

Review Article

The Role of Inflammation in Heart Failure: New Therapeutic Approaches

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Key words:

Inflammation, heart failure, proinflammatory cytokines.

Manuscript received:
October 21, 2009;
Accepted:
February 10, 2010.

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Hear failure (HF) is a syndrome that has shown increasing morbidity and mortality during the last decades. Apart from myocardial hypertrophy, the pathogenetic mechanisms of HF also include deregulation of the neurohormonal system, with disturbance of the balance between sympathetic and parasympathetic tone, and disruption of the renin-angiotensin-aldosterone system.¹⁻⁵ The important role of inflammation in HF has also been recognised.⁶ The inflammatory process can cause myocardial damage, while inflammatory agents contribute to the worsening and progression of HF.^{6,7} In this article we will review the latest data concerning the relation between HF and inflammation.

The role of inflammation in heart failure

The first data concerning the relation between HF and inflammation were recorded in 1955,⁸ when a positive correlation was found between levels of C-reactive protein (CRP) and the severity of congestive HF. In 1990, Levine et al⁶ documented a positive correlation between tumour necrosis factor alpha and chronic HF. Research carried out since then has produced new data concerning the relation between many cytokines and HF. It seems that the HF syndrome is in large

part due to an imbalance between increases in inflammatory and anti-inflammatory mediators. Table 1 gives a summary of the many cytokines that are implicated in the pathogenesis of HF.

Tumour necrosis factor alpha (TNF- α)

This factor, which is also produced in myocardial cells, took its name from the initial observation that it exerts an inhibitory effect on various tumour cells.^{31,32} It seems that both TNF- α and other related molecules cause apoptosis of myocardial cells via mechanisms of cell death (Table 2).³³ From an analysis of the VEST trial it was found that levels of this factor were directly related with the New York Heart Association (NYHA) functional stage of patients with HF and that the highest levels of TNF- α were associated with a worse prognosis. According to the investigators, this was due to negative inotropic action and a disturbance of beta-adrenergic receptor sensitivity caused by TNF- α via the inducible nitric oxide synthase (iNOS) system.⁹ Newer data show that in patients with recent onset HF the increased TNF- α levels are associated with a disturbance of left atrial function and an advanced degree of left ventricular diastolic and systolic dysfunction.³⁸ The effect of TNF- α appears to be exerted via the TNFR1 and

Table 1. Proinflammatory and anti-inflammatory agents that are elevated in patients with heart failure.

Proinflammatory effects

- TNF- α ^{6,9}
- sTNFR1^{9,10}
- sTNFR2^{9,10}
- sFas¹¹
- CD40L¹²
- TRAIL¹³
- Activin A^{14,15}
- Myeloperoxidase¹⁶
- Pentraxin-3¹⁷
- RANTES¹⁸
- CRP¹⁹⁻²²
- IL-6²³
- Cardiotrophin 1²⁴
- IL-8²⁵
- MCP-1¹⁸
- MIP-1a¹⁸

Anti-inflammatory effects

- IL-10²⁶
- IL-13²⁷
- IL-18²⁸

Proinflammatory and anti-inflammatory effects

- Adiponectin²⁹
- Resistin³⁰

TNF – tumour necrosis factor; sTNFR1/sTNFR2 – soluble TNF receptor 1/2; TRAIL – TNF- α related apoptosis-inducing ligand; RANTES – regulated on activation normally T-cell expressed and secreted; CRP – C-reactive protein; IL – interleukin; MCP – macrophage chemoattractant protein; MIP – macrophage inflammatory protein.

TNFR2 receptors. In a recent study of patients with myocardial infarction, it was shown that TNFR1 was the most powerful independent risk factor for HF and death.³⁴ The TNF- α receptors (TNFR1 and TNFR2), according to experimental data, have opposite effects as regards the remodelling, hypertrophy, nuclear factor-kappaB production, inflammation, and apoptosis that are observed in HF. TNFR1 appears to promote these processes, while TNFR2 seems to inhibit them. Nevertheless, both receptors are necessary in order to cause these pathophysiological sequelae.³⁹

Fas protein (apoptosis stimulating fragment)

Blood levels of the soluble apoptosis-stimulating protein sFas appear to be positively correlated with the severity of HF and are an independent prognostic index for outcomes in these patients.¹¹ Indeed, recent research has shown that the risk of cardiac death and hospitalisation for worsening HF increases with the sFas concentration ($p < 0.001$) and that this risk is two- to threefold greater in patients who are in the highest quartile as regards sFas concentrations, compared with those in the lowest quartile.⁷

TRAIL protein (TNF- α related apoptosis-inducing ligand)

This apoptosis-inducing protein is a connector molecule that is associated with TNF- α . TRAIL levels are

Table 2. Studies of the relation between tumour necrosis factor-alpha (and related molecules) and heart failure.

