Heart Fail Rev (2010) 15:331–341
DOI 10.1007/s10741-009-9140-3

Biomarkers of inflammation in heart failure

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Published online: 12 April 2009

Abstract Heart failure (HF) is characterized by the elaboration of a portfolio of pro-inflammatory cytokines and inflammatory mediators that are considered to contribute to disease progression by virtue of the deleterious effects that these molecules exert on the heart and circulation. Recent studies have suggested that these inflammatory mediators may serve as relevant markers of disease severity and HF prognosis. Moreover, there is evidence that changes in the levels of inflammatory biomarkers may prove useful in following the change in patient clinical status following institution of appropriate HF therapy. This review will focus on the emerging role of inflammatory biomarkers, including pro-inflammatory cytokines, C-reactive protein, and erythrocyte sedimentation rate in patients with HF.

Keywords Inflammation · Heart failure · Biomarkers · Cytokines · Chemokines · Tumor necrosis factor (TNF) · Interleukin-6 (IL-6) · Erythrocyte sedimentation rate (ESR) · C-reactive protein (CRP)

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Introduction

Chronic heart failure (HF) is characterized by an ongoing inflammatory response that correlates with HF disease severity and prognosis. The link between HF and inflammation was formally recognized and reported in 1990 by Levine et al. [1] who noted that levels of an inflammatory cytokine, tumor necrosis factor (TNF), were elevated in the setting of HF. Since this first report, a number of studies have shown that in addition to TNF, other pro-inflammatory cytokines and chemokines are also involved in cardiac depression and the progression of HF (Table 1) [2–7]. In this article, we will review the implications of inflammatory biomarkers in HF, with emphasis on inflammatory biomarkers that correlate with disease severity, prognosis, and clinical outcomes in HF.

Overview of cytokines involved in heart failure

The term *cytokine* is applied to a group of relatively small molecular weight protein molecules (generally 15–30 KDa) which are secreted by cells in response to a variety of stimuli. Classically, cytokines are thought to be secreted by "producer cells" and act in an autocrine, juxtacrine, or paracrine fashion to influence the biological behavior of neighboring "target cells" [8]. The group of cytokines that is responsible for initiating both the primary host response to a bacterial infection, as well as the repair of tissue following injury has been termed "pro-inflammatory cytokines." Thus far, two major classes of cytokines have been identified in HF: vasoconstrictor cytokines, such as endothelin; and vasodepressor pro-inflammatory cytokines, such as TNF, interleukin (IL)-6, and IL-1 [4]. These inflammatory mediators are now

Table 1 Peripheral levels of cytokines and cytokine receptors in heart failure

	Cytokines					Cytokine receptors				
	TNF-α	IL-1	IL-2	IL-6	IFN-γ	sTNFR1	STNFR2	IL- 1RA	ST-2	IL-6R
Levine et al. [1]	+	nd	nd	nd	nd	nd	nd	nd	nd	nd
McMurray et al. [32]	+	nd	nd	nd	nd	nd	nd	nd	nd	nd
Dutka et al. [11]	+	nd	nd	nd	nd	nd	nd	nd	nd	nd
Wiederman et al. [18]	+	−	nd	+	−	nd	nd	nd	nd	nd
Katz et al. [12]	+	−	+	nd	nd	nd	nd	nd	nd	nd
Matsumori et al. [10]	+	−	−	−	−	nd	nd	nd	nd	nd
Ferrari et al. [19]	+	nd	nd	nd	nd	+	+	nd	nd	nd
Torre-Amione et al. [6]	+	nd	nd	nd	nd	+	+	nd	nd	nd
Torre-Amione et al. [5]	+	nd	nd	+	nd	nd	nd	nd	nd	nd
Milani et al. [82]	+	nd	nd	nd	nd	+	nd	+	nd	nd
Munger et al. [20]	-	-	nd	+	nd	nd	nd	nd	nd	Nd
Testa et al. [30]	+	+	−	+	nd	nd	+	+	nd	+
Anker et al. [83]	+	nd	nd	nd	nd	nd	nd	nd	nd	nd
MacGowan et al. [21]	+	nd	nd	+	nd	nd	nd	nd	nd	nd
Mohler et al. [41]	+	nd	nd	+	nd	nd	nd	nd	nd	nd
Nishigaki et al. [84]	+	nd	nd	+	nd	nd	nd	nd	nd	nd
Anker et al. [17]	+	nd	nd	nd	nd	+	+	nd	nd	nd
Tsutamoto et al. [24]	+	nd	nd	+	nd	nd	nd	nd	nd	nd
Aukrust et al. [13]	+	nd	nd	+	nd	+	+	nd	nd	−
Dibbs et al. [25]	+	nd	nd	+	nd	nd	nd	nd	nd	−
Rauchhaus et al. [26]	+	nd	nd	+	nd	+	+	nd	nd	nd
Deswal et al. [34]	+	nd	nd	+	nd	+	+	nd	nd	nd
Weinberg et al. [14]	nd	nd	nd	nd	nd	nd	nd	nd	+	nd

