent spillover of

cytokines that were produced locally within the myocardium; the third hypothesis is that the elaboration of TNF-α is the result of underperfusion of systemic tissues.

Several lines of evidence support the immune system as an important source for cytokine production in heart failure. First, studies have repeatedly demonstrated abnormalities of both cellular and humoral immunity in HF.[39] Second, the monocyte has traditionally been held to be a major source for cytokine production.[40] Third, it has been shown that neopterin levels (a marker of monocyte activation) are elevated in patients with advanced HF.[41] Nonetheless, TNF-α itself can stimulate monocytes to produce neopterin. An alternative hypothesis for the source of inflammatory cytokine production is that the failing heart itself is the source for TNF-á production in HF. It has been shown that the adult cardiac myocyte is capable of expressing TNF-á after hemodynamic overloading or myocardial stretch or both. Local myocardial production of TNF-á becomes, along with neurotransmitter-derived norepinephrine, autocrine or paracrine produced endothelin, and hormonally or cytokine derived angiotensin II, a serious candidate for mediation of the progression in myocardial dysfunction and remodeling that is part of the natural history of chronic heart failure. Proinflammatory cytokines produced by the heart in response to a superimposed stress might spillover in the peripheral circulation and directly activate the immune system by upregulating cell adhesion molecules as well as by directly stimulating peripheral blood mononuclear cells to synthesize proinflammatory cytokines. Both increased cell adhesion molecules and immune cell activation amplify cytokine production in the peripheral circulation.[42]

A third hypothesis for the elaboration of TNF-α in HF is that a decreased cardiac output in heart failure leads to the elaboration of TNF-α by underperfused metabolic tissues. It is known that pharmacologic agents that elevate cyclic AMP, such as pentoxifylline and amrinone, suppress cytokine production.[43,44] Elevated levels of TNF-α in HF reflect increased cytokine biosynthesis. Increased cytokine levels may result from altered distribution, degradation or clearance of these molecules from the plasma.[45] The persistently elevated levels of TNF-α in patients with HF explains that once TNF-α is elaborated, this homotrimeric protein becomes bound and stabilized by sTNFR1 and sTNFR2 (which can increase three to four fold in patients with heart failure). Bound TNF-α is less likely to dissociate into active monomers that are biologically inactive. Thus sTNFRs act as a reservoir for trapping and slowly releasing biologically active TNF-α into the circulation.[16]

The role of cytokines, cytokine receptors in heart failure

The cytokine hypothesis for heart failure suggests that HF progresses because cytokine cascades that are activated after myocardial injury exert deleterious effects on the heart and circulation. TNF-α and IL-6 become activated after left ventricular injury or myocardial stretch (Fig. 2). These stress-activated cytokines can exert autocrine/paracrine effects within the myocardium by binding to specific cytokine receptors. If cytokine expression is excessive, however, these molecules may produce left ventricular dysfunction and dilatation. Cytokines may also spillover into the circulation when overproduced and lead to secondary activation of the immune system, which is then capable of amplifying cytokine signal in the periphery.[46] Clinical data suggest that TNF-α and IL-6 constitute the major portfolio of stress-activated cytokines that are elaborated in the setting of HF. TNF-α may produce myocardial depression through a direct effect on calcium handling and/or through nitric oxide production.[28]

TNF-α. Elevated levels of TNF-α have consistently been identified in patients with advanced heart failure. Levine et al, in an attempt to identify factors responsible for cardiac cachexia, first reported that TNF-α (also known as cachectin) levels were elevated in chronic heart failure.[47] TNF-α can increase protein catabolism causing weight loss in end stage HF patients.[48] Several studies suggest that there is increasing cytokine elaboration in direct relation to the severity of the disease process. [4,36,46,49,50,] As shown in Fig.3, there is a progressive increase in TNF-α levels in dirtect relation to deteriorating NYHA functional class. [50]