Study	Proinflammatory molecule	Population	Comments
Levine et al ⁶	TNF- α	33 HF patients, 33 controls	First to document positive correlation between TNF- α and HF
Ueland et al ¹²	sCD40L	352 HF patients, 30 controls	Positive correlation between sCD40L and acute or chronic HF
Niessner et al ⁷	sFas, TRAIL	351 HF patients	Endpoints death or rehospitalisation. Positive correlation found for sFas and negative for TRAIL
Valmingli M et al (C-Alpha) ³⁴	TNFR1	184 patients post AMI	Powerful predictive factor for HF or death in these patients
Deswal A (VEST) ⁹	TNF	1200 HF patients	Positive correlation between TNF- α levels and death
Parissis et al ³⁵	Fas, Fas-Ligand	137 HF patients	Patients with more severe symptoms had higher levels of these molecules
Ueland et al ³⁶	Osteoprotogerin	230 HF patients post AMI	Correlation between high osteoprotogerin levels and adverse outcome
Suzuki et al ³⁷	IL-1 β , IL-6, TNF- α	73 patients with acute decompensation of HF, 32 controls.	Levels elevated in patients up to 4 weeks later

HF – heart failure; sFas soluble apoptosis-stimulating fragment; AMI – acute myocardial infarction. Other abbreviations as in Table 1.

elevated in patients with HF.¹³ It seems that this protein plays an important role in the rupture of atherosclerotic plaque and in triggering acute myocardial infarction, which is one of the main causes of HF.⁴⁰⁻⁴² However, levels of soluble TRAIL protein have an inverse relation with the presence of coronary artery disease.⁴³ From a recent study, which examined 351 patients with a severe degree of HF, it was found that elevated levels of soluble TRAIL were associated with a better prognosis. Indeed, in patients whose serum levels of this protein were in the highest quartile there was 70% lower mortality compared to patients whose levels of TRAIL were in the lowest quartile ($p=0.001$).⁷

Other molecules that belong to the TNF family

Various molecules belonging to the TNF- α family have been shown to have a receptor-ligand relation. Such molecules include CD27/CD27L, CD30/CD30L, and CD40/CD40L. These molecules seem to be expressed in a higher proportion in the myocardium of patients with myocarditis and dilated cardiomyopathy.⁴⁴ Levels of CD40L, in particular, have been found to be elevated in patients with acute HF following an infarction compared with healthy controls.¹² Higher levels of CD40L have also been found in patients with chronic HF compared to controls, regardless of whether the HF aetiology was ischaemic or dilated. An increase in CD40L also appears to be correlated with a worsening of HF.¹²

Interleukin 6 (IL-6)

This is a cytokine with proinflammatory effects. It seems to have prognostic significance for the development of HF, since it was found that elderly people with elevated IL-6 levels were at increased risk of suffering from HF in the future.⁴⁵ Studies have shown that IL-6 is related with the NYHA functional stage of HF and with survival.²³ Moreover, another study has recently shown that the functional status of HF patients, as assessed by the use of the Kansas City Cardiomyopathy Questionnaire (KCCQ-s), is inversely associated with IL-6 levels.³⁵ Another study, which included 101 patients with recently diagnosed HF, found that IL-6 was associated with impaired left atrial function and more advanced left ventricular diastolic and systolic dysfunction. Specifically, IL-6 levels were inversely associated with both left atrial kinetic energy and the systolic wave measured at the level of the mitral annulus using tissue Doppler.³⁸

Cardiotrophin-1 (CT-1) also belongs to the IL-6 family, being a cytokine that shares a common receptor system with IL-6. This cytokine is associated with a large range of cardiovascular events and its production appears to be stimulated by ventricular dilation.^{46,47} It also seems that in patients with congestive HF the measurement of CT-1 levels has additional prognostic value, either alone or in combination with levels of brain natriuretic peptide.⁴⁸