nd: Not done, +: levels elevated, −: levels not elevated

TNF-α Tumor necrosis factor alpha, *IL-1* Interleukin-1, *IL-2* Interleukin-2, *IL-6* Interleukin-6, *IFN-γ* interferon gamma, *sTNFR1* soluble TNF receptor R1, *sTNFR2* soluble TNF receptor R2, *IL-1RA* IL-1 receptor antagonist, *IL-6R* IL-6 receptor, *sST2* soluble ST2-member of IL-1 receptor family

known to be expressed by all the nucleated cell types residing in the myocardium, including the cardiac myocyte, suggesting that these molecules may do more than simply orchestrate inflammatory responses in the heart [9]. Peripheral-circulating as well as intracardiac levels of these cytokines are elevated in patients with HF [1, 4, 6, 10–12]. Table 1 provides a summary of the studies that examined circulating levels of cytokines and cytokine receptors in patients with HF. As shown in the table, most of these studies have consistently described elevated levels of TNF in HF, and a number of studies have demonstrated elevated levels of IL-6. However, fewer studies have examined and have not consistently found elevated levels of IL-1, IL-2, IL-18, and IFN-γ in HF.

The pro-inflammatory cytokine response is controlled by a series of immunoregulatory molecules, termed the "anti-inflammatory" cytokines. These cytokines act in concert with specific cytokine inhibitors and soluble cytokine receptors to regulate the human immune response. Their physiologic role in inflammation and pathologic role in HF are being increasingly recognized [3]. Major anti-inflammatory cytokines include interleukin-1 receptor antagonist (IL-1ra), IL-10, IL-11, and IL-13. Specific cytokine receptors for IL-1, TNF, and IL-18 also function as pro-inflammatory cytokine inhibitors. Hence, in several inflammatory disorders, the potential pathogenic effect of inflammatory cytokines will depend on the balance in the cytokine network, particularly on the levels of counteracting anti-inflammatory mediators. For example, patients with severe HF were found to have decreased levels of transforming growth factor beta-1 and inadequately raised levels of IL-10 in relation to the elevated TNF concentrations, and these abnormalities in the cytokine network were most pronounced in patients with the most severe HF [13].

Recently, there has been considerable interest in ST2, a member of the IL-1 receptor family and a protein secreted by cultured myocytes subjected to mechanical strain [14]. The protein product of ST2 encodes a membrane receptor of the IL-1 receptor family and a truncated soluble receptor (sST2) that can be detected in human serum. The

trans-membrane form of ST2 is considered to play a role in modulating responses of T helper type 2 cells, whereas the soluble form of ST2 is upregulated in growth-stimulated fibroblasts. Infusion of sST2 appears to dampen inflammatory responses by suppressing the production of the inflammatory cytokines IL-6 and IL-12. Interruption of the ST2 gene results in progressive myocardial fibrosis and hypertrophy in experimental models. Despite the potential role played by ST2 in inflammation, significant parallels between ST2 and natriuretic peptides exist: the ST2 gene is markedly upregulated in states of myocyte stretch, similar to the induction of the BNP gene, and, in analogy to the phenotype seen in BNP-deficient mice, mice deficient in ST2 develop dilated and hypertrophied left ventricles, lower ejection fractions, and reduced survival. This raises the possibility for a pluripotent role for ST2, representing a bridge between inflammatory and neurohormonal systems. The ligand for ST2 was recently identified as IL-33, a product released by endothelial cells, fibroblasts, and myocytes in response to stretch [15]. Similar to ST2, IL-33 has been suggested to play, at least, a dual role, acting as a pro-inflammatory cytokine as well as an intracellular nuclear factor with transcriptional regulatory properties. ST2 might act as a soluble decoy receptor for IL-33, mitigating the effects of excessive IL-33 exposure and therefore mediating the interaction between cardiac myocytes, fibroblasts, and possibly endothelial cells [16].