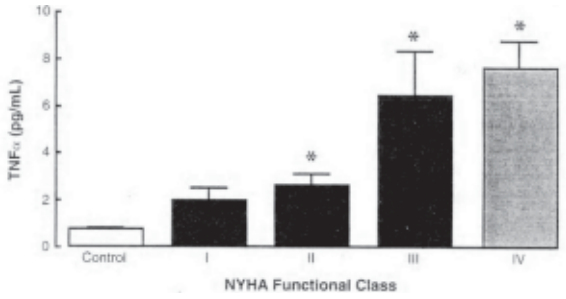

Fig.-3: *TNF-á levels in patients with class I-IV HF*[47]
Figure 4. Relation between TNF-á and LVEF[47]

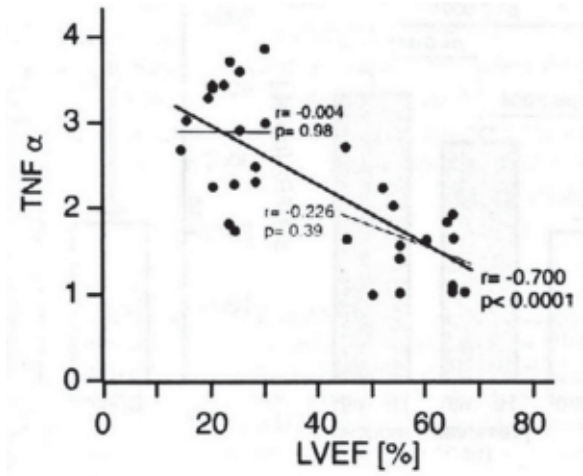

Fig.-4: *Relation between TNF-a LVEF47*

In analysis of cytokine levels in the Studies of Left Ventricular Dysfunction (SOLVD) database, there was a trend (P=0.07) toward increasing mortality with increasing levels of TNF- α and survival.[47] There is excellent evidence for the increase in immune activation and proinflammatory cytokines in patients with heart failure and decreased systolic function[1]. These cytokines contribute to the central and peripheral manifestations of HF and lead to the progression of heart failure.[1, 2] They are also predictors of short and long-term prognosis of patients with HF.[3,4] In the study Niethammera et al, in patients with stable HF compared a group of decreased systolic function (HF-S) , preserved ejection fraction (or diastolic dysfunction [HF-D]) and normal controls found that the proinflammatory cytokines are all elevated in HF-S compared with controls, with intermediate increases in patients with HF-D (Fig. 6 and 7).

There was a negative correlation between TNF-α and LVEF (Fig.4). In patients with HF-D, TNF-α as well as sTNFR1 and sTNFR2 were also elevated (Fig.5). It appears that HF-D with its raised proinflammatory cytokines may be a precursor of the later stage of HF-S. Thus patients with HF and preserved EF showing signs of systemic-immune activation may contribute to the impaired prognosis and the progression to HF with reduced EF.[11]

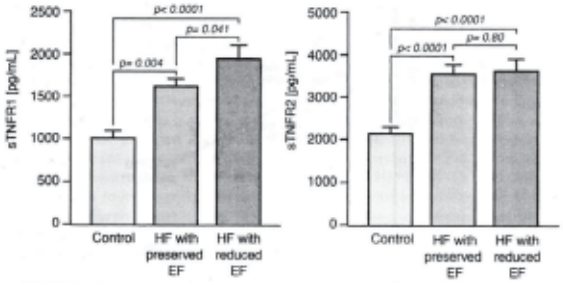

Fig.-5: *Serum TNFR1 and TNFR2 concentrations in patients with HF and preserved/reduced EF compared with controls*[11]

IL-6. Although the mechanism for increased elaboration of IL-6 in HF is not clear, TNF-á is sufficient to induce IL-6 gene and protein expression in a variety of cell types, suggesting that there may be a cytokine cascade in the setting of HF. Studies have identified a significant correlation between elevated levels of TNF-α and elevated levels of IL-6. There was a statistically significant correlation between elevated levels of IL-6 and elevated right heart pressures.[33,36] Serum IL-6 and IL-10 concentrations were elevated (Fig 6) both in patients with HF and decreased systolic function (HF-S) as well as HF and preserved ejection fraction (HF-D).[11] 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. Their 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.[51]