Activin A

Activin A belongs to the family of transforming growth factor-beta. There are ample data to show that this cytokine plays some role in the inflammation process, as elevated levels have been found in patients with inflammatory disorders.¹⁴ Elevated levels of serum activin A have also been found in patients with HF, increasing with the severity of the disease as determined by clinical, haemodynamic and neurohormonal parameters.¹⁵ There are data indicating a possible pathogenetic role of this cytokine in myocardial remodelling. It appears to cause up-regulation of monocyte chemoattractant protein-1 by myocardial cells, thus contributing to local inflammation.⁴⁹ It has also been found to increase expression of the genes responsible for atrial and brain natriuretic peptides.⁴⁹

Cytokines originating from adipocytes

Resistin and adiponectin are proteins with proinflammatory and anti-inflammatory properties whose production by fatty tissue seems to be associated with the concentrations of other cytokines in the serum.^{50,51} High concentrations of resistin have been correlated with the presence of coronary artery disease,⁵¹⁻⁵⁴ while other studies found no such correlation.^{55,56} In one study of patients with HF it was found that high resistin levels were associated with greater disease severity and predicted an unfavourable prognosis.⁵⁷ Another study found that high resistin concentrations were associated with an increased risk of future development of HF.³⁶ Comparable findings were reported recently from the Framingham Offspring Study, which included 2739 subjects. A multi-factorial analysis showed that those patients with the highest resistin levels were more likely to suffer from HF in the future.³⁰ As regards adiponectin, there are studies that found an association between elevated levels of this cytokine and higher mortality among HF patients, independently of other prognostic risk factors.^{29,58}

Other indexes of inflammation

Apart from the cytokines described above, there is a host of other molecules that contribute to the process of inflammation and whose relation with HF has been the subject of much research in the studies summarised in Table 3.

C-reactive protein

C-reactive protein (CRP) is a widely known acute-phase protein that is produced by the liver in response to stimulation by proinflammatory cytokines such as IL-6, TNF- α , etc.⁶³ Although not an ideal index, it seems to be strongly associated with cardiovascular risk.⁶⁴ Its ease of measurement and the availability of the method make it attractive as an index for the evaluation of the inflammatory status in patients with heart disease. A series of studies have shown both low- and high-sensitivity CRP to be associated with the existence of HF.¹⁹⁻²² Large prospective studies show that high CRP levels in the elderly predict the

development of HF.²² Recently, in a large study that involved 4691 subjects from the general population, it was found that the relative risk of hospital admission for HF was twofold in those whose CRP levels were above 3 mg/L.⁶² Indeed, some studies have found an association between CRP and the stage of HF and claim that CRP levels predict the probability of readmission to hospital due to a deterioration in the functional stage of HF.^{20,65} However, it remains to be elucidated whether CRP is associated with left ventricular ejection fraction. Some studies found no statistically significant correlation between CRP and left ventricular ejection fraction,^{19,20,65} whereas others found a stronger correlation.⁶⁰

Adhesion molecules

Here we refer to a variety of molecules such as vascular cell adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1), and P, E and L selectins. These molecules are expressed on the cell surface and assist in the adhesion of cells to oth-

Table 3. Studies of the association of proinflammatory molecules and cytokines with heart failure.

Study	Factors studied	Population	Comments
Yamaoka et al ²⁶	TNF- α , IL-10, IL-10R	68 HF patients, 31 controls	Positive correlation
Ohtsuka et al ²⁷	VEGF, IL-10	30 patients with dilated HF, 15 controls	Higher levels of these agents in patients
Yamaoka-Tojo et al ²⁸	Il-18, IL-10, hsCRP, BNP	86 HF patients	Patients with higher NYHA stage had higher levels
Tousoulis et al ⁵⁹	VCAM-1, ICAM-1	12 patients with dilated HF & 23 with ischaemic HF, 11 controls	Higher levels found in HF patients. VCAM-1 levels related to NYHA stage
Shah et al ⁶⁰	CRP	98 patients	Positive correlation of CRP and BNP with LVEF
Adamopoulos et al ⁶¹	TNF, sTNFR1, sTNFR2, IL6, sIL-6R, sFas, sFas ligand	24 HF patients & 20 controls	Reduction in these indexes with exercise programme
George et al ²⁹	Adiponectin, NTpro-BNP	175 HF patients & healthy controls	Elevated adiponectin levels found in patients + positive correlation with NYHA stage and NTpro-BNP
Chrysochoou et al ³⁸	IL-6, TNF- α , CD14	101 HF patients	Positive correlation with indexes of LV diastolic & systolic function and left atrial diastolic dysfunction
Frankel et al ³⁰ (Framingham Offspring Study)	Resistin, adiponectin	2739 subjects monitored for a mean of 6 years	Positive correlation between resistin levels and future development of HF
Engstrom et al ⁶²	CRP	4691 subjects monitored for a mean of 13 years	Positive correlation between high CRP levels and future development of HF

