Review Article

Heart failure — an inflammatory paradigm

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Together with the growing clinical problem of heart failure, new information at a cellular and molecular level is influencing our current paradigms or 'patterned thoughts', challenging traditional pathophysiological theories and expanding newer ones.

The clinical syndrome that we recognise as chronic heart failure (CHF) relates to the body's compensatory response to an initial cardiac insult. Neither the 'forward and backward' nor the 'cardiocirculatory' theories of heart failure helped our understanding of the progressive nature of the condition. In the SOLVD prevention study (in which 80% of patients enrolled were asymptomatic more than 3 months after myocardial infarction), overt heart failure developed a median of 8.3 months after randomisation in the placebo arm.[1] The processes involved in this progressive decline include ongoing myocyte loss due to myocyte necrosis and apoptosis, altered myocardial energetics and proliferation failure. The 'neurohormonal' model of heart failure developed in the 1980s partly explained the progressive nature of the disease, implicating angiotensin II and catecholamines.

Cell death, not accompanied by histological evidence of necrosis, is being increasingly recognised as a possible fundamental defect in CHF. Programmed cell death or apoptosis may be the final common pathway of cell death caused by a spectrum of toxic stimuli, including inflammatory factors.

Cytokines

Cytokines as a group are difficult to define, but they share certain characteristics. In general they mediate cell growth, inflammation, immunity, differentiation and repair. They are small to medium-sized peptides produced by a variety of different cell types, in a number of different tissues that allow contact-independent communication between cells. Biological activities are shared by more than one cytokine.

The resultant biological effect of a cytokine relates to the type of target cell, the intracellular milieu and the *biological context of its release* — alerting one to the necessity for caution in extrapolating effect observed *in vitro* to the behaviour of the cytokine *in vivo*. Cytokines implicated in mediating myocardial depression in systemic sepsis and other forms of cardiac dysfunction are outlined in Table I.[2-4]

TABLE I. CYTOKINES MEDIATING MYOCARDIAL DEPRESSION

Source	*Cytokine*	*Other actions*
M, T	TNF-alpha	Inflammation, fever, septic shock. Tumour cytotoxicity. Infection resistance
M, F	IL-1ß	Pyrogen, pro-inflammatory. Induces other cytokines. Proliferates T, B cells
T	IL-2	T-cell growth factor
CD4T, M MC, F	IL-6	Pro-inflammatory. B- and T-cell growth factor
T	IFNy	Antiviral. Vital for cell-mediated immunity. Macrophage activator. Inhibits inappropriate antibody production

M = macrophage; T = T lymphocyte; F = fibroblast; MC = mast cell; IL = interleukin; IFN = interferon.

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The syndrome of CHF, cachexia and tumour necrosis factor (TNF)

Since Hippocrates, physicians have witnessed the cachexia of heart failure: 'The flesh is consumed and becomes water . . ., the abdomen fills with water, the feet and legs swell, the shoulders, clavicle, chest and thighs melt away.'

Cachexia is an independent risk factor for mortality in CHF.[5] It was found that a combination of CHF and a peak VO_2 < 14 ml/kg/min with cachexia had a worse prognosis than a peak VO_2 < 14 ml/kg/min and no cachexia, with cardiac cachexia being a predictor of death independent of age, functional class, ejection fraction, peak VO_2, effort tolerance or serum sodium concentration. Using a cytotoxic assay, circulating levels of TNF were increased in cachectic CHF patients.[6] Although the elaboration of TNF-alpha in CHF was therefore originally proposed as an important cachectic mechanism, there is now an increasing awareness that it probably plays a broader pathophysiological role. An endotoxin-induced serum factor that caused necrosis of tumours was named tumour necrosis factor.[7] In a review, entitled 'Cachectin: More than a tumour necrosis factor',[8] it was emphasised that irrespective of its original casting role, TNF was an important mediator of inflammation and involved in diverse human disease processes. TNF-alpha has since been found to be raised in cardiac conditions other than heart failure,[9] including acute myocarditis and hypertrophic cardiomyopathy. In this study,[9] as well as others,[6,10,11] TNF was not found to be consistently raised in patients with CHF. No TNF was detectable in 90% of cases of non-cachetic severe CHF, and only raised in 44% of cachectic CHF patients.[10] The effects of TNF-alpha in chronic disease may relate more to prolonged exposure, but TNF-alpha was not detected at least once in all of 16 CHF patients prospectively followed up for 1 year.[11]