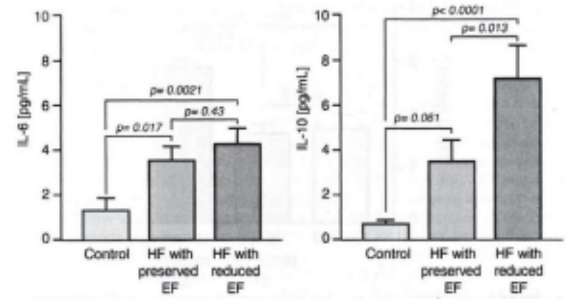

Fig.-6: *Serum IL-6 and IL-10 concentrations in patients with HF and preserved/reduced EF compared with controls*[11]

Cytokine receptors. Elevated circulating levels of cytokine receptors and cytokine receptor antagonists are found in heart failure, including sTNFR1 and sTNFR2 (Fig.5), IL-1RA and IL-6R. sTNFRs may provide an immediate short-term benefit to the host by buffering the potentially untoward effects of TNF-α; however, in the long-term, elevated levels of these receptors may be maladaptive by stabilizing biologically active TNF-α and slowly releasing it into the circulation. Studies have demonstrated that elevated circulating levels of sTNFR1 and sTNFR2 are present in patients with HF.[4,11,29,49] Elevated levels of sTNFR2 have been shown to correlate with an adverse clinical outcome in hospitalized heart failure patients.[49]

ST2 receptors. Biomarker testing has led to a better understanding of the underlying pathology and pathophysiology of various acute medical conditions such as heart failure (HF) and acute coronary syndromes while simultaneously being useful for clinical evaluation and management in these settings.[52-54] A logical marker to examine for a role in the evaluation of dyspneic patients may be the soluble isoform of the ST2 protein, a member of the interleukin-1 receptor superfamily. The value of the novel ST2 receptors for prognostication in patients suspected of having HF is recent of interest.[18-20] In a state of acute myocardial stretch, the ST2 gene is notably up regulated and elevated serum concentrations have been reported in patients with HF. Jannuzi et al[53] measured ST2 concentrations (Fig.8) in dyspnoeic patients presenting to the Emergency Department (ED) and found that though NT-proBNP was superior to ST2 in diagnosing acutely decompensated HF (ADHF), there was a very strong relationship between ST2 concentrations and 1 year mortality (HR 5.6, p<0.001). The median concentrations of ST2 were significantly higher among heart failure patients than non-heart failure patients, and in those who died than in survivors (1.03 ng/ml vs 0.18 ng/ml; p<0.001). Elevation of the ST2 marker was associated with the highest rate of death in patients with ADHF. Investigators suggested that a multi-marker approach using both ST2 and NT-proBNP might be the most effective approach in determining prognosis of ADHF patients.

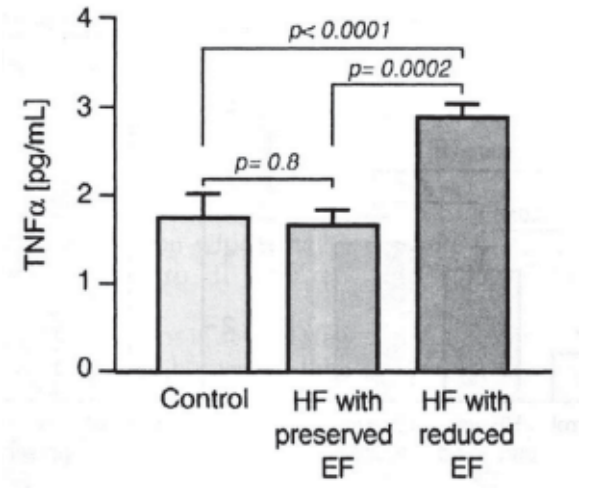

Fig.-7: *Serum TNF-α concentrations in patients with HF and preserved / reduced EF compared with controls.*[53]