Cytokine levels are elevated and correlate with disease severity in heart failure

Circulating levels of TNF, IL-6, and IL-18 are elevated in patients with HF (Table 2) [1, 6, 10–12, 17–30]. Because they were initially identified in patients with cardiac cachexia [31, 32], and edematous decompensation [33], these cytokines were considered to be expressed only in patients with end-stage HF. However, as reported in several studies [1, 3, 6, 10–13, 20, 27, 34, 35], pro-inflammatory molecules are activated starting at earlier phases of HF (i.e., NYHA functional class II HF) [6] or asymptomatic left ventricular dysfunction [27], and continue to rise in direct relation to worsening NYHA functional class [6, 24, 34, 36] (Fig. 1) regardless of the etiology of HF [3, 6, 20, 30].

In addition to the inflammatory cytokines, circulating levels of cytokine receptors are elevated in HF. These include the soluble TNF receptors (sTNFR1 and sTNFR2) [19, 22, 37–39], and soluble transmembrane glycoprotein 130 (one of the receptors for IL-6 family) which are increased in HF in close relation to functional class [13, 27, 39, 40]. Of note, even though IL-6 and glycoprotein 130 levels are elevated, soluble IL-6 receptor (IL-6R) levels are not increased in HF patients (Table 2) [13, 25]. Levels of soluble ST2 are significantly higher in patients with advanced chronic HF as well as acute decompensated HF compared with control subjects [14, 16]. Similar to the abovementioned neutralizing soluble receptor levels, IL-1 receptor antagonist levels are also elevated in patients with HF [13, 22, 30]. Although HF patients have enhanced expression of anti-inflammatory cytokine IL-10 compared to the normal population [22], in patients with severe HF, the levels of transforming growth factor beta-1 are decreased and IL-10 levels in relation to the elevated TNF concentrations are considered inadequately raised [27]. Therefore, the balance is tipped toward enhanced expression of pro-inflammatory cytokines relative to anti-inflammatory cytokines in the HF population.

Pro-inflammatory cytokines predict poor prognosis in heart failure

In addition to correlating with disease severity (i.e., with worsening functional class), elevated blood levels of pro-inflammatory cytokines correlate with increased mortality in patients with HF. Circulating levels of TNF [26, 34], IL-6 [24, 34, 41–44] and TNF soluble receptors (sTNFR1 and sTNFR2) [26, 34] have been reported to predict poorer survival. As shown in Fig. 2a, data on 384 patients with moderate-to-severe HF in the placebo arm of the Vesnarinone Trial (VEST) have demonstrated that there is decline in survival as a function of increasing TNF levels, with the worst survival in patients with TNF levels >75th percentile [34]. Similar findings were observed with circulating levels of IL-6 (Fig. 2b) and levels of soluble TNF receptors type 1 and type 2 (Fig. 2c, d). When each cytokine and/or cytokine receptor was separately entered into a multivariate Cox proportional hazards model that included age, sex, etiology of HF, 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. However, when all the cytokines and receptors were entered into the model together, only sTNFR2 remained a significant predictor of mortality [34]. Of interest, in another study of 37 patients with HF and 26 age-matched control subjects, the circulating levels of sTNFR2 also appeared to be the most powerful predictor of mortality [19]. In a larger study of 152 patients with HF, Rauchhaus et al., however, reported that sTNF-R1 was the strongest and most accurate prognosticator, as the receiver operating characteristic area under the curve for sTNF-R1 was greater than for sTNF-R2 at 6, 12, and 18 months (all $P < 0.05$) [26]. Most studies have evaluated patients with HF and depressed ejection, but a recent community-based study demonstrated that higher TNF levels were independently associated with a greater risk of mortality even in patients with HF and preserved ejection fraction [35]. Although these clinical