VEGF – vascular endothelial growth factor; NYHA – New York Heart Association; VCAM – vascular cell adhesion molecule; ICAM – intracellular adhesion molecule; hsCRP – high sensitivity C-reactive protein; BNP – brain natriuretic peptide; LV – left ventricular; EF – ejection fraction; NTpro-BNP – N-terminal pro-BNP. Other abbreviations as in previous tables.

er cells and to the extracellular matrix. The expression of adhesion molecules is regulated by proinflammatory cytokines and their presence is associated with a variety of cardiovascular diseases.⁶⁶ One study found that plasma levels of ICAM-1 were higher in patients with HF of either dilated or ischaemic aetiology compared to healthy controls, while plasma levels of VCAM-1 were higher in the HF group taken as a whole than in controls. The same study also found that HF patients in NYHA stage IV had higher VCAM-1 levels than those in stages II and III.⁵⁹ The same finding was reported by another study, where HF patients with a worse functional stage had higher levels of VCAM-1.³⁵ It also appears that patients with an acute coronary syndrome who have higher levels of adhesion molecules have a worse prognosis, with a greater probability of developing HF.^{67,68} According to a recent study, plasma levels of ICAM-1 in patients with HF are an independent prognostic factor for the symptoms of depression that are observed in these patients.⁶⁹

Myeloperoxidase

This is an enzyme that is mostly found in the granulocytes of neutrophils and monocytes. It is released when these cells are activated and so contributes to the immune response. It catalyses low-density lipoprotein (LDL) oxidation, thus contributing to the development of atherosclerotic lesions.⁷⁰ It also appears to be involved in causing endothelial dysfunction via a reduction in nitric oxide (NO).⁷¹ Recently, in an experimental model, it was found that myeloperoxidase can participate in the remodelling and dilation of the left ventricle after a myocardial infarction, thus contributing to the development of HF.^{72,73} A number of studies have demonstrated interesting associations between HF and myeloperoxidase. In one recent study, which included 285 patients with congestive HF and 35 healthy controls, it was found that the HF patients had statistically significantly higher levels of serum myeloperoxidase.¹⁶ In HF patients the levels of myeloperoxidase were positively correlated with NYHA stage, while the type of HF (ischaemic or other cause) made no difference. Moreover, it was found that the combination of serum myeloperoxidase levels and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) was a more reliable predictor of mortality than NT-pro-BNP levels alone.^{16,74} Finally, we found that short-term treatment with rosuvastatin regulates the inflammatory process in patients with heart fail-

ure by significantly reducing plasma levels of myeloperoxidase.⁷⁵

Lipoprotein-associated phospholipase a2 (Lp-PLA2)

This phospholipase is an enzyme that is found in the circulation, bound with LDL. This enzyme has both proinflammatory and anti-inflammatory properties. There is an association between the risk of developing coronary artery disease and Lp-PLA2, while recent data show a correlation between endothelial dysfunction in the coronary vessels and this phospholipid.^{66,76-79} These data confirm the proinflammatory effects of Lp-PLA2. In a subpopulation of the Rotterdam study, Lp-PLA2 levels were measured in 1820 individuals and were found to be positively related to the development of HF. Specifically, it was found that for each unit of increase of Lp-PLA2 the relative risk of HF increased by 1.03, while for those who were in the top quartile the relative risk was almost double compared to those in the bottom quartile.⁸⁰

Pentraxin-3

This is a long pentraxin that is produced by a variety of cells in response to inflammatory stimuli such as IL-1 or TNF- α .⁸¹ Thus, plasma levels of pentraxin-3 increase within a matter of hours after the experimental administration of proinflammatory cytokines.^{81,82} They also appear to be related to acute myocardial infarction.⁸³ Studies have shown that levels of this protein are elevated in patients with HF compared to healthy controls, while the increase is proportional to the NYHA stage of HF. Patients with higher levels of pentraxin-3 have also been found to have more cardiac events than those with lower levels.¹⁷

Apart from the above, many other inflammatory molecules and cytokines have been studied in relation to HF. Some of these studies are summarised in Table 3.

