

Growth hormone in heart failure revisited: An old story retold

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Abstract

Heart failure (HF) is a disease characterized by increasing prevalence, huge direct and indirect costs, and an ominous prognosis, worse than many cancers. At the beginning of the 90s, growth hormone (GH) was proposed as potential adjunctive therapy in HF mostly due to its growth-promoting, vasodilating, and anti-apoptotic actions. However, although several uncontrolled clinical studies showed that GH therapy improved several cardiovascular parameters, two robust trials failed to confirm these findings. Dwelling upon potential explanations for such apparent discrepancy led to the hypothesis that HF patients exhibit an inhomogeneous basal activity of the GH/insulin-like growth factor 1 (IGF-1) axis, ranging from GH/IGF-1 deficiency to GH resistance. This complex phenomenon was then reconsidered in the context of the so-called multiple hormone deficiency syndrome (MHD), that is the recognition that HF is characterized not only by the hyperactivation of several signaling pathways including the adrenergic, the renin-angiotensin-aldosterone and cytokine systems, but also by a reduced anabolic drive leading to a state of anabolic/catabolic imbalance. Mounting evidence support the concept that such imbalance is not a mere epiphenomenon, since it exerts a significant impact on clinical performance and more importantly, on survival. Therefore, the paradigm shift to reconsider HF as MHD represented the underpinning to implement clinical trials focused on hormone replacement therapies in congestive heart failure (CHF). With regard to GH replacement therapy, one controlled single-blind study yielded promising results, and we are currently conducting a double-blind controlled trial, as well a large Registry study to evaluate the impact of MHD on HF progression.

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Beginning of the story: Rationale for a growth factor approach to heart failure

Several lines of experimental evidence support the concept that the activation of the growth hormone/IGF-1 axis exerts beneficial effects on the cardiovascular system. Growth hormone (GH) and IGF-1 induce a unique pattern of myocardial growth, characterized by unchanged capillary density, preserved diastolic function, and normal or augmented systolic function [1]. This has been shown in several rodent models, as well as in acromegalic patients with short disease duration, and in controls subjects undergoing GH therapy [2-6]. Of note, at gene level, there is no evidence of maladaptive reprogramming, with attendant changes of major calcium regulating proteins. In this concern, IGF-1 has been shown to acutely augment mammalian intrinsic contractility with a unique mechanism of calcium sensitization of the myofilaments [7]. Also in chronic models of GH/IGF-1 excess in rats, myocardial contractility is improved primarily due to an increase of myofilament responsiveness [8]. It should be mentioned that inotropic drugs acting as calcium sensitizers without changes in intracellular Ca²⁺ flux are eagerly searched for insofar as this mechanism is not associated with untoward effects such as arrhythmias. Activation of *akt* signaling, which lies downstream of IGF-1 receptor, appears to induce SERCA2 upregulation in several animal models, that in turn provides benefits in heart failure (HF) [9]. Furthermore, evidence has been accumulated pointing to a distinct role of IGF-1, the main effector of GH action, as a survival factor. Specifically, IGF-1 is endowed with peculiar cardioprotective functions mediated by the inhibition of cardiomyocytes apoptosis [10]. IGF-1 and its downstream cascade appears to play a significant role in the intricate framework of myocardial growth and survival activating PI3k/Akt signaling, as opposed by negative feedback controlled by several alternative pathways, including SOCSs [11]. Such observations prompted numerous studies that have consistently demonstrated beneficial effects of IGF-1 in the setting of experimental heart failure, using either exogenous administration or gene manipulation [12-14].

With regard to vascular physiology, IGF-1 provides for the tonic production of nitric oxide from the endothelial cells and for preserving endothelial function [15]. Because of the wide spectrum of atherogenic mechanisms that are inhibited by NO [16], IGF-1 acts as vasculoprotective and anti-atherogenic factor [17]. Indeed, subjects with chronically impaired IGF-1 production display endothelial dysfunction and undergo premature atherosclerosis and major vascular clinical events [18-20].