Table 2 Role of Inflammatory Biomarkers in Heart Failure

	TNF-α	IL-6	IL-18	sTNF-R1	sTNF-R2	IL-1 RA	sST2	IL-10	Chemokines (MCP-1)	CRP	ESR
Levels are elevated in HF	+++	++	+	++	++	+	+	+	+	++	++
Supporting References	[1, 5, 6, 10–13, 17–21, 24–26, 30, 32, 34, 35, 41, 82–84]	[22, 27, 40]	[23]	[19, 37, 38]	[22, 38]	[22]	[14, 16]	[22]	[3]	[71, 73, 74]	[76, 79]
Levels correlate with disease severity	+++	+++	n/d	++	++	+	n/d	n/d	+	++	n/d
Supporting references	[1, 5, 11, 13, 27, 30–32, 34]	[5, 20, 24, 27, 28, 30, 34, 40]		[28, 30, 34, 39]	[28, 30, 34, 39]	[30]			[3]	[71, 74]	
Levels correlate with prognosis and HF outcomes	+++	+++	n/d	++	++	n/d	+	n/d	n/d	++	+
Supporting references	[19, 24, 26, 34, 35, 41–44]	[24, 41–44]		[26, 34]	[26, 34]		[14, 16, 85]			[43, 73–75]	[76, 79][a]
Levels predict development of HF in asymptomatic patients	++	++	n/d	n/d	n/d	n/d		n/d	n/d	++	n/d
Supporting references	[27]	[27]								[27]	
Levels change with HF therapy	+++	+++	n/d	++	++	n/d		++	n/d	+	n/d
Supporting references	[47, 48, 51, 52, 54, 55, 57, 58, 86]	[42, 47, 50, 56]		[22, 58]	[22, 51, 54, 57, 58]			[22, 52, 54]		[64, 86]	

TNF-α Tumor necrosis factor alpha, *IL-6* Interleukin-6, *IL-18* Interleukin-18, *sTNFR1* soluble TNF receptor R1, *sTNFR2* soluble TNF receptor R2, *IL-1RA* IL-1 receptor antagonist, *sST2* soluble ST2-member of IL-1 receptor family, *IL-10* Interleukin-10, *MCP-1* Monocyte chemoattractant protein-1, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *HF* heart failure, *n/d* no data available

+++ Supported by large number of studies and more than one large-scale clinical trial; ++ supported by several number of studies and/or small-scale clinical trials and/or one large-scale clinical trial; + supported by one small study or one small clinical trial;

[a] One study suggested that elevated levels were associated with increased mortality [76], whereas the other study suggested that elevated levels were associated with better prognosis [79]

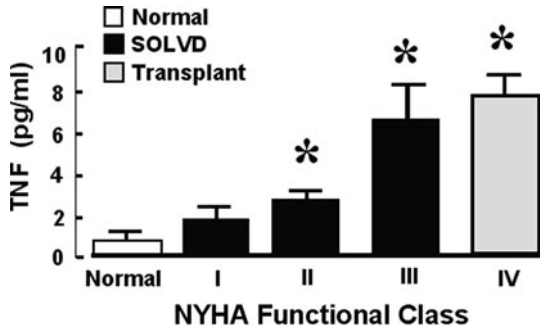

Fig. 1 TNF levels in patients with class I to IV heart failure. Compared with age-matched control subjects (*open bar*), there was a progressive increase in serum TNF-α levels in direct relation to decreasing functional heart failure classification. The *solid bars* denote values for patients enrolled in Studies of Left Ventricular Dysfunction (SOLVD) [5]; the *shaded bar* denotes values for NYHA class IV patients who were undergoing cardiac transplantation [6]. *Significantly different from normal. Reproduced from Seta et al. [36], by permission of Churchill Livingstone ©1996

