Editorial

Growth hormone and proinflammatory cytokine activation in heart failure

Just a new verse to an old sirens’ song?

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Despite recent advances in pharmacotherapy, patients living with heart failure carry a heavy burden in terms of morbidity and mortality. For example, in a recently completed large-scale clinical trial, 30% of patients with stable NYHA class II or III heart failure died during a mean follow-up period of less than 3 1/2 years; at the same time, 25% of these patients were hospitalized at least once for worsening heart failure, despite optimal combination treatment with an ACE-inhibitor, AT1-receptor antagonist, and β-blocker.1 Apparently, we have reached a therapeutic ceiling with traditional neurohormonal approaches for treating heart failure. Fortunately, however, additional therapeutic strategies are actively being explored. In this context, growth hormone (GH) has been proposed as a treatment modality for heart failure patients.2 Remarkably, the scientific rationale that has stimulated research into growth hormone as an adjunctive therapy for heart failure appears to be diametrically opposed to the concept that gave rise to the aforementioned neurohormonal strategies for treating heart failure. The neurohormonal concept of heart failure predicts that persistent activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system promotes maladaptive cardiac hypertrophy that results in contractile dysfunction and progressive ventricular dilatation.3–5 Neurohormonal antagonists halt or even reverse this deleterious hypertrophy/remodeling process.6 Treatment with GH, by contrast, promotes cardiac hypertrophy in heart failure patients.7,8 It has been argued that the concentric pattern of left ventricular (LV) hypertrophy induced by GH yields favourable effects on LV contractile function and remodelling by reducing LV wall stress according to Laplace’s law.9 Moreover, experimental studies have demonstrated that treatment with GH enhances intrinsic cardiac myocyte contractile function, restores myocardial sarcomplasmic reticulum Ca2+-ATPase expression levels, and increases myocardial capillary density in the failing heart, suggesting that GH may promote an ‘adaptive’ form of cardiac hypertrophy.9,10 In addition to these purported beneficial cardiac effects, GH treatment reportedly promotes favourable non-cardiac effects in chronic heart failure by reducing skeletal muscle atrophy and enhancing skeletal muscle strength, and by correcting peripheral vascular endothelial dysfunction.11,12

In this issue, Adamopoulos et al. propose yet another mechanism whereby treatment with GH might exert beneficial effects in heart failure. Using a randomized crossover design in 12 patients with idiopathic dilated cardiomyopathy, the authors show that a 3 month course of GH reduces circulating levels of proinflammatory cytokines and inflammatory markers, including tumor necrosis factor-α (TNFα), interleukin-6 (IL-6), granulocyte-macrophage colony-stimulating factor and its soluble receptor, macrophage chemoattractant protein-1, and soluble adhesion molecules.13 Consistent with some earlier reports, GH treatment promoted increases in LV wall thickness, LV contractile indices, and exercise capacity, and a decrease in LV wall stress.13 Adamopoulos et al. propose that suppression of proinflammatory markers by GH is a desirable treatment effect. Considering that recent clinical trials evaluating the therapeutic efficacy of selective TNFα-antagonists have produced negative results,14 that IL-6 related cytokines may actually promote beneficial effects in the failing heart,15 and that we know little about the pathophysiological role in the setting of heart failure (if any) of the other ‘inflammatory markers’ suppressed by GH, such a conclusion is speculative at the present time. These caveats in mind, it is possible that suppression of inflammatory markers by GH is beneficial in heart
failure, given the substantial body of evidence that sustained activation of proinflammatory cytokines (especially TNFα) produces maladaptive effects in the failing heart. As recently discussed by Douglas Mann, previous targeted anti-TNFα therapies may have failed because the biological agents that were used in these trials had intrinsic toxicity. Therefore, the concept of cytokine-antagonism as a therapeutic strategy in heart failure may still be alive, and GH may represent a novel and comprehensive anti-inflammatory approach in this regard.

As outlined above, the ode to GH as a therapeutic adjunct for heart failure patients has many verses already, and a new one has just been added. Unfortunately, we still do not know whether we are, in fact, listening to a Sirens’ song. Despite a wealth of experimental studies and early clinical reports, suggesting that GH improves cardiac function and functional capacity in heart failure, (small-scale) randomized studies have failed to confirm that GH promotes functional improvement in heart failure patients (reviewed in [2]). Will someone have the courage (and the financial support) to carry out a randomized, placebo-controlled clinical trial with sufficient statistical power to address the impact of growth hormone on morbidity and mortality in heart failure patients?

References