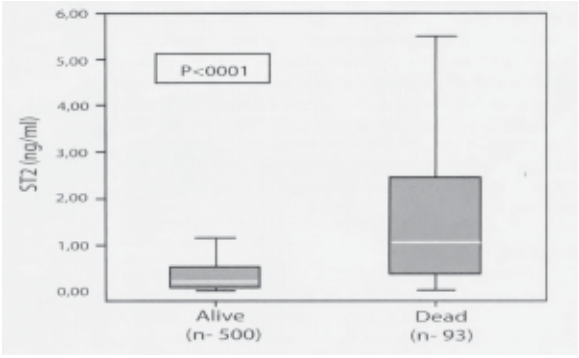

Fig.-8: *ST2 concentrations at presentation as a function of survival at 1 year. Medians are depicted; boxes represent the 25th and 75th centile, whereas whiskers represent the 5th and 95th centile.*[53]

Galectin-3 is a protein produced by activated cardiac macrophages during an inflammatory response. As inflammatory mechanisms have been identified as potential facilitators of heart failure progression, galectin-3 has been described as a potential biomarker for patients with HF. Galectin-3 is upregulated in cardiomyopathy and heart failure, it plays a role in the progression of HF and remodeling, The search for biomarkers that can forecast risk of heart failure worsening and hospitalization, one of the most active research areas in cardiology, has turned up a promising one in the inflammation and fibrosis mediator galectin-3. In a multi-marker analysis of dyspnoeic patients

presenting to the ED, serum galectin-3 concentrations were significantly elevated in patients with heart failure in comparison to those without , and galectin-3 had a greater area under the receiver operating curves (AUC) of 0.74 (p=0.0001) than NT-pro-BNP's prognostic capability. [55-57] Thus provides encouraging support for the future development of multi-marker heart failure algorithms.

Growth differentiation factor (GDF)-15 has recently emerged as a potential new biomarker for heart failure. A member of the transforming growth factor-â cytokine superfamily, GDF-15 expression is upregulated in the cardiac myocytes in responses to mechanical stretch and promotes antiapoptotic, antihypertrophic and antiremodeling effects on the injured heart. Kempf et al[5] recently analysed 455 CHF patients with known GDF-15 concentrations and showed that increasing values of GDF-15 translated to higher mortality risk in patients with HF. According to the study, after adjustments for known clinical variables and established prognostic biomarkers, GDF-15 remained an independent predictor of mortality (HR 2.26, p<0.001) and added important prognostic information to various patient subgroups, including those defined by age, BMI, heart failure aetiology, NYHA functional class and left ventricular EF. These results suggest that GDF-15 may add prognostic information beyond that of current methods, and thus merits further exploration.

Pharmacologic and nonpharmacologic regulation of cytokines and cytokine receptors in heart failure

Anti cytokine therapy

Many reasons may call for using anti-inflammatory strategies in patients with CHF. For example, the excessive elaboration of proinflammatory cytokines seems to mimic many aspects of the CHF phenotype, many of the deleterious effects of inflammatory mediators are potentially reversible once inflammation subsides, and CHF remains a progressive disease process despite optimal therapy with antifailure therapy.[57]

One natural question that arises from the previous discussion regarding the role of cytokines in the pathogenesis and progression of heart failure is whether modulation of cytokine production or cytokine bioactivity that lead to prevent or reverse myocardial dysfunction or remodeling may be used a method for treating patients with HF. In one of the early studies, Parrilo et al[58] randomly assigned 102 patients to either treatment with **prednisone** (60 mg/day) or placebo. After 3 months of therapy, an increase in ejection fraction of 5% or greater in 53% of the patients receiving prednisone, whearas 27% of the controls had a significant improvement in ejection fraction (p=0.005). Although specific cytokine levels were not measured in this study, data suggest that patients with idiopathic dilated cardiomyopathy may have some improvement when given a high dose of prednisone daily. Thus, this early study raises the possibility that suppression of cytokine production may be used as therapeutic tool in treating patients with HF.

