CME CREDIT

TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

Heart failure is a fever: The cytokine connection

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ABSTRACT

Inflammation probably contributes to the development and progress of heart failure. Proteins called cytokines, which are produced by damaged tissues and leukocytes as part of the inflammatory response, affect the heart both directly and indirectly. They exacerbate hemodynamic imbalances, act as negative inotropes, stimulate left ventricular hypertrophy, and promote the production of still more cytokines, which continue the cycle. Several medications counter these effects in vitro, and some are in clinical testing.

INFLAMMATION is a largely ignored contributor to the complex, multifactorial disease of heart failure. An exploration of the role of inflammation may lead to additional therapies that will reduce the death toll from this disease.

PREVALENCE OF HEART FAILURE

More than 5 million Americans have congestive heart failure; perhaps 3 or 4 times that many have systolic or diastolic left ventricular dysfunction. Despite therapeutic advances, men with a diagnosis of symptomatic heart failure can expect to live only about 2 years; women, 3 years.

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CHANGES IN THE THEORY OF HEART FAILURE

Over the past 40 years, concepts of heart failure have evolved radically. Heart failure was once considered primarily a congestive state to be treated with diuretics. By the 1970s, the condition was considered a hemodynamic abnormality; vasodilators were used to lower preload and afterload, and research focused on developing inotropes. Ten years later, researchers were exploring the effects of the adrenergic and neurohormonal systems: epinephrine and norepinephrine, the renin-angiotensin system, vasopressin, and atrial natriuretic peptide.

More recently, attention has focused at the cellular level. Mature heart myocytes are so-called terminally differentiated cells, not designed to grow or reproduce. When forced to grow by hypertension or the ischemic death of neighboring cells, they do so abnormally; specifically, the membrane receptors involved in receiving adrenergic signals fail to function correctly. These changes contribute to left ventricular hypertrophy and fibrosis, which impair systolic function, diastolic function, or both. Systemic blood flow is reduced and organ perfusion is impaired, which triggers autoregulatory mechanisms that, in turn, act on the heart in an attempt to increase cardiac output.

Each of these new concepts of heart disease has contributed to our understanding. We believe that all the mechanisms—hemodynamic, neurohormonal, and cellular—interact in complex feedback loops to produce the clinical manifestations of heart failure: congestive heart failure, acute pulmonary edema, or sudden cardiac death.

Heart failure is an interaction between congestive, hemodynamic, adrenergic, neurohormonal, and inflammatory factors

INFLAMMATION AS A FACTOR

For at least a century, certain inflammatory conditions have been known to be associated with hypotension and cardiogenic shock, as well as with tumor necrosis. At the beginning of the 20th century, a physician named William Couley found that a suspension of streptococci and *Bacillus prodigiosus* could induce tumor necrosis in unresectable metastatic malignancies, but could also produce fatal hypotensive shock and pulmonary edema. Fifty years later, Irvine Page at the Cleveland Clinic found that a similar "pyrogenic" cocktail could temporarily lower arterial pressure in patients with malignant hypertension, but was fatal to those with cardiac decompensation.

Inflammation is now known to be caused by inflammatory cytokines, small proteins that are involved in the response to bacterial infection, the repair of damaged tissue, and the swelling and elevated temperature typical of inflammation. One of these inflammatory cytokines, tumor necrosis factor alpha or TNF-alpha, is also involved in tumor necrosis, as well as in the cachexia and anemia that develop in patients with cancer or chronic disease.

Inflammatory cytokines involved include TNF-alpha, IL-1, and IL-6

Significantly, chronic advanced heart failure is also associated with cachexia mimicking that of advanced cancer, as well as with anemia and fever without infection. The link between heart failure and cytokines was first established in a 1990 report showing that TNF was elevated in cachectic patients with heart failure.[1] Many other symptoms of advanced congestive heart failure are also typical of cytokine activation: anorexia, malnutrition, hypoalbuminemia, leukopenia, low cholesterol, elevated sedimentation rate, and high levels of fibrinogen and acute-phase reactants.

