Review Article

Immune-Inflammatory Activation in Heart Failure

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Summary

Despite being relatively recent, a growing and significant accumulation of experimental and clinical evidence has been observed that points to a gradual state of immune-inflammatory activation in patients with heart failure (HF). High levels of several cytokines are found in the circulation and cardiac muscle of individuals with HF, and invariably correlate with the severity of the disease. These cytokines act on endothelial dysfunction, oxidative stress, induction of anemia, myocyte apoptosis, and on the progressive loss of skeletal muscle mass – which is conventionally called the inflammatory paradigm of HF.

Not only the myocardium, but also several tissues seem to synthesize these cytokines and perpetuate this continuous inflammatory state at a low degree, including leukocytes, monocytes, skeletal muscle cells and endothelial cells – in response to hemodynamic and infectious stimuli, to hypoxia, to oxidative stress, to neurohumoral activation, and others. Thus, a network of molecules that interact with each other is formed, and connections with other axes that effectively contribute to the clinical deterioration of the patients are also established – which fits into the pathophysiological model of multisystemic involvement that has been increasingly attributed to HF.

Although the determination of these biomarkers in peripheral blood provides solid evidence of prognostic power, the results of therapeutic trials that modulated the immune-inflammatory loop in the clinical phase have been, so far, hardly encouraging. Therefore, we believe that a better understanding of the inflammatory activation and its multifaceted relation with the axes of decompensation of the disease is key for new therapeutic perspectives with a relevant impact to be established in the near future.

Introduction

Congestive heart failure (HF) syndrome has become an alarming public health problem for most countries, achieving a very high socioeconomic impact that results mainly from hospitalization, medication and intervention expenses, as well as from indirect costs related to the reduction in the quality of life and to productivity loss[1-3].

Two million Brazilians are currently estimated to live with HF, and up to one third of hospital admissions in the Brazilian public health system are estimated to result from this disease[2,3]; moreover, among patients older than 60 years of age, HF is the major cause of hospital admissions and mortality in Brazil and in the rest of the Western world[1,3]. The epidemiological setting seems to be even more discouraging: there is enough evidence suggesting that this problem will worsen in the future, since prevalence and mortality rates only increase year after year, in direct contrast to what has been observed for several other cardiovascular disorders[2,3].

All these considerations, that were formulated for a disease whose pathophysiological mechanisms have been recurrently reviewed and reformulated in the past years, only show how challenging it is to bring out the multifaceted character and the multisystemic progression inherent to HF[1,4]. The development of HF, as we understand it today, involves changes in several homeostatic systems, so that the syndrome may be seen as a progressive multiorgan disorder which, once originated in the heart, spreads and affects many other extracardiac sites[4,5]. These pathophysiological processes encompass metabolic pathways which, although distinct, are interlinked and interact with each other, thus contributing to perpetuate and promote heart failure and cardiac remodeling, skeletal muscle cachexia, and endothelial dysfunction that characterize the most advanced forms of the disease[1,4]. Even in the milder and more incipient forms of HF, these changes are already present and have been recently evaluated as potential markers for an early diagnosis and can, moreover, be useful as indicators of risk and prognosis[4].

In this sense, immune and inflammatory changes have been recognized and evaluated with increasing interest in the past years. This results mainly from the reproduction of the changes that these mediators can produce in experimental models, mimicking phenotypes and different clinical patterns of the HF syndrome, notably in the subcellular and cellular processes associated with remodeling[4,5].

By extrapolating these experimental evidences to clinical studies, high levels of cytokines such as TNF-α, IL1 and IL6 in the circulation and in the cardiac muscle of individuals with HF have been observed to bring important prognostic information, so that these substances have been recurrently implicated in the mechanisms of progression of the disease[4-11]. These studies have generated an inexorable accumulation of evidence pointing to a progressive and repetitive state of immune-inflammatory activation associated with the progression of ventricular dysfunction, with an intense release and activation of cytokines, complement, autoantibodies, adhesion molecules and other substances in the bloodstream[4,5].

Key words

Adjuvants, immunologic; cytokines; cardiac output, low/immunology; inflammation.