Another potentially important pharmacologic method for suppressing cytokine production is thought the use of agents that elevates cAMP level, such as **dobutamine**, which suppresses TNF-α production. It was the speculation that one of the mechanisms for the sustained benefit of intravenous infusions of dobutamine may be through suppression of proinflammatory cytokines, such as TNF-α.[59] This point of view is not supported by a full length publication, in which it was shown that treatment with either intravenous dobutamine or milrinone had no effects in terms of decreasing circulating TNF-α levels. Phosphodiesterase inhibitors can also serve as potent inhibitors to TNF-α production. The phosphodiesterase inhibitor pentoxifylline demonstrates salutary effects on HF signs and symptoms while substantially decreasing the circulating TNF-á level.[60] However, other studies failed to show an effect of cyclic adenosine monophosphate, cyclic adenosine monophosphate derivatives, or ß-adrenergic agonists on TNF- α production.[61] Adenosine may have an important role in regulating myocardial cytokine expression.[62] Other inhibitors of cytokine expression include amiodarone, ouabain, and estrogen.

Vesnarinone, a phosphodiesterase inhibitor which raises cAMP and might there be expected to decrease TNF-α levels. Vesnarinone is also a potassium channel antagonist.[4,61,63] One or both of these effects may have been responsible for the

increase in mortality [62,64] which is required more selective TNF-α inhibitors. One such compound, a soluble TNF-á receptor antagonist that neutralizes the biologic effects of circulating TNF-á . Deswal et al showed that after administration of TNF receptor fusion protein (TNPR:F_c), there was an improvement of LV function, amelioration of symptoms, exercise tolerance and quality of life in patients with advanced heart failure.[65]

In a pilot study of patients with ST-segment elevation AMI, IL-1 blockade with **anakinra** was safe and favorably affected by LV remodeling. If confirmed in larger trials, IL-1 blockade might represent a novel therapeutic strategy to prevent heart failure after AMI.[66]

Darbepoetin- reduces circulating pro-inflammatory cytokine IL-6 and apoptotic mediator soluble Fas ligand in CHF patients with anemia, with a parallel improvement of cardiac performance and exercise capacity.[67]

Renaissance, Recover and Renewal

In the anticytokine clinical trials, the use of either a soluble TNF receptor (RENEWAL) or an anti-TNF antibody (ATTACH) was not beneficial to patients with HF. Etanercept is a recombinant human TNF receptor protein that binds to circulating TNF and functionally inactivates TNF by preventing it from binding to its receptors on cell surface membranes. Moreover, phase I safety studies showed that a single intravenous infusion of etanercept was safe and well tolerated and led to an improvement in the functional status of patients with HF.[68] In a subsequent study, biweekly injections of etanercept for 3 months resulted in a significant increase in LVEF and a significant decrease in LV volumes.

Two multicenter clinical trials were designed to test the effect of etanercept on patient functional status and morbidity/ mortality:[69] the American arm RENAISSANCE (Randomized Etanercept North American Strategy to Study Antagonism of Cytokines) and the European arm RECOVER (Research into Etanercept: Cytokine Antagonism in Ventricular Dysfunction). The combined analysis of the two trials was termed RENEWAL (Randomized Etanercept Worldwide Evaluation). Patients with NYHA class II to IV chronic HF and an LVEF d" 0.30 were enrolled in two clinical trials that differed only in the doses of etanercept used. Both trials were terminated prematurely because of lack of benefit. Analysis of the effect of the two higher doses of etanercept on the combined outcome of death or hospitalization for chronic HF from the two studies was also planned (RENEWAL).

ATTACH Trial

The ATTACH trial (Anti-TNF-a Therapy Against Chronic HF) enrolled 150 patients with CHF to investigate the impact of treatment with infliximab, a chimeric (mouse/ human) immunoglobulin-G1 monoclonal antibody that binds both soluble and membrane bound TNF-a.[70] Similar to RENAISSANCE and RECOVER, the ATTACH trial was a multicenter, randomized, double-blind, placebo-controlled study. It also was stopped prematurely. However, when analyzing the data from ATTACH, it is noteworthy that the plasma values of infliximab achieved in the patients were many times higher than expected. This may account for the increased risk of death in the group receiving the higher dose of infliximab (10 mg/kg body weight) observed in this study (P< .05). There was no adverse risk associated with 5 mg/kg body weight infliximab; in fact, LVEF improved in patients receiving this dose (P< .05).