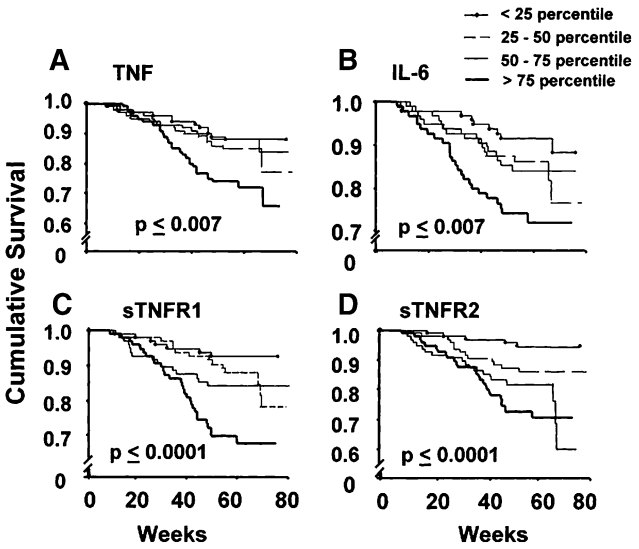

Fig. 2 Kaplan–Meier survival analysis. The circulating levels of TNF (**a**), IL-6 (**b**), sTNFR1 (**c**), and sTNFR2 (**d**) were examined in relation to patient survival during follow-up (mean duration 55 weeks; maximum duration 78 weeks). For this analysis, the circulating levels of cytokines and cytokine receptors were arbitrarily divided into quartiles. Reproduced with permission from Deswal et al. [34], by permission of the American Heart Association ©2001

studies cannot address the issue of whether elevated circulating levels of cytokines and cytokine receptors represent an epiphenomenon that is associated with, but not causally related to, worsening disease severity and outcomes, the preponderance of data supports the theory that pro-inflammatory cytokines, TNF and IL-6 contribute further to the progression of HF and worse outcomes in HF.

It has also been suggested that sST2 levels may correlate with prognosis. A study by Weinberg demonstrated that an increase in ST2 levels over a 2-week period was a significant predictor of mortality or transplantation independent of BNP or ProANP in patients with advanced chronic HF [14]. In addition, Mueller et al. showed that increased sST2 plasma concentrations in patients presenting with acute decompensated HF were independently and strongly associated with 1-year mortality [85].

Inflammatory cytokines as markers for monitoring response to therapy in heart failure

There have been several studies examining the changes in levels of inflammatory cytokines during standard therapy for HF. Some of these changes can be attributed to direct interaction of the medications used, such as the interaction between neurohormonal antagonists and the pro-inflammatory cytokines [46, 47]. Clinical studies have shown that treatment with angiotensin receptor antagonists can lead to significant reductions in circulating levels of TNF and/or cell adhesion molecules in patients with HF [48]. β-Adrenergic blockade has also been shown to prevent the expression of inflammatory mediators in post-infarction animal models [49], and result in significant reductions in pro-inflammatory cytokine levels in clinical studies with HF patients [22, 50–55]. Compared to angiotensin receptor blockers and β blockers, the effect of angiotensin converting enzyme (ACE) inhibitors on inflammatory cytokines is not as clear. In a study by Gage et al., TNF production was significantly lower in patients receiving ACE inhibitors and there was a trend toward lower levels of serum IL-6 in patients receiving both ACE inhibitors and beta blockers [52]. Again, in the same study, the ratios of interferon gamma to IL-10 levels were lower in patients receiving a combination of beta-blocker and ACE inhibitor therapy. In an animal infarct model, use of ACE inhibitors for a period of 28 days resulted in reduction of cardiac cytokine expression [47]. Contrarily, in a clinical study by Gullestad and colleagues, treatment with ACE inhibitors for a period of 34 weeks resulted in a rise in the peripheral levels of chemokines, cell adhesion molecules, and pro-inflammatory cytokines except those of IL-6 [56]. There is little information regarding inflammatory cytokines and other medications used in the treatment of HF. Mohler et al. demonstrated that treatment with the long-acting dihydropyridine calcium antagonist, amlodipine, for a period of 26 weeks lowered plasma IL-6 levels in patients with HF [41]. Other studies have noted that optimization of background standard therapy of HF with diuretics, ACE inhibitors, beta blockers, and digoxin can result in significant reductions in circulating levels of TNF and IL-6 [42]. Physical training reduces plasma levels of TNF, IL-6, sTNFR1, sTNFR2, and sIL-6R in patients with HF [57, 58]. Furthermore, in patients with advanced HF, mechanical circulatory support with ventricular assist device

results in markedly reduced myocardial expression of TNF after several weeks of support [59, 60].