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Cytokines are molecules that interlink, amplify and propagate the immune response, and are involved in recruiting cells to areas of inflammation, stimulating cell division, proliferation and differentiation[4]. Not only immune cells, but also fibroblasts, platelets, endothelium, vascular smooth muscle, and cardiomyocytes themselves, especially under stimulus of hypoxia, mechanical stress and endotoxins, are able to produce a broad and varied spectrum of these biological peptides[4-6]. The action of cytokines on the cardiovascular system is well supported by experimental bases that demonstrate a promotion of inflammation, endothelial dysfunction, intravascular coagulation, uncoupling of beta-adrenergic stimuli, generation of free radicals, progressive muscle mass wasting and exercise intolerance, among other effects[4-6]. The main actions observed for cytokines in myocardial cell cultures and in experimental models of heart failure are shown in Table 1.

In parallel with these observations, several researchers have started to study how cytokines would be activated in patients with HF – what would be the stimuli working as "provokers" – and what production sites would lead to the elevation of their circulating levels[4,5,8]. All these studies are necessarily based on the understanding that, once the origin and pathways of production of these substances were known, we could contribute to halt the progression of the multisystemic failure that is inherent to advanced HF.

Table 1 – *In vitro* cytokine actions on the cardiovascular system

Direct toxic lesion on cardiomyocytes
Stimulus to apoptosis and cardiomyocyte hypertrophy
Direct stimulus on metalloproteinases of the extracellular matrix
Generation of free radicals in the cardiac tissue
Stimulus to the synthesis of other proinflammatory cytokines (IL-1, IL-6, for instance)
Skeletal myopathy: direct stimulus to apoptosis and myofibril necrosis
Direct alteration of the intramyocytic calcium metabolism
Promotion of endothelial dysfunction
Promotion of synthesis of adhesion molecules and acute phase proteins

Mechanisms of cytokine synthesis in heart failure

Myocardial production

Experimental evidence of TNF-α synthesis in feline myocardium was initially observed by Torre-Amione et al[8,9] when they correlated, in a directly proportional manner, the degree of distension of the left ventricular (LV) cavity with the local TNF-α production. Shortly afterwards, the same researchers and Ferrari et al[10] were pioneers in observing the presence of mRNA and cytokine receptors in human myocytes isolated from necropsy hearts. Based on these observations, Torre-Amione et al[8,9] considered a mechanism of myocardial production of TNF-α to justify the elevated levels of cytokines in HF, where the diastolic wall distention associated with increased filling pressures would lead to a local overexpression of TNF-α, and cytokines would spillover to the circulation, thus contributing to the immune activation and systemic inflammatory status, as shown in Figure 1.

Extramyocardial production

Hasper et al[11] hypothesized that the inefficient vasodilator response and the reduced aerobic enzyme activity characteristic of the multiorgan involvement of HF would be sufficient stimuli to cause a systemic cytokine overexpression, notably in skeletal muscles. Tissue hypoxia and free radical generation are potent stimuli for the synthesis of NFκ-β-associated cytokines in immunocompetent cells of the whole body[4,11]; with the progression of the disease, the inexorably elevated levels of cytokines would worsen the endothelial dysfunction,