Clinical trials

Most animal studies have reported beneficial effects of enhanced myocardial GH/IGF-1 signaling, obtained with various approaches, from exogenous GH or IGF-1 administration, to gene therapy or myocardial IGF-1 overexpression [21-24]. A wide array of improved cardiovascular outcome measures was described including attenuated left ventricular

remodeling, reduced apoptosis and wall stress, improved cardiac mechanics, and, most importantly, prolonged survival. However, at variance with experimental investigations, human trials have yielded conflicting results. The first study from Fazio's group demonstrated that recombinant human GH administered for three months to patients with idiopathic dilated cardiomyopathy increased myocardial mass and reduced the size of the left ventricular chamber, resulting in improvement in hemodynamics, myocardial energy metabolism, and clinical status [25]. Such findings were subsequently confirmed [26] and expanded by several independent groups, although employing uncontrolled study designs [27,28]. However, the interest toward GH therapy in heart failure tended to vanish when two robust double-blind placebo-controlled trials failed to confirm such findings [29,30].

Pitfalls of GH trials in congestive heart failure: Lack of evaluation of basal GH/IGF-1 status

What were the main reasons of such inconsistencies? An obvious answer is the lack of a placebo arm, that may clearly impair the study results by neutralizing the placebo effect. A second reason might be related to the relatively short duration of GH therapy: it is possible myocardial, skeletal, and ventilatory muscles may change their properties only after a longer exposure to GH/IGF-1. Another argument that has been put forward are the questionable end-points employed in these trials. For instance, Osterziel and colleagues calculated the sample size using ejection fraction changes as primary end-point [29]. Apart from the criticism on ejection fraction as erroneously assumed measure of myocardial contractility [31], most clinical trials currently employ indexes of physical performance such as peak oxygen consumption, since an increase of systolic function may be associated with augmented oxygen demand, that may negatively reverberate on survival.

However, the greatest pitfall in GH human trials appears to be the lack of evaluation of the basal GH/IGF-1 status. This stems from the observation that when the same authors of the largest randomized controlled trial re-analyzed their findings, they found a correlation between the changes in IGF-1 and those in LV mass, and a significant increase of ejection fraction in those patients displaying GH-induced increases of IGF-1 of more than the median value of 80 pg/mL [32]. Similar conclusions were reached in a meta-analysis by Le Corvoisier and colleagues [33]. Thus, the hypothesis has been put forward that since HF patients display a large variability of GH/IGF-1 activity, ranging from an intact axis to GH/IGF-1 deficiency to GH resistance, it is reasonable to expect different responses in IGF-1 production following GH administration, and, consequently, a high variability of the selected clinical outcomes. Indeed, several studies have clearly demonstrated that patients with HF may display an intact GH/IGF-1 axis, reduced IGF-1 circulating levels, GH deficiency or conditions of GH resistance, particularly in advanced stages of the disease, characterized by concomitant high GH and low IGF-1 serum levels [34,35]. While treating patients with GH/IGF-1 deficiency may in theory improve cardiovascular status, it is reasonable to speculate that replacement or even higher GH doses may yield subtle or neutral effects in patients with an intact axis and particularly in those with GH resistance.

Paradigm shift: HF as a multiple hormonal deficiency syndrome

The observation that a subset of HF patients is affected with GH/IGF-1 deficiency may be viewed in a larger perspective, *i.e.* the presence of hormonal comorbidities, particularly those involving the anabolic drive.