Calcium channel blocker & cytokines

Mohler et al examined the effects of amlodipine on circulating levels of TNF-α and IL-6 in a subset analysis of patients enrolled in the PRAISE trial.[71] They observed that although treatment with amlodipine had no effect on TNF-α levels, there was a statistically significant decrease in IL-6 levels after 24 weeks of treatment in patients with nonischemic CHF. A reduction in levels of IL-6 has been proposed to be of importance for the beneficial effect of amlodipine on their survival in the PRAISE-I Heart Failure Study. However, the subsequent definitive PRAISE-II study did not show an amlodipine-induced reduction in mortality rates in a larger population of patients with CHF with normal results for coronary arteriography.[72]

ACE inhibitors & Cytokines

Increasing evidence suggests that proinflammatory effects of angiotensin II are directly involved in atherosclerosis development and thrombus formation. Angiotensin II exerts vasoconstrictive,

growth, and remodeling effects primarily through activation of the angiotensin II type 1 (AT_1) receptors. Activation of AT_1 receptors results in nuclear factor (NF)-κ B activation, which is now considered one of the major transcription factors in regulating many of the functions in the vessel wall. NF-κ B activation results in production of various cytokines and adhesion molecules, such as TNF-α, IL-6, IL-8, monocyte chemotactic protein-1, vascular cell adhesion molecule-1, E selectin, and TGF-â. In the study of Gullestad et al,[73] it has been shown that high-dose angiotensin-converting enzyme therapy was associated with a significant decrease in IL-6 activity in patients with severe CHF. Similar reductions in cytokines have been noted in patients with heart failure treated with an ACE inhibitor and â-blockers and in other studies in patients with coronary artery disease.[74-76] This may help explain the benefit of angiotensin II disruption in cardiovascular diseases.

Beta blocker and cytokines

A potential immunoregulatory role of **beta-blockers** in modifying the dysregulated cytokine network has been reported in patients with heart failure.[74,77] The positive influence of beta-blockers on survival in patients with HF is well known. One of the mechanism of such result might be related to its immunomodulatory effects which require further investigation in large trials.

Carvedilol

A single-center, prospective, randomized study enrolled 60 patients with DCM (35 ischemic and 25 nonischemic) with an LVEF less than 40%. Patients had been receiving digoxin, angiotensin-converting enzyme inhibitors, and diuretics for 6 months. The patients were randomly assigned to receive carvedilol or placebo. Carvedilol suppressed the plasma levels of TNF-α and IL-6 in both ischemic and nonischemic patients. The carvedilol effect was more pronounced in patients with nonischemic DCM than in those with ischemic disease.[78]

Metoprolol

In a double-blind trial,[79] patients with CHF were randomized to metoprolol or placebo. Plasma levels of TNF-α, IL-6, IL-10, soluble IL-2 receptor, monocyte chemoattractant peptide-1, and IL-8 were measured at baseline, after 3 months, and at the end of the study. During treatment with metoprolol, but not with placebo, there was a significant decrease in soluble IL-2 receptor after 3 months, with a return to baseline at the end of the study, possibly reflecting down-modulation of T-cell activation. However, an enhanced immune activation also persisted in the metoprolol group, suggesting a potential for more specific immunomodulatory therapy in CHF.

The additional improvement in myocardial function seen with carvedilol compared with metoprolol may be closely related to the greater reduction in IL-6 in idiopathic dilated cardiomyopathy.

Cytokines and statin

Statins have been shown to have pleiotropic effects beyond lowering low-density lipoprotein including inhibition of inflammatory cytokine synthesis and reactive oxygen species production.[80,81] In the study of Castro et al[81], 38 patients with stable systolic chronic heart failure received a 4-week placebo course, followed by atorvastatin 20 mg/day for 8 weeks. Atorvastatin induced a significant decrease of matrix metalloproteinase activity, high-sensitivity CRP, TNF- α, IL-6 and malondialdehyde, and a significant increase of superoxide dismutase activity when compared with placebo. Conraads et al[80] showed the similar positive influence of pravastatin on cytokine and cytokine receptors in patients with HF.