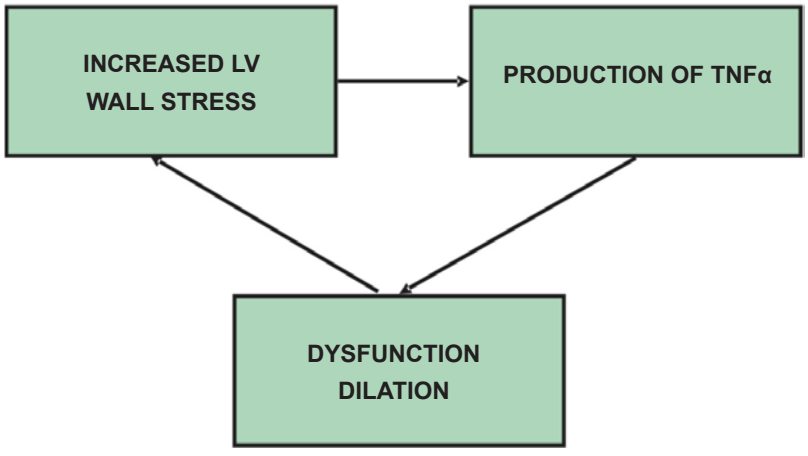

Fig. 1 - *Hypothesis of myocardial cytokine production in HF.*

tissue hypoxia, and skeletal muscle apoptosis even more, and this would serve as a stimulus for the systemic synthesis of cytokines and oxidative stress, thus creating a vicious cycle of perpetuation of the disease and promotion of cachexia that is faithfully close to the model of multisystemic progression of HF[12,13]. These relations are shown in Figure 2.

Intestinal production: the endotoxin-cytokine hypothesis

When Anker et al[14] observed a concomitant TNF-α and soluble CD14 receptor (sCD14) elevation in the peripheral blood of patients with advanced HF, they conceived a model of cytokine activation in HF that would necessarily involve the production of endotoxins derived from intestinal bacteria. They analyzed the peripheral levels of these substances in 47 patients with advanced HF (29 of ischemic etiology) and in 17 healthy controls without structural heart disease or acute/chronic inflammatory conditions[14]. The levels of sCD14 were increased in patients with HF, especially in cachectic ones, and a strong correlation between the levels of sCD14 and of TNF-α, sTNF-R1 and sTNF-R2 was observed – thus suggesting that endotoxins (ETX) were somehow involved in the immune-inflammatory activation of HF[14].

Thus, Anker et al[14] hypothesized that, in patients with HF, the interaction between CD14 receptors of immunocompetent cells and ETX released by gram-negative bacteria (GNB), possibly from the gastrointestinal tract, would result in the signal transduction required for the production of IL6, TNF-α, and other proinflammatory cytokines. This interaction is actually documented as the most potent endogenous reaction capable of releasing TNF-α[4,14,15]. With the purpose of corroborating the initial hypothesis, these investigators later demonstrated that patients with HF and peripheral edema have higher levels of sCD14, TNFα and ETX than those without edema, and the latter present higher levels than healthy controls without the disease[15]. Moreover, after a mean 40-day treatment with diuretics, a significant decrease in ETX levels and a tendency of decrease in TNF-α levels were observed[15].

Anker et al[14] suggest that their results support the hypothesis that the congestion of the intestinal wall (deemed present in patients with systemic venous congestion) would induce a proliferation of indigenous bacteria, with translocation and/or ETX release in the bloodstream.

The indigenous microflora of the human gastrointestinal tract comprises a colony of more than 10^{16} microorganisms of more than 400 different species in a complex, yet stable, symbiotic relationship with the cells from the mucosal layer[16]. This usually stable pattern of colonization may undergo significant changes in several diseases, such as liver failure and HF, in food deprivation states and in the critically ill patient in general[17]. There is a consensus, resulting mainly from clinical studies conducted in intensive care settings, that translocation of bacteria and/or their products through the intestine plays a key role in starting or sustaining the clinical failure not only via the systemic dissemination of bacteria, but also fundamentally via the local production of proinflammatory factors in the lymphoid tissue and in the bloodstream[17,18]. How far we can extrapolate these observations on intestinal translocation in severely ill patients and experimental shock models to the context of HF remains a source of endless debate.

Thus, in Anker et al's hypothesis[14], after translocation there would be immune activation via binding of circulating ETX to CD14 receptors, with release of sCD14 into the bloodstream, which can be detected in plasma[15,18,19]. Despite the small sample used, Anker et al's studies[14] represent, to date, the main basis for what has been conventionally called the hypothesis of bacterial-endotoxin-induced cytokine production, or simply "endotoxin-cytokine hypothesis"[18]. The cellular and subcellular mechanisms of this hypothesis are shown in Figures 3A and 3B.