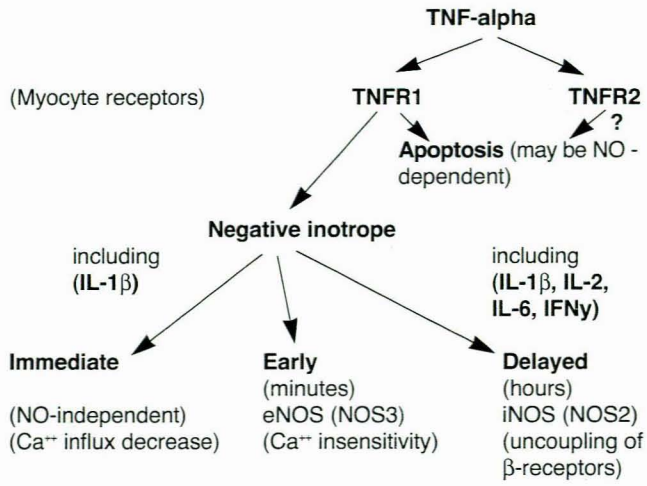
Potential causes of cytokine activation in CHF

While it became established that TNF-alpha was raised in some patients with CHF, there was little information available as to the factors that may cause this rise. Initially it was hypothesised that raised prostaglandin E levels were instrumental.[6] However, no correlation between raised TNF-alpha levels and circulating neurohormones, as well as no correlation with TNF-alpha levels and mortality, could be found in a small series.[11] It was considered that neurohormones would play a role in the cachexia of heart failure, as cachexia is associated with a hypermetabolic state. An association was found between cachexia, hyponatraemia and high levels of circulating TNF and renin activity, but not catecholamines.[6]

In the SOLVD trial, plasma noradrenaline, renin, atrial natriuretic peptide (ANP) and vasopressin levels were significantly raised in the prevention as well as the treatment arms when compared with controls.[12] Randomly selecting from the same patients enrolled in the neurohormonal substudies of the SOLVD trial,[13] it was found that plasma TNF-alpha levels were elevated in direct proportion to the patients in functional classes I - III, while plasma levels of interleukin-6 (IL-6) were elevated maximally in patients in functional class II and did not increase further. It was therefore tempting to correlate the increased neurohormonal levels with the increased cytokine levels, but no such correlation was found except between ANP and TNF-alpha, and this correlation was weak. It therefore appeared that raised neurohormones could not adequately explain the increase in pro-inflammatory cytokines. A recent paper[14] hypothesised that mesenteric venous congestion leading to increased bowel permeability, resulting in bacteria entering the circulation and releasing endotoxin, was in some but not all cases a possible explanation for the immune activation seen in chronic heart failure. mRNA for TNF has been isolated in failing human hearts, and the possibility that within the pathophysiological context of heart failure the heart itself is responsible for the production of TNF, other cytokines and peptide autacoids in this syndrome is intriguing.

TNF and the heart

Fig. 1 illustrates the mechanisms by which TNF-alpha may contribute to cardiac myocyte contractile dysfunction by nitric oxide (NO)-dependent and NO-independent mechanisms. Other cytokines may have similar mechanisms of action.



TNFR1, 2 = TNF receptor 1, TNF receptor 2; NO = nitric oxide; eNOS = endothelial constitutive nitric oxide synthase; iNOS = cytokine inducible nitric oxide synthase; Ca^{++} = intracellular calcium.