These studies suggest that there are important interactions between the renin–angiotensin, adrenergic systems, and pro-inflammatory cytokines, and many of the conventional therapies for HF may work, at least in part, through the modulation of pro-inflammatory cytokines. Nevertheless, it should be noted despite these temporal parallel changes in the levels of cytokines with optimal HF therapy, we currently do not have data from large-scale trials on the changes in inflammatory biomarkers over time correlating with morbidity and mortality in HF patients. Furthermore, the sensitivity, specificity, and negative and positive predictive values of inflammatory biomarkers in predicting response to therapy for HF are not known, and whether any of the inflammatory markers provide additional information over and above the established variables remains to be established [25].

Pro-inflammatory cytokines as predictors for development of heart failure in asymptomatic patients

Elevated levels of IL-6 and TNF have been reported in patients with left ventricular dysfunction in the absence of clinical symptoms of HF [5, 61]; however only recently, the predictive role of pro-inflammatory cytokines for development of HF in asymptomatic patients has been described. In a subgroup consisting of 732 elderly subjects without prior HF enrolled in Framingham study, Vasan and colleagues reported that baseline levels of IL-6 and spontaneous production of TNF by peripheral blood mononuclear cells (PMBC) were predictive of development of HF in the next 5 years [27]. After adjustment for established risk factors, including the occurrence of myocardial infarction during follow-up, the investigators found that the risk of developing HF increased from $\sim$1.6-fold to 1.7-fold per tertile increment in PBMC TNF and IL-6 levels. Subjects with elevated serum IL-6 and PBMC TNF greater than median values as well as CRP $\geq$5 mg/dL had a 4.1-fold risk for developing HF. The study population consisted of predominantly elderly, white subjects (67% female) with a high prevalence of hypertension ($\sim$70%), atrial fibrillation ($\sim$7%), and pre-existing cardiovascular disease without prior documented myocardial infarction. It is important to point out that in this study, there was no assessment of left ventricular function at baseline. Elevated inflammatory markers in this study may have identified patients with vascular disease at risk for myocardial infarction [62, 63] or patients with preexisting subclinical left ventricular dysfunction [64]. Without a baseline assessment of ventricular function, it is not possible to determine whether elevated levels of IL-6, TNF, and CRP predict the de novo development of cardiomyopathy versus the transition from subclinical left ventricular dysfunction to overt HF.

Chemokines

Chemokines are potent pro-inflammatory and immune modulators. Chemokines regulate several biological processes such as chemotaxis, activation and migration of leukocytes to areas of inflammation, collagen turnover, angiogenesis, and apoptosis [3]. TNF and other pro-inflammatory cytokines, such as IL-1β and IL-6 or interferon-γ are known to induce these chemotactic polypeptides [65]. Potent chemokines such as macrophage chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein- 1alpha (MIP-1α) not only can attract the monocytes and the lymphocytes, but also can modulate other functions of these cells, e.g. generation of reactive oxygen species [3]. Monocyte chemoattractant protein-1 has been reported to be upregulated in experimental models of HF with pressure or volume-overload [66, 67]. Furthermore, transgenic overexpression of MCP-1 in the myocardium has been shown to result in myocarditis and subsequent development of HF in experimental models [68]. Similar to the pro-inflammatory cytokines, the failing human heart expresses chemokine and chemokine receptors [69]. Increased expression of chemokines, e.g., monocyte chemoattractant protein-1, has recently been described in clinical HF [3]. Aukrust and colleagues reported that HF patients had significantly elevated levels of all the chemokines with the highest levels in patients in New York Heart Association functional class IV [3]. In this study, MCP-1 and MIP-1α levels significantly and inversely correlated with left ventricular ejection fraction. Further studies on cells isolated from peripheral blood of these patients suggest that platelets, CD3+ lymphocytes, and in particular, monocytes, may contribute to the elevated chemokine levels in HF [3].

C-reactive protein

C-reactive protein (CRP) is a phylogenetically highly conserved plasma protein that participates in the systemic response to inflammation [70]. It is exclusively produced in the liver and its plasma concentration increases during inflammatory states, a characteristic that has long been employed for clinical purposes. With the recent recognition of its diagnostic and prognostic role in ischemic heart disease and acute coronary syndromes, CRP has aroused an interest as a laboratory marker for standard testing. As will be reviewed in the following paragraph, CRP has been

described to correlate with disease severity and prognosis in patients with HF.