In an excellent pilot study, Conraads et al[20] were pioneers in evaluating the therapeutic potential of selective intestinal decontamination (SID) on inflammatory activation in advanced HF. The authors studied 10 patients with NYHA FC III and IV undergoing a SID regimen with nonabsorbable antibiotics (polymyxin B and tobramycin for eight weeks) and observed that the treatment was able to eradicate intestinal GNB and

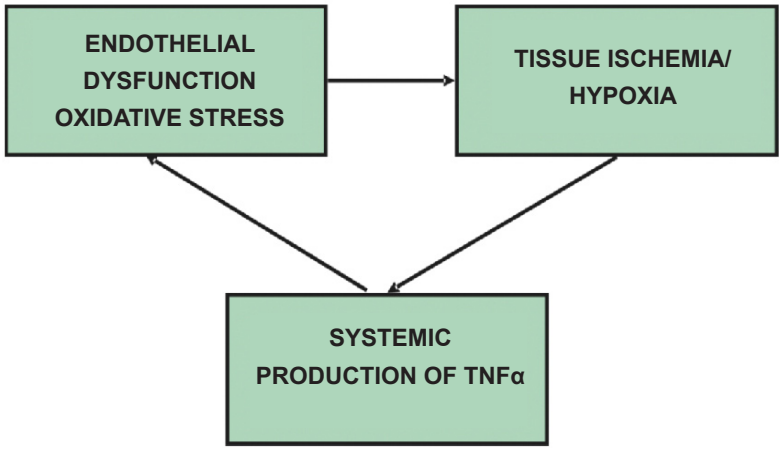

Fig. 2 - *Hypothesis of extramyocardial cytokine production in HF.*

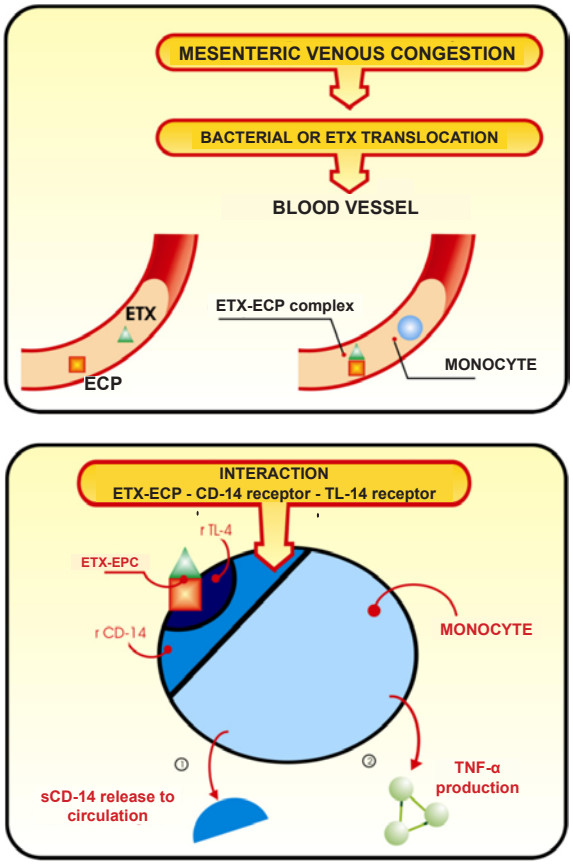

Fig. 3 - *Cellular (A) and subcellular (B) mechanisms related to the immune-inflammatory activation by serum ETX in HF. ETX - endotoxin; ECP - ETX carrier protein; rTL-4 - tool-like receptor 4; rCD14 - CD14 receptor; sCD14 - soluble portion of CD14 receptor.*

to significantly reduce blood and fecal levels of ETX, as well as serum levels of IL1, IL6 and TNF-α. With these results, these authors open the possibility for further studies on the intestinal bacteria approach to prove, with a higher power and better statistical design, their initial favorable impressions. Our team is conducting a randomized, double-blind, placebo-controlled study in patients with advanced HF – who are those with the highest level of inflammatory activity among those with the disease, and we intend to confirm whether the judicious eradication of ETX-producing enterobacteria is actually able to reduce the degree of inflammatory activity in HF.