TNF-ALPHA ACTS DIRECTLY AND INDIRECTLY

Further studies suggested that TNF-alpha not only induces cachexia in heart failure patients but also directly and indirectly promotes heart failure itself. In isolated myocyte preparations, muscle preparations, and animal models, TNF-alpha is a dose-dependent negative inotrope. A fusion protein made from TNF receptor reverses TNF-induced left ventricular dysfunction. In rats and mice, TNF-alpha infusion or genetic overproduction of TNF-alpha results in progressive left ventricular dysfunction, hypertrophy, and heart failure. Although TNF-alpha is known to induce both necrosis and apoptosis, the left ventricular hypertrophy appears instead to be a response to TNF-induced collagen breakdown.[2]

TNF-alpha increases capillary permeability. The mediator of endotoxemic shock, TNF-alpha has long been known to produce so-called "non-cardiogenic" pulmonary edema and is probably a mediator of cardiogenic pulmonary edema as well. TNF-alpha is elevated in a variety of cardiac disease states in situations where other causes can be ruled out.[3]

As heart failure becomes more severe, levels of TNF, IL-6, and natriuretic peptides rise. In fact, the TNF-alpha level may be an independent predictor of adverse outcome.[4]

DAMAGED HEART MUSCLE BECOMES INFLAMED

Although TNF-alpha is primarily produced by macrophages and leukocytes, it is also produced by myocytes and fibroblasts. The myocyte can be induced to produce TNF-alpha by endotoxin but also by pressure overload or injury. Thus, in my opinion, we could classify TNF-alpha as a stress protein.

In a vicious circle, TNF-alpha also stimulates macrophages and other cell types to produce more TNF-alpha as well as other inflammatory cytokines such as IL-1 and IL-6, which are responsible for fever and malaise and perpetuate the left ventricular remodeling.

In summary, the cytokine hypothesis holds that cytokines exacerbate hemodynamic abnormalities or exert direct toxic effects on the heart to produce and worsen heart failure. Thus, the cytokine mechanism is coupled with all the other mechanisms behind heart failure.

Inflammation is repair, a response to injury. It makes sense that injured myocardium is also inflamed myocardium. Why we ignored the implications for heart disease for so long is a bit of a mystery to me.

CYTOKINES AND THERAPY FOR HEART FAILURE

It certainly seems possible to come up with agents that would reverse or attenuate the effects of inflammatory cytokines on the heart, although it will be important to screen for side effects that might be harmful in patients with heart failure.

A number of current medications are known or suspected to have anti-TNF-alpha effects. The **phosphodiesterase inhibitors** down-regulate production of cytokines including TNF, although, unfortunately, these drugs are inotropes and increase mortality in patients with heart failure. **Pentoxifylline,** a medication approved for treating intermittent claudication, is a potent cytokine inhibitor. In fact, its effectiveness in claudication and peripheral vascular disease may result in part from its anticytokine effects.

The antiarrhythmic medication **amiodarone,** when given in doses so small as to be subtherapeutic against arrhythmia, benefits heart failure patients.[5,6] A different mechanism of action may be at work, and this mechanism may be anticytokine. Other potential anticytokine agents include **thalidomide** and the new **angiotensin II receptor antagonists.**

On the immunologic front, antibodies and antagonists to TNF-alpha and TNF receptor have been developed. **Etanercept (Enbrel),** which is very effective for rheumatoid arthritis, interferes with TNF-alpha systemically and in the heart. In a safety study in patients with heart failure, etanercept decreased levels of biologically active TNF-alpha, made a small but significant improvement in ejection fraction, and produced a marked improvement in patients' perceived quality of life.[7] This experience set the stage for clinical testing in several ongoing trials: the Randomized Etanercept North AmerIcan Strategy to Study AntagoNism of CytokinEs (RENAISSANCE) and the RENEWAL and RECOVER trials.

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