Relation between inflammatory cytokines and HF

A series of studies have documented the pathogenetic role of inflammation in HF and in particular the role of inflammatory cytokines. The so-called “cytokine hypothesis” (Figure 1) asserts that the progression of HF is due, at least in part, to the destructive action of these factors and that many of the pathogenetic sequelae of HF are due to inflammatory cytokines.

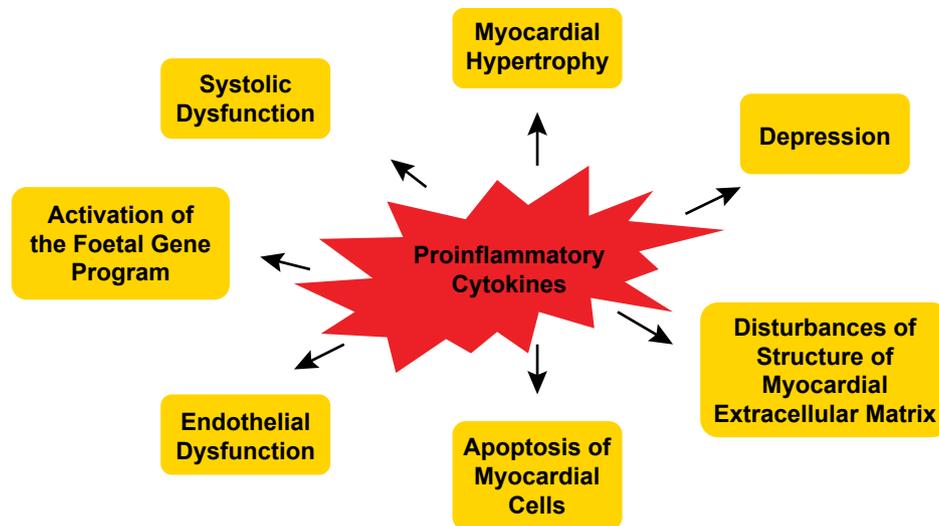


Figure 1. Proinflammatory cytokines act on cardiac and extra-cardiac tissues, thereby participating in the pathogenesis and progression of heart failure.

Effect of cytokines on left ventricular function

Findings from a number of studies have shown the effect of proinflammatory cytokines and other mediators of inflammation on left ventricular function.^{34,38,60,84-86} Recent data show that inflammatory cytokines such as TNF- α , TNFR1 and IL-6 are related with echocardiographic indexes of both systolic and diastolic left ventricular function.^{34,38} Indeed, experimental data have shown that a reduction in the effect of inflammatory cytokines on the myocardium inhibits the progression to HF. Thus, after the induction of myocardial infarction in animals, blocking the action of nuclear factor-kappaB, an agent that regulates inflammatory processes, appeared to improve their left ventricular systolic and diastolic function.^{85,86}

Effect of cytokines on left ventricular remodelling

By the term “remodelling” we mean the changes that occur in the shape, size and composition of the myocardium in response to harmful agents. Inflammatory cytokines exert significant effects on the process of ventricular remodelling. Most of the data we have refer to the effects of IL-1 and TNF- α . Experimental data show that a lack of IL-1 β and IL-18 reduces ventricular dilation after a myocardial infarction.⁸⁷ Also, ventricular dilation and changes in collagen composition have been observed in animals that have over-expression of TNF- α .⁸⁸ Finally, the administration of IL-10 to animals caused a reduction in inflammatory

processes and a reduction in ventricular remodelling after the induction of myocardial infarction.⁸⁹ The same occurs after blockage of the action of nuclear factor-kappaB, when there is a relative inhibition of remodelling after experimentally induced myocardial infarction.⁸⁶

Effect of cytokines on the endothelium

Patients with HF are characterised by endothelial dysfunction that not only causes a disturbance of myocardial function, but is also responsible for a reduced blood supply to peripheral organs, partly explaining features of HF such as reduced exercise tolerance and hepatic dysfunction. Inflammatory cytokines cause endothelial dysfunction in a variety of ways. Firstly, they induce the production of adhesion molecules and cytokines by endothelial cells, which in turn increase the inflammatory response of the vascular wall and lead to a cycle that causes excessive activation of the endothelium in HF. Secondly, cytokines alter the balance between endogenous vasodilators (such as NO) and vasoconstrictors (e.g. endothelin-1), causing a state of vasoconstriction.⁹⁰ This mechanism is particularly important, since interventions with drugs, such as statins, that increase the bioavailability of NO improve the endothelial function of patients with HF.⁹¹⁻⁹³ Thirdly, a number of studies have shown that molecules of the TNF- α family, which are known to be elevated in chronic HF, can directly induce the apoptosis of endothelial cells, caus-

ing further endothelial dysfunction.⁹⁴ Also important is the ability of inflammatory cytokines to stimulate the production of reactive oxygen species, which in their turn cause additional disturbance of endothelial function.⁹⁰ Finally, statin therapy increases the number of circulating endothelial progenitor cells in patients with heart failure, irrespectively of changes in the inflammatory and oxidative status.⁹⁵