Main cytokines implied in inflammatory activation of heart failure

Tumor necrosis factor alpha

The main TNF-α production site is the activated macrophage, but many other cell types, such as fibroblasts, neutrophils, endothelial cells, vascular smooth muscle, and cardiomyocytes themselves have also already been implicated as sources under stimuli of hypoxia, mechanical stress and endotoxins[5,6]. TNF-α is released as a stable homotrimer; under this form, the molecule has an extremely short half-life of approximately 30 minutes, and is measured in the serum by using both immunoreactive and cytotoxic assays[6].

The biological actions of TNF-α are mediated by two types of cell receptors located all over the body, known as receptors 1 and 2 (TNF-R1 and TNF-R2)[8-10]. Among them, TNF-R1 is the most important because it mediates the main cell effects, initiating a cascade of cytotoxic and apoptotic responses[6,10]. Experimental evidence suggests that it is via TNF-R1 that cytokines also determine a direct stimulus on fibroblast proliferation and synthesis of prostaglandin E2 and superoxide dismutase, in addition to antiviral activity and bacterial resistance[8].

Many of the clinical patterns observed in patients with HF are reproduced in pre-clinical models by the direct action of TNF-α[4,6]. Several studies corroborate a very close experimental relationship between TNF-α and cardiac muscle hypertrophy and necrosis, in addition to extracellular membrane (ECM) disarrangement and intramyocytic calcium mobilization[6].

TNF-α also induces increased baseline catabolism by stimulating apoptosis, both in vivo and in vitro, by activating the caspases pathway – which could contribute to a very particular aspect of the HF syndrome, the one that has been conventionally named cardiac cachexia[12]. TNF-α also induces myocyte necrosis via a cytotoxic mechanism related to the complement pathway, to the induction of NO synthase, and to the increased local production of free radicals[6,12].

Nuclear factor κ-β

NFκ-β is a transcription factor that regulates several proinflammatory substances and may be activated by multiple stimuli such as hypoxia, reactive O_2 species, bacterial endotoxins, cytokines and others[6,21]. The myocardial tissue of patients with HF of different etiologies exhibits overexpression of this molecule and of the genes that it regulates, such as that associated with the synthesis of TNF-α, NO, leukocyte-adhesion molecules, and metalloproteinases[21]. It has already been demonstrated that many cell types such as endothelial cells, macrophages, leukocytes, and cardiomyocytes in culture synthesize NFκ-β in response to some cytokine stimuli in a positive feedback pattern that sustains the inflammatory activation per se[21].

Interleukin-6

IL-6 is a multifunctional cytokine which, thanks to the accumulation of experimental and clinical evidence, is linked to the progression of cardiac dysfunction because of the worsening of functional limitation and rehospitalizations due to decompensated disease[13,22]. IL-6 promotes lymphocyte proliferation and maturation, cardiomyocyte hypertrophy, and stimulates the synthesis of caspases and of hepatic mediators of the acute response, such as CRP[6,22]. IL-6 also proved to be able to induce in vitro muscle proteolysis, thus leading to wasting and weight loss[13].

In a recent study, Plenz et al[22] observed hearts of patients with advanced HF at the moment of organ explantation for transplantation and found a mRNA, IL-6 and IL-6 receptor

expression inside the myocardial tissue significantly greater than that found in RV biopsy specimens of individuals with no structural disease undergoing electrophysiological study[22].

Although myocardial production of IL-6 may seem significant, an equally or even more significant peripheral synthesis is suggested. A prognostic study showed that peripheral IL-6 levels are not only significantly increased in femoral artery and veins of patients with HF, but also an IL-6 spillover to the circulation would occur, represented by the arteriovenous difference of IL-6 for one determined patient, that increases with the severity of the disease, and is independently and significantly correlated with a worse prognosis[13].

Munger et al[23] conducted a retrospective study with 78 patients with FC III and IV HF and found a significant increase in IL-6 levels in patients with more advanced disease and worse progression, regardless of the etiology[23]. Lommi et al[24] observed that IL-6 levels are directly related to filling pressures, and inversely related to cardiac output, thus apparently reflecting a hemodynamic deterioration.