The first observation of increased concentrations of CRP in HF was published in 1990. In this study, the serum concentration of CRP was higher than normal in 70% of the HF patients, and the concentration was directly related to the severity of HF and the stage of decompensation [71]. Subsequently, another group measured CRP values in 188 patients with idiopathic-dilated cardiomyopathy and left ventricular ejection fraction <40% [72]. Those patients who died during a follow-up period of 5 years had significantly higher CRP concentrations than those who survived (1.05 ± 1.37 vs. 0.49 ± 1.04 mg/dL, $P < 0.05$). Sixty-two percent of the patients with CRP > 1.0 mg/dL died within 5 years. Similarly, Milo et al. reported that in 30 patients admitted with acute HF, CRP levels were elevated in nonischemic as well as ischemic patients compared to those in controls [73]. In another study of 76 patients hospitalized for HF, the mean CRP level was found to be significantly higher in patients with HF compared to a control group (3.94 ± 5.87 vs. 0.84 ± 1 mg/dL), CRP levels were increased in relation to NYHA class and the HF patients with elevated CRP levels (>0.9 mg/dl) were at greater risk of hospitalization during the 18 month follow-up period compared to patients with normal CRP levels [74]. Similarly, Cesari et al. reported that among elderly patients, for every one standard deviation increase in CRP the risk of HF events increased by 48% [75]. These studies underline the association of CRP with disease severity and prognosis in HF patients.

Recently, Vasan and colleagues reported the role of CRP in the prediction of "development of HF" [27]. They examined CRP as an antecedent to HF among elderly subjects enrolled in the Framingham Heart Study. Elevated CRP (serum CRP level ≥5 mg/dL) was associated with a 2.8-fold increased risk of development of HF during a follow-up period of approximately 5 years compared to subjects with normal CRP levels [27]. Given the association of CRP to atherosclerotic coronary events, it should be noted that in the studies by Vasan et al. [27] and Cesari et al. [75], the subjects were free of ischemic heart disease at the time of entry; however, the outcomes included both ischemic and nonischemic HF events.

Lastly, it is important to note that use of ACE inhibitors and beta blockers has been associated with lower levels of CRP in HF patients [64]. At the present time, despite its clear associations with HF disease severity and outcomes, it is not clear whether CRP is merely a marker of inflammation with no particular role in the development of HF or whether it is involved in the pathogenesis and progression of HF. It is also not clear whether it can be used as a biomarker for monitoring success of therapy for HF.

Erythrocyte sedimentation rate

Erythrocyte sedimentation rate (ESR) has been of particular interest in HF due its low cost, easy applicability, and reproducibility. However, clinical studies which are historically separated from each other by decades have yielded controversial results on its role in HF. Based on the potential misinterpretation of the results in a single report published in 1936, physicians have long believed that the ESR is low in patients with HF [76–78]. To reevaluate this concept in the modern era, Haber et al. measured the ESR in 242 HF patients and reported that the ESR was low (<5 mm per hour) in only 10% of the patients, but was higher (above 25 mm per hour) in 50%. Surprisingly, patients with low or normal sedimentation rates (less than or equal to 25 mm per hour) had more severe hemodynamic abnormalities, worse New York Heart Association functional class symptoms, and worse 1-year survival compared with patients with elevated ESR [76]. Subsequently, in 2001, Sharma and colleagues studied ESR in relation to plasma levels of inflammatory cytokines and mortality in 159 HF patients [79]. The ESR ranged from 1 to 96 mm/h (median 14 mm/h) and, similar to the study by Haber et al. [76], only 16% of the patients in this study had an ESR < 5 mm/h. Therefore, we can conclude that both reports suggest that the ESR is high in HF. In the study by Sharma and colleagues, the ESR correlated with TNF, sTNFR1, sTNFR2 and IL-6 levels. However, contrary to the findings in Haber's study, high ESR levels indicated a poor prognosis, which was independent of age, NYHA class, ejection fraction, and peak oxygen consumption. Patients with ESR above the median (≥15 mm/h) compared to patients with ESR < 15 mm/h had an impaired survival (hazard ratio 2.62) (Fig. 3). The authors suggested