Fig. 1. Action of TNF-alpha on the heart.[4]

After several hours of substantially higher concentrations, a cytokine-inducible 'high-output' isoform of nitric oxide synthase (NOS) (iNOS or NOS 2) is responsible for the sustained negative inotropic effect.

Is TNF biologically active in heart failure?

Although levels of TNF-alpha are raised in chronic heart failure, and the myocardium elaborates receptors for this cytokine, what evidence is there that TNF-alpha is biologically active with bearing on the primary progression of the

disease itself, or is it merely a marker of disease severity, i.e. an epiphenomenon?

After interaction of TNF-alpha with its receptor, the soluble extracellular domain fragment of both receptors is shed and can be detected as sTNFR1 and sTNFR2.[15] Raised sTNFR1 and 2 have been found in heart failure[16] and appear to be far more sensitive markers of cytokine-receptor interaction than isolated increased plasma TNF-alpha levels. Following TNF receptor activation, intracellular levels of tetrahydrobiopterin (an important co-factor for NO biosynthesis) are increased together with its inactive metabolic neopterin. Systemic neopterin has been found to be increased in severe heart failure and especially in patients with high levels of TNF-alpha.[17]

The presence of soluble receptors in the plasma therefore reflects early events and raised neopterin levels reflect events beyond the receptor, implying biological activity.

The loss of the soluble extracellular domain can be seen as a form of down-regulation of the TNF receptor, reducing the number of active receptors and possibly preventing further cell damage and 'protecting' the heart from the deleterious negative inotropic effects of TNF-alpha. Patients with CHF have been found to have reduced levels of total myocardial TNF receptor proteins,[18] implying that the heart is a target organ.

sTNFR1 and 2 appear to bind and neutralise most of the circulating TNF in the short term, but the circulating soluble receptor-TNF complex may stabilise and prevent degradation of TNF-alpha in the long term, providing therefore an enhancing, maladaptive function.

TNF and the clinical syndrome of CHF

Now that we have established that raised TNF-alpha levels in CHF are probably biologically active, can this cytokine produce the features that we observe in the syndrome? TNF-alpha overexpression has been shown to produce left ventricular dysfunction and pulmonary oedema in humans; experimentally it promotes left ventricular remodelling and abnormalities in myocardial metabolism, produces anorexia and cachexia, causes endothelial dysfunction, and impairs synthesis and increases catabolism of skeletal muscle protein.[19] As many aspects of CHF can be explained by these known biological effects of pro-inflammatory cytokines, the rationale for studying them becomes compelling.[19]

It has been stated that 'it now seems possible that the failing heart synthesises a locally active cytokine that induces the heart to commit suicide, literally at the most fundamental molecular level'.[15]

The role of the peripheral foci of TNF-alpha production and release is still being clarified. It is difficult to explain why TNF-alpha increases with increasing functional class, although the degree of left ventricular dysfunction is similar in functional class I - III, on a primary cardiac source of the cytokine. There is also a disproportionate increase in TNF-alpha levels from class III to IV, although the mean ejection fraction in class IV is generally only 5% less than in class III.

Therapeutic manipulation of TNF-alpha in CHF

In a very interesting study,[20] it was shown that CHF patients without raised circulating TNF-alpha had the worst forearm blood flow response to increasing acetylcholine concentrations, when compared with those with raised TNF-alpha and normal controls. It appears therefore that TNF-alpha possibly contributes to vasodilation via NO production, playing an important role in the regulation of endothelial function and vasomotor tone in CHF. This may be seen as a short-term 'beneficial' action of TNF-alpha, but its main long-term effect (negative inotropy, apoptosis) appears to be adverse.