In an intriguing study, Kell et al[25] analyzed plasma concentrations of IL-1, IL-6, IL-10, IL-12, TNF-α, and s-CD-14 in 91 patients with NYHA FC III HF, and EF < 40%. After a 22 ± 13-month follow-up, and using the multivariate regression analysis, IL-6 proved to be the prognostic marker of survival with the greatest independent predictive power in one year. Moreover, the combination of EF and VO_2 values increased the risk prediction.

Interleukin-1

All mammalian species are able to express two genes associated with IL-1 synthesis in monocytes; in humans, most of the body cell types can produce IL-1 under optimal conditions[6].

The mechanism through which IL-1 triggers its proinflammatory effects seems to involve prostaglandin synthesis and, perhaps, a direct action on beta-receptor uncoupling[6]. Thaik et al[26] studied rat cardiomyocyte cultures and observed that the IL-1β stimulus is able to cause hypertrophy via a NO-independent mechanism, with induction of fetal gene synthesis and downregulation of genes that regulate intramyocytic calcium dynamics. Francis et al[27] attributed a negative inotropic effect to IL-1 that could depress myocardial contractility by directly stimulating NO synthesis.

IL-1 soluble receptors have been considered the most sensitive and reliable markers of activation of the IL-1 loop, and are more strongly correlated with the severity of several diseases such as HF or sepsis, where peripheral levels of IL-1 are usually low, which makes them difficult to be detected through the currently available assays[6]. Recently, peripheral detection of a soluble form of IL-1 membrane receptor called sT2 has been reported as predictive of events in experimental models of HF and MI[28].

C reactive protein (CRP)

Despite all the recent technological armamentarium, liver release of CRP seems to be a pretty sensitive, specific indicator with a high prognostic correlation in different degrees of inflammatory states – and this results from the CRP property of interfering with practically all stages of the immunoinflammatory response, once released in the circulation[29].

Several stimuli seem to be involved in the direct regulation of the hepatic synthesis of CRP, however IL-6 seems to be the major one[22,29]. Other cytokines such as IL-1β and TNF-α also influence directly the in vitro release of CRP, albeit to a lower extent[29].

Sato et al[30] observed high CRP levels (2.6 ± 0.8 mg/dl) in patients with decompensated HF free of associated ischemic or infectious events; these levels were significantly reduced after resolution of the symptoms related to the acute manifestations. Other authors reached similar conclusions in groups of patients with decompensated HF – recently, Mueller et al[31] and Lamblin et al[32] confirmed the prognostic impact of CRP determination in patients with decompensated HF by randomizing a group of almost 800 patients and confirming a strong and independent association between serum levels of CRP and mortality.

Our team also analyzed the prognostic value of serum levels of CRP in patients with decompensated HF: after a mean one-year follow-up of 119 patients with NYHA functional class III or IV, the best cut-off point determined for CRP was 3 mg/dl, a value close to that found by Sato et al[30] in a similar group of patients. Thus, CRP ≥ 3 mg/dl suggests a population of patients with HF at a higher risk – whose mortality reached 49% by the end of 12 months in our case series. These CRP levels are much higher than those found in primary and secondary prevention of ischemic disease. Among all the variables tested in the study, CRP was the one that best correlated with survival time, using Cox regression test.

In fact, when CRP is elevated in patients with decompensated HF, it seems to be a low-cost, easily available independent predictor of survival; what still remains unclear is whether CRP is elevated as a mere passive marker of the process, or whether it actually works as a direct effector in the inflammatory component associated with both the instability of atherosclerosis and the endothelial dysfunction that characterizes the progression of HF[32,33].

Uric acid

Serum uric acid is significantly elevated in patients with HF in relation to individuals without the disease, regardless of renal function or diuretic treatment, and is directly correlated with the functional limitation and survival, mainly in cachectic patients[34,35]. Hyperuricemia is a quite reliable marker of inflammatory cytokine activation, of endothelial dysfunction, and of oxidative stress; in fact, uric acid synthesis catalyzed by xanthine-oxidase also generates superoxide radicals, hydroxyl, and hydrogen peroxide[35].