Tousoulis et al.[82] examined the effect of statins on endothelial function and inflammatory markers in patients with NYHA class II to IV HF. Patients were randomized to atorvastatin 10 mg daily versus placebo for 4 weeks. Atorvastatin administration was associated with a significant increase in forearm blood flow and a reduction in levels of TNF-á and IL-6, compared with the placebo group in 38 patients with HF.

GISSI-HF [83] investigators evaluated the effect of Rosuvasatin on heart failure in a double blind randomized placebo controlled trial and concluded that there is no benefit.

Growth hormone and cytokines

Recent experimental and clinical data suggest that growth hormone (GH) treatment improves cardiac function by both increasing myocardial contractility and decreasing peripheral vascular resistance in CHF.[84] This beneficial action include vasodilation, enhancement in cardiac contractility,

improvement in cardiac myocyte metabolic imbalance, increase in calcium sensitivity of cardiac myofilaments, and prevention of cardiomyocyte apoptosis and may be translated into better functional capacity and exercise performance of patients with CHF.[85,86] Stamatis et al[12] investigated the effects of growth hormone (GH) administration on serum levels of proinflammatory cytokines and soluble apoptosis mediators in patients with chronic heart failure secondary to idiopathic dilated cardiomyopathy (IDC). Serum levels of TNF-α, its soluble receptors (sTNFR1, sTNFR2), IL-6, soluble IL-6 receptor (sIL-6R), soluble Fas (sFas) and soluble Fas Ligand (sFasL) were determined in 10 patients with IDC (NYHA class III) before and after a 3-month subcutaneous administration of 4 IU GH every other day. This study describes for the first time the immunomodulatory role of GH administration in patients with CHF secondary to IDC, manifested with significant reductions in circulating levels of major proinflammatory cytokines (TNF-α and IL-6) and their soluble receptors, as well as soluble apoptosis mediators (sFas and sFasL). As they all are enhancers of myocytes (both cardiac and skeletal) and endothelial cell apoptosis, all actively involved in cardiovascular maladaptive remodeling, and associated with the progression of the syndrome. These immunomodulatory effects may be related to the improvement in functional status of patients with CHF.[87]

Device therapy and cytokines

In a small but interesting study, Lappegard and Bjornstad [88] investigated whether cardiac resynchronization therapy (CRT) treatment affects the immune system. Eight patients with HF scheduled for CRT were studied for immune activation before and 6 months after CRT treatment. After 6 months, all patients had improved in NYHA class and LVEF, and there was a statistically significant reduction in serum N-terminal pro-brain natriuretic peptide. There was a statistically significant reduction in plasma levels of the chemokines monocyte chemoattractant protein-1 and IL-8 and IL-6. They observed no changes in the levels of IL-1ß, TNF-α, IL-10, or complement activation products.

Hasper et al studied influence of **biventricular assist device** (BVAD) systems on systemic inflammation in patients with advanced stage of chronic heart failure. They hypothesized that chronic heart failure as a model of systemic hypoxia may result in systemic inflammation and the signs of systemic inflammatory responses should disappear after successful mechanical circulatory support using BVAD systems which have been shown to be effective tools for bridging the time until heart transplantation.[89]

Physical exercise and Cytokines

In addition, it was demonstrated that physical training reduces peripheral markers of inflammation [90] and modulates the cytokine network in CHF.[91]

Yoga improved exercise tolerance and positively affected levels of inflammatory markers in patients with HF, and there was also a trend toward improvements in QoL.[92]

Conclusion:

Heart failure has been shown to be associated with neuroendocrine and inflammatory activations. Both the neuroendocrine and inflammatory biomarkers are significantly and positively associated with the symptom severity of the disease. The inflammatory biomarkers could be used for diagnostic and prognostic purpose as well as for monitoring the progression of HF and objectively assessing the effects of treatments, especially in subpopulations where symptom severity cannot be reliably assessed. However, further longitudinal studies with more patients are needed to determine to what extent markers of inflammatory activation provide incremental information that improves management of HF. Future studies should examine the responses of ST2, galectin-3 during therapies in patients with HF and the value of therapeutic interventions directed toward immunomodulation and whether such interventions would be accompanied by improvements in outcome.

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