Effect of cytokines on the muscles (cachexia) and other organs

Chronic HF is a dynamic disturbance of many organs and systems. Thus, apart from the myocardium, its effects extend to the function of the gastrointestinal system, the kidneys, and the musculoskeletal system. Cardiac cachexia is characterised by a loss of mass and the atrophy of muscles and tissues in other organic systems. Cachexia is accompanied by anorexia, weight loss, loss of muscle mass and body fat, and a change in the metabolism of glucose and lipids by the liver, and is associated with a poor prognosis. Cachexia is considered to be the result of an interaction between various cytokines, neuropeptides, stress hormones, and intermediate factors in lipid metabolism.⁹⁴ Given that TNF- α was initially named cachectin, it comes as no surprise that inflammatory cytokines play a central role in the pathogenesis of cardiac cachexia.⁹⁶ Thus, studies have shown that TNF- α , IL-1 and IL-6 are related with proteolysis, alterations in lipid metabolism (i.e. an increase in lipolysis and a reduction in lipoprotein lipase activity), muscle atrophy, and with apoptosis of muscle cells and weight loss.⁹⁶ To conclude, we can say that cardiac cachexia is not due only to neurohormonal disturbances, but to the systemic inflammation that accompanies HF.

Effect of cytokines on haematopoiesis

Anaemia is a common feature in chronic HF and exacerbates both the functional incapacity of the myocardium and the symptoms of the disease, causing a reduction in exercise tolerance and easy tiring. Anaemia predisposes to poor survival, independently of other known prognostic indexes.⁹⁷ The anaemia that accompanies HF is due to various factors, such as suppression of bone marrow, reduced iron uptake in the bowel, and haemodilution. Systemic inflammation is what all these have in common.⁹⁸ Specifically, TNF- α , IL-1 and IL-6 interfere with erythropoietin production and cause resistance to its action. In ad-

dition, inflammatory cytokines are likely to have a direct effect on bone marrow, disturbing erythropoiesis via progenitor cell apoptosis.⁹⁹ This is also suggested by the disturbance of bone marrow haematopoiesis that is observed after experimental induction of HF.¹⁰⁰ We also know that, in conditions characterised by chronic inflammation, IL-6 induces the production of hepcidin by hepatocytes, which inhibits iron release by macrophages and prevents the absorption of iron by the bowel, leading to a reduction in iron reserves.¹⁰¹ The same mechanism may occur in chronic HF, when IL-6 levels are known to be elevated.

Effect of cytokines on emotion

It is well known that HF and depression often coexist. Sufferers from both HF and depression show increased mortality and have a worse quality of life.¹⁰²⁻¹⁰⁴ The “cytokine model” proposes that proinflammatory cytokines are implicated in the pathogenesis of depression.^{105,106} Studies have shown that proinflammatory cytokines such as TNF- α , soluble tumour necrosis factor receptor, IL-1, IL-2 and IL-6 are elevated both in HF and in depression, and that their increase is related with the symptomatology of depression.¹⁰⁷⁻¹⁰⁹ Indeed, it appears that antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRI), serotonin nor-epinephrine reuptake inhibitors (SNRI), and tricyclic antidepressants (TCA), when given to patients with HF and depression, reduce the levels of inflammatory cytokines such as TNF- α and CRP. The level of reduction in inflammatory agents depends on the kind of antidepressant agent administered, since patients treated with SNRI or TCA show lower levels of TNF- α and CRP than those treated with SSRI.¹¹⁰

Conclusions

Patients with HF are characterised by systemic inflammation, as evidenced by increased levels of a variety of cytokines, while the degree of elevation is related to the severity of the disease. Although the precise mechanism of systemic inflammation is unknown, a growing body of data shows that inflammation plays a role in both the development and the progression of HF, and influences not only myocardial function but that of other organs, thus actively participating in the full manifestation of the complex syndrome of HF. Further studies will be necessary in order to investigate the role of inflammation and to seek possible therapeutic approaches.

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