NO generation by NOS requires oxygen, nicotinamide-adenine dinucleotide (reduced) and the rate-limiting amino acid (L-arginine). In a randomised, double-blind, placebo-controlled study, supplemental oral L-arginine was given for 6 weeks to 17 patients in CHF with a mean ejection fraction (EF) of 18%.[21] During forearm exercise, significant increases in forearm blood flow, subjective patient scores and 6-minute walk tests were found in the treatment group. Until recently[22] it was not clear why supplemental doses of L-arginine would augment NO production. It was shown experimentally that L-arginine concentrations in endothelial cells are such as to saturate endothelial NOS, and can be maintained despite continuous release of NO. A novel enzymatic pathway by which NO may be generated by a reaction between hydrogen peroxide (H_2O_2) and arginine has now been described where L-arginine recouples electron transport in NOS to drive reactive oxygen species (H_2O_2, O_2^-) formed in disease states into forming NO.

What appears to be a beneficial effect of TNF-alpha peripherally is counterbalanced by the negative inotropic action of TNF-alpha also mediated via NO, antagonised by N^G-monomethyl-L-arginine (L-NMMA — a NOS inhibitor) and reversed by L-arginine.[23] This negative inotropic effect of TNF-alpha appears to be mediated via myocardial and not endothelial NOS. These two contrasting studies emphasise the therapeutic dilemmas facing us when we try to manipulate the cytokine system — counterbalancing effects with unknown long-term sequelae.

Vesnarinone, an oral positive inotrope (phosphodiesterase inhibitor), was reported in a randomised, double-blind, placebo-controlled study (477 patients) in which it was used at a dosage of 60 mg daily to cause a 50% decrease in the risk of death from any cause or worsening heart failure and a 62% reduction in risk of death during the 6-month study period.[24] The 120 mg dosage arm was stopped prematurely as it caused a doubling of mortality. Immunodulating effects of vesnarinone were then described in animals[25-27] and humans,[28] prompting the authors to conclude that 'the reduction of cytokine release contributes to beneficial effects of the drug in the treatment of heart failure'.

The VEST study[29] then found that vesnarinone caused a dose-dependent increase in mortality (sudden death) with 30 mg daily (12% increase in mortality) and 60 mg (23% increase in mortality). This study emphasises the importance of studying large cohorts of patients (3 833 patients in the VEST trial and 477 in the first vesnarinone trial[24]) to avoid creating erroneous conclusions for the enthusiasts of so-called evidence-based medicine.

In a murine viral model of CHF, it was found[30] that amlodipine inhibited NO production by macrophages. The PRAISE study[31] showed that amlodipine conferred a 16% lower risk of death ($P = 0.07$). In a subset of patients in the PRAISE trial, amlodipine had no significant suppressive effect on TNF-alpha, but did lower IL-6 levels.[32] The authors conclude that 'the beneficial effect of amlodipine in CHF may be due to a reduction of cytokine such as IL-6'. While a *beneficial* effect of amlodipine remains in question, it seems premature to ascribe an unproven effect to a barely statistical reduction in IL-6.

Oxpentifylline has been shown to inhibit endotoxin-induced production of TNF-alpha in a dose-dependent manner,[33] and pentoxifylline may provide a therapeutic modality in heart failure.[34]

Dietary supplementation with long-chain n-3 fatty acids can suppress IL-1 and TNF-alpha.[35]

New agents, including inactivating recombinant proteins that neutralise TNF and other cytokines, are being studied in phase 1 trials.

Conclusion

Elaboration of cytokines may contribute to the disease progression in CHF. They are potentially important role players in transforming asymptomatic left ventricular systolic dysfunction to symptomatic heart failure.

Questions that remain include what are the trigger mechanisms for the release of cytokines in CHF, and will cytokine suppression reduce symptoms, prolong life and prolong the asymptomatic phase?

The role of cytokines in the natural history of CHF remains unknown. Ongoing research into these and other questions is, it is hoped, going to provide answers and with them may herald a novel approach in the management of this fatal condition we recognise as heart failure.

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