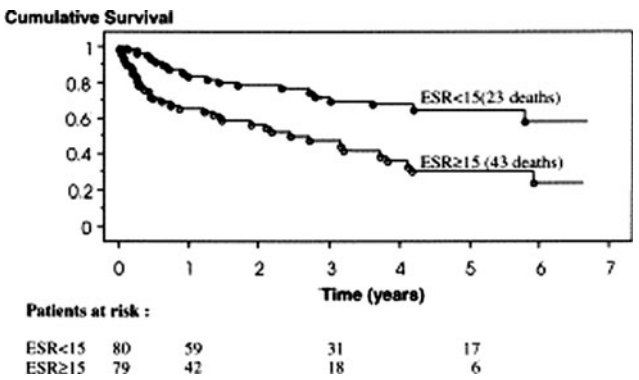

Fig. 3 Kaplan–Meier survival plot for 159 patients with chronic heart failure. Patients were subgrouped according to ESR. The group of patients with high ESR (≥15 mm/h) had an impaired survival compared with patients with ESR < 15 mm/h (RR 2.62, 95% CI 1.58–4.36, $P < 0.0001$. Reproduced with permission from Sharma et al. [79], by permission of the American College of Cardiology and Elsevier Science Inc. ©2000

that the difference between their findings and those of Haber's findings may be due to the temporal changes in the treatment of HF with ACE inhibitors or other agents between the two studies.

Use of inflammatory biomarkers in the management of patients with heart failure

Although the development of clinical practice guidelines and disease management strategies for patients with HF has resulted in dramatic overall improvements in patient care and outcomes, the day-to-day management of individual patients with HF remains challenging. This is partly due to the fact that HF management is quite complex involving numerous therapies; including but not limited to lifestyle modification with diet and exercise, defibrillator or pacing devices, anti-remodeling surgery, and medications that need to be up-titrated to clinically proven doses, and that may have side effects limiting their utilization. Furthermore, there may be racial, gender, age-specific differences in the way patients respond to these therapies. Thus, there is a need for useful biomarkers to help individualize management strategies and guide appropriate selection, timing and/or dosing of therapies in patients with HF [80]. Data from large-scale, well-designed clinical trials provide evidence that changes in neurohormonal levels over time are associated with changes in morbidity and mortality in HF patients [81]. However, at the present time, it is not clear whether clinicians should use changes in levels of these biomarkers, such as plasma norepinephrine levels and/or brain natriuretic peptide, to guide HF management [80]. Furthermore, we currently do not have similar data from large-scale trials on the changes in inflammatory biomarkers over time correlating with morbidity and mortality in HF patients.

To be useful for a large, general population, a screening test should be sensitive, accurate, reliable, easily standardized, and inexpensive. The assay should be relatively easy to perform and analyze so that the information is readily available to the clinician while the patient is still in the treatment area. The inflammatory biomarkers currently do not fulfill these criteria. The sensitivity, specificity, negative, and positive predictive values of inflammatory biomarkers in the setting of HF are not well described; whether any of the inflammatory markers provide meaningful information over and above established variables remains to be proven; the assays of cytokines or chemokines are not uniformly standardized; and the degree of natural variability in circulating cytokine levels increases with time in patients with HF [25]. Thus, the concept of utilization of inflammatory biomarkers to guide therapy in HF remains at experimental levels as of now.

Summary

In the foregoing review, we have discussed the diagnostic and prognostic importance of biomarkers of inflammation in patients with HF. As noted, some of these biomarkers, such as pro-inflammatory cytokines and chemokines, may be involved in the pathogenesis and progression of HF, whereas others such as CRP or ESR may simply reflect the degree of systemic inflammation. Table 2 provides a summary of the inflammatory biomarkers that have been implicated in HF thus far, as well as whether they are (1) involved in the pathogenesis of HF, (2) correlate with disease severity or prognosis in HF, (3) predict the development of HF in asymptomatic patients, (4) change with HF therapy, and (5) represent potential targets for future therapies. As noted above, there is insufficient evidence to embrace the concept of utilizing inflammatory biomarkers to guide therapy in HF at the present time. However, it is possible that multimarker strategies that combine inflammatory biomarkers may ultimately prove beneficial in guiding HF therapy in the future.

Acknowledgements Dr. Bozkurt is a recipient of a Merit Entry Level grant support from Veterans Affairs Medical Research Service (MRS). Dr. Deswal is a recipient of an Advanced Career Development Award (# 612 A) from the Veterans Affairs Cooperative Studies Program. This research was financially supported under grants HL58081, HL42250, HL073017, and UO-1HL084890-01 from the National Institutes of Health.

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