In addition to the oxidative potential, uric acid could also induce several direct harmful effects, such as the stimulation of smooth muscle proliferation, renin synthesis, reduction of intramyocardial NO synthesis, and reduction of calcium release by the sarcoplasmic reticulum in cardiomyocytes[34].

Anker et al[34] studied 294 patients hospitalized for decompensated NYHA FC II and III HF, and observed that the best value predictive of mortality for uric acid was 9.50 mg/dl at 12 and 18 months of follow-up; uric acid levels above this value were related to a survival of 52% and 36% at 12 and 18 months, respectively.

The group of patients with uric acid ≤ 9.50 mg/dl, in turn, had a survival of 92% and 86% at 12 and 18 months, respectively.

Regardless of the theoretical considerations that emerge from experimental analyses, there seems to be clear clinical evidence that the oxidative stress is the link between uric acid and the different alterations related to the progression of HF, such as endothelial dysfunction, cytokine activation, and cardiomyocyte apoptosis[34,35]. It is still relatively early to know whether hyperuricemia and the oxidative stress that it triggers are actually key actors in this process. A large study with allopurinol is being conducted and shall bring many explanations in this sense[36].

Immune-inflammatory activation in Chagas heart disease

Similarly to what is seen in idiopathic cardiomyopathy, plasma levels of TNF-α and IL-10 are only mildly elevated in the indeterminate phase of Chagas heart disease, and increasing levels are found in individuals with overt heart disease. Despite the broad spectrum of myocardial involvement, alterations in the endothelial function, in the oxidative balance, and in the homeostasis of the immune system are already present in asymptomatic individuals, and become marked in patients with severe ventricular dysfunction[37,38].

In acute myocarditis caused by *Trypanossoma cruzi*, the major mechanism implicated seems to be a direct autoimmune aggression against myosin chains, as a result of mimicry of parasite epitopes[39]. This molecular mimicry is similar to that seen, for instance, in the cross-reaction between beta-hemolytic streptococci and cardiac tissues in patients with rheumatic heart disease[40]. In chronic Chagas heart disease, there are evidences of a persistent aberrant cytotoxic immune response to *T. cruzi* antigens that is related to the progression of the disease, in a mechanism that is not seen in idiopathic or ischemic dilated cardiomyopathy[41]. In fact, the persistence of the parasite that occurs in the indeterminate and advanced phases of the disease suggests a deficiency in the suppression mediated by T cells, in lymphocytic polyclonal activation, and in the mechanisms of apoptotic clearance that may also contribute directly to myocardial aggression[41].

However, the reason why only a minority of individuals with the latent form of the disease will progress to the spectrum of cardiac involvement still remains unclear; the mechanisms associated with the relations of tropism between the various strains of *T. cruzi* and the cardiac tissue, the different and unforeseeable participations of T-cell-mediated response, and polymorphisms in cytokine synthesis in those patients are potential sources of studies for further clarification of these questions[39,41].

Clinical evidences

Levine et al[7] were the first ones to report that serum levels of TNF-α were much higher in patients with HF (115 ± 25 U/ml) than in healthy controls (9 ± 3 U/ml, $p < 0.001$), and that individuals with higher levels of TNF-α were the most cachectic and those with the most advanced stage of the disease. Soon afterwards, Torre-Amione et al[8] examined hearts explanted from cardiac transplantation recipients and established that the failing heart is able to produce cytokines, as previously explained. Ever since, many other authors confirmed the significant and independent correlation between peripheral levels of TNF-α and its soluble receptors with a worse prognosis and mortality both in the short and in the long term in patients with advanced HF[42-44].