There is an active research area aimed at identifying and treating relevant comorbidities in HF that may affect its progression. Non-cardiac comorbidities playing a significant role include chronic obstructive pulmonary disease, renal dysfunction, arthritis, cognitive dysfunction and depression, and anemia/iron deficiency [36]. As a prototype, treating a subset of patients with coexisting HF and iron deficiency or anemia with iron therapy or epoietin [37,38] may confer beneficial effects, as in other non-cardiac conditions [39]. In this context, mounting evidence support the concept that multiple anabolic deficiencies are common in chronic HF and identify subgroups of patients with higher mortality [40]. The first evidence concerning the role of anabolic deficiencies in HF patients comes from a landmark study by Jankowska *et al.* [40]; specifically, deficit of each anabolic axis [adrenal, gonadal and somatotrophic axes] represents an independent marker of poor outcome in HF patients and the coexistence of more than one deficiency identifies a subgroup of patients with a higher mortality. The most involved hormonal axes include GH, its tissue effector IGF-1, thyroid hormone, insulin and anabolic steroids. Taken together, these alterations could be recognized as multiple hormone deficiency syndrome (MHD) in HF patients [41]. MHD bears a significant impact on cardiac performance, clinical status, HF progression and survival [41-43]. In other words, despite the effectiveness of the neurohormonal model to explain disease progression and the many insights that provided the basis for the development of new therapies, such model clearly fails to fully explain disease progression. MHD may represent a complementary model of HF progression, based on the observation that HF is not only characterized by excessive stimulation of the adrenergic, the renin-angiotensin-aldosterone, and the cytokine system, but also by the reduced activity of the principal anabolic axes of the human body, thus leading to an anabolic/catabolic imbalance [44].

GH deficiency in heart failure

Chief among these is the reduced activity of the GH/IGF-1 axis. Low levels of IGF-1 correlate with the degree of systolic dysfunction, the presence of cachexia and skeletal muscle weakness, and indices of neurohormonal and cytokine activation [45]. Several independent groups have documented low IGF-1 levels in congestive heart failure (CHF). Broglio *et al.* reported low IGF-1 levels in well-nourished patients with severe LV dysfunction, as well as blunted response to GHRH, both alone or combined with arginine [46,47]. This finding was subsequently confirmed by Anwar *et al.* in an elderly population of patients hospitalized for HF [48] and by Kontoleon *et al.* in 23 ambulatory patients with stable HF [49]. Anker and co-workers did not find reduced IGF-1 levels in non-cachectic patients with HF, while in cachectic patients circulating IGF-1 was significantly decreased compared with controls [50]. These authors also provided evidence for GH resistance, defined as high GH levels and low IGF-1 levels, in 60-70% of cachectic and 20-30% of non-cachectic patients with HF. In 158 consecutive patients with HF, we recently found the prevalence of GH deficiency to be 40% [51,52]. This finding is not unexpected considering that Broglio and coworkers reported a similar prevalence of GH deficiency [47] and that Jankowska *et al.* have recently reported an average prevalence of 64% of IGF-1 deficiency in 208 patients with HF NYHA class I-IV [40].

Apart from HF, GH deficiency increases cardiovascular mortality. Although data regarding the mortality rates of patients with GH deficiency are limited, an increased mortality rate among hypopituitary patients compared with the general population has been clearly documented. The first report dates back to 1990 [53], and it has been confirmed subsequently by several independent groups [54-55]. Cardiovascular disease has been suggested as a primary cause of death, whereas cancer statistics might be influenced by the number of malignancies.

nancies causing the pituitary disease. To support the concept that the pathophysiological link between increased mortality and hypopituitarism is GH deficiency, two studies showed a normal mortality rate in GH deficient patients treated with GH compared with the general population [57]. On the other hand, it has been suggested that hypopituitarism affects several cardiac diseases including Takotsubo cardiomyopathy [57,58].

The pivotal role of low IGF-1 levels in determining future cardiovascular problems is further demonstrated by large population-based studies. In fact, in the general population low IGF-1 levels predict the development of ischemic heart disease, HF, and cardiovascular mortality [59-61].

Taken together, low IGF-1 levels are associated with increased mortality in the normal population and in GH deficient humans. On the other hand, low IGF-1 levels are commonly found in HF. Therefore, it is reasonable to expect a worse prognosis in patients with coexisting HF and low IGF-1 levels. This brings us back to the study of Jankowska and colleagues, showing that multiple anabolic deficiencies, including IGF-1 levels below the tenth percentile of healthy peers, increase mortality in a population of CHF patients [40], and by Petretta *et al.*, that also demonstrated that a low IGF-1/GH ratio and high NT-proBNP levels are independent predictors of death in HF patients without cachexia [62], and more recently by Arcopinto and colleagues [63]. Therefore, it appears that the finding of low IGF-1 circulating levels in CHF is not an epiphenomenon or a mere biochemical marker, but is mechanistically linked to CHF clinical status and to disease progression.