Rauchhaus et al[43] followed 152 patients with HF for at least 12 months and observed that high serum levels of TNF-α, sTNF-R1, sTNF-R2, sCD14 and IL-6 proved to be independent predictors of a poor prognosis in the long term for all functional classes of HF, from the milder to the most severe forms of the disease. In the multivariate analysis, the determination of sTNF-R1 levels proved to be the most powerful tool predictive of survival, regardless of the NYHA FC, peak VO_2, EF or presence of cachexia. In this study, patients in the highest quartile for sTNF-R1 had a risk of all-cause mortality that was 12-fold higher than those in the lowest quartile of the study. In another analysis, the authors observed that all main results, including those on the particular importance of sTNF-R1 as an independent risk marker, remained valid even if cachectic patients, therefore with a more advanced disease, were excluded from the sample (28.9% of the total)[43].

The largest study to assess the immune-inflammatory profile in patients with HF was conducted by Deswal et al[44], who studied almost 1200 patients with NYHA FC III and IV from the placebo group of a multicenter clinical trial. The levels of TNF-α, IL-6, and their respective soluble receptors were determined prior to randomization and were considered significantly higher in patients with NYHA FC IV than in those with FC III. Cox univariate analysis showed that serum levels of TNF-α, IL6, sTNF-R1 and sTNF-R2 can be used as independent risk predictors in patients with HF; when considered together and associated with other variables, only sTNF-R2, NYHA FC and EF remained as significant predictors of survival[44].

Recent attempts to modulate the TNF-α loop randomized more than 1500 patients with NYHA FC III (70%) and IV HF and EF < 30% in the United States and Europe. All together, the ATTACH, RECOVER and RENASSAINCE studies conducted at the same time, albeit by different groups, had the same primary objective of clinical and quality of life improvement, and left survival analyses to a secondary assessment. Unfortunately, the three groups of researchers found disappointing negative results in all analyses, thus limiting perspectives of further therapeutic trials with this objective[45,46]. However, we hypothesize that there are several explanations for this fact.

The benefit of patients who could have profited more from the anti-TNFα therapy (for instance, patients with a higher immune activation, like those with cardiac cachexia or disease decompensation) may have been diluted when patients with less severe HF were included in the recruitment (a hypothesis corroborated by the fact that subgroup analyses were not provided by the authors of the three trials). Very high doses of the drugs, especially in the case of infliximab, are also supposed to have determined prohibitive serum levels – a limitation resulting from the sudden transition of phase I studies to the studies mentioned above, with a high number of patients, without establishing a solid safety profile in the smaller studies. Another possible explanation may be

the loss of TNFα cytotoxic action on viruses and of its effects in amplifying leukocyte migration and margination, which may have worsened the myocardial lesion in those patients. However, although we hypothesize these two reasons, it seems clear that the immune activation in HF is broad and widespread, so that blocking a specific pathway is not enough to abolish all the adverse effects of the complex cascade – quite the contrary, TNFα in merely a component of a network of molecules that stimulate each other, repress each other, potentiate each other, and any attempt to modulate one single element of this network seems simplistic and, perhaps, doomed to failure[45,46].

Conclusions

Many studies in humans have confirmed the hypothesis that peripheral levels of cytokines may be a new and potential indicator of prognosis in patients with HF in the short, mid, and long term, from milder to more severe forms of the disease, especially in the latter.

The real contribution of cytokines on the pathophysiology of HF still remains unclear – whether they are mere passive markers or whether they actually work as effectors in the progression of the disease. The confirmation of the prognostic value of the immune-inflammatory activation in HF does not assume a definitive cause-effect relationship – although many experimental evidences support the harmful effects of cytokines, especially of TNF-α, on the cardiovascular system.

The progressive character of HF and its growing prevalence suggest, however, that all therapeutic advances provided by several clinical trials on neurohumoral modulation drugs do not yet represent the gold standard we can offer to our patients. In fact, the growing morbidity and mortality rates of HF in the Western world suggest that there are important pathophysiological mechanisms related to the progression of the disease that remain active and are under little or no influence of the recently incorporated therapeutic modalities.

We suppose that the immune-inflammatory activation may represent this therapeutic opportunity; trying to understand it in its completeness of an intricate cellular and subcellular orchestration is the challenge we intend to face, as a means of contributing to reverse the epidemiological character that makes HF a malignant and extremely defying disease which will become the major cause of death in the Western world in the coming decades, if we do not take direct measures to halt it.

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