From this background, IGF-1 emerges as a molecule endowed with potential beneficial effects on the cardiovascular system, and its reduced production increases mortality in normal individuals and, in particular, in patients with chronic HF.

Ongoing studies

Given this solid background, several clinical studies were implemented to evaluate the effects of GH replacement therapy in patients with coexisting GH deficiency and CHF. In a randomized, single-blind, controlled trial, one hundred fifty-eight patients with CHF, New York Heart Association class II-IV, underwent a GH stimulation test [51]. Interestingly, as many as 40% of patients with CHF were GH deficient. Moreover, compared to GH deficient patients, GH sufficient patients showed smaller end-diastolic and end-systolic LV volumes, lower LV end-systolic wall stress, higher RV performance, lower estimated systolic pulmonary artery pressure, higher peak VO₂ and increased ventilatory efficiency. GH deficiency was also associated with increased all-cause mortality [52]. Sixty-three patients satisfied the criteria for GH deficiency, and 56 of them were enrolled in the pharmacological trial. The treated group received GH at a replacement dose of 0.012 mg/kg every second day (2.5 IU). GH replacement therapy in these patients improves exercise capacity, vascular reactivity, left ventricular function, and indices of quality of life [51]. After 4 years of follow-up, such beneficial actions not only were sustained, but improved consistently [64].

A major limitation of these trials was the lack of a placebo arm, and, accordingly, a double-blind-placebo controlled study is currently ongoing in our Department, sponsored by the GGI 2016 award (<https://www.grantforgrowthinnovation.org/en/ggi2016/winners.html>). Specifically, the objective of the study is to determine whether treatment of GH deficiency in patients with chronic HF improves peak oxygen consumption, a recognized surrogate end-point of HF progression, and several secondary end-points including NT-proBNP, measures of left ventricular architecture and function, quality of life, and anxiety and depression scores.

Another major ongoing study in this field is the T.O.S.CA. (Trattamento Ormonale nello Scompensamento Cardiaco; Hormone Therapy in Heart Failure) Registry (clinicaltrials.gov: NCT02335801) which tests the hypothesis that anabolic deficiencies reduce survival in a large population of mild-to-moderate CHF patients. The T.O.S.CA. Registry is a prospective multicenter observational study coordinated by the "Federico II" University of Naples, and involves 19 centers situated throughout Italy. Thyroid hormones, insulin-like growth factor-1, total testosterone, dehydropianoandrosterone and insulin are measured at baseline and every year for a patient-average follow-up of 3 years. Subjects with chronic HF are divided into two groups: patients with 1 or no anabolic deficiency, and patients with 2 or more anabolic deficiencies at baseline. The primary endpoint is the composite of all-cause mortality and cardiovascular hospitalization. Secondary endpoints include the composite of all-cause mortality and hospitalization, the composite of cardiovascular mortality and cardiovascular hospitalization, and change of peak oxygen consumption. Patient enrollment started in April 2013, and was completed in July 2017. Demographics and main clinical characteristics of enrolled patients are provided in this article. Detailed cross-sectional results will be available in late 2018 [65].

The T.O.S.CA Registry represents the most robust prospective observational trial on MHD in the field of HF. The study findings will advance our knowledge with regard to the intimate mechanisms of HF progression and hopefully pave the way for future randomized clinical trials of single or multiple hormonal replacement therapies in CHF.

Conclusions

GH therapy in HF looks like an old story retold. Although the rationale for its use is still solid, the choice of the right population to treat turned out to be wrong. Not all HF patients will probably benefit from a growth factor approach, but only the subset of subjects displaying coexisting GH deficiency and HF. This approach is currently viewed in the context of the larger scenario of HF comorbidities, and in particular, of hormone deficiencies. Whether MHD is a mere cluster of biochemical hormone abnormalities or a strong independent predictor of HF progression is still unknown. Ongoing studies will soon provide a definitive answer to these outstanding questions.

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