

Role of growth hormone in chronic heart failure: therapeutic implications

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Chronic heart failure is a multi-etiological cardiovascular disorder with high prevalence and poor prognosis. Medical treatment of dilated cardiomyopathy is aimed at alleviating heart failure symptoms. Diuretics, angiotensin-converting enzyme (ACE) inhibitors and very recently, beta-blockers have been shown to have favorable effects on symptoms, exercise capacity and mortality. Growth hormone (GH) and insulin-like growth factor (IGF)-1 are involved in several physiological processes such as the control of muscle mass and function, body composition and regulation of nutrient metabolism. The role of GH and IGF-1 as modulators of myocardial structure and function is well established. Receptors for both GH and IGF-1 are expressed by cardiac myocytes; therefore, GH may act directly on the heart or via the induction of local or systemic IGF-1, while IGF-1 may act by endocrine, paracrine or autocrine mechanisms.

Patients with acromegaly have an increased propensity to develop ventricular hypertrophy and cardiovascular diseases; impaired cardiac efficiency can also be observed in patients with GH deficiency.

Animal models of pressure and volume overload have demonstrated up-regulation of cardiac IGF-1 production and expression of GH and IGF-1 receptors, implying that the local regulation of these factors is influenced by hemodynamic changes. Moreover, experimental studies suggest that GH and IGF-1 have stimulatory effects on myocardial contractility, possibly mediated by changes in intracellular calcium handling.

Heart failure is due to ventricular dilation with inadequate wall thickening that leads to impaired cardiac performance; therefore, based on previous evidence we would expect beneficial effects from the use of GH in these patients.

Several papers have highlighted the positive influence of GH in the regulation of heart development and performance. In patients with GH deficiency, GH administration dramatically improves cardiac function. In small open studies, acute and chronic GH treatment has demonstrated beneficial effects in patients with heart failure due to ischemic or idiopathic cardiomyopathy. Recently, two randomized, placebo-controlled studies did not show any significant GH-mediated improvement in cardiac performance in patients with dilated cardiomyopathy, despite significant increases in IGF-1.

Acquired GH resistance might be an important feature of severe heart failure and explain the diverse responses to GH therapy observed in different patients.

Whether GH treatment will finally find a place in the treatment of heart failure, and with which modalities, remains to be established.

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Growth hormone and the heart: physiological and pathophysiological aspects

Growth hormone: structure, metabolism and actions. *Structure.* Growth hormone (GH) is secreted by the somatotrope cells of the anterior pituitary gland¹. GH, a 191 amino acid with a molecular weight of 22 kD, single-chain peptide sharing marked structural homology with human placental lactogen and prolactin, is central to the endocrine control of growth. The gene encod-

ing GH in humans is located on the long arm of chromosome 17. Several minor variants of GH exist in the circulation. A 20 kD variant devoid of residues 32-46 lacks both the insulin-mimetic and lipolytic properties of the 22 kD native hormone². The GH gene and its mRNA transcript have five exons separated by four introns. The human adenohypophysis contains 5 to 10 mg of GH, which is synthesized and stored in somatotrophic cells. These cells make up 35 to 45% of the gland. They are not uniformly

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distributed but are located predominantly in the lateral wings of the pituitary.

Metabolism³. GH disappears from plasma after release from the pituitary with an initial half-life of about 20 to 25 min. The clearance rate for human GH as determined by the constant infusion method is between 100 and 150 ml/m² of body surface/min. Clearance rate is not influenced by age or sex. GH secretory rates cannot be estimated from basal GH levels and the metabolic clearance of GH because of the marked fluctuations in hormone concentration throughout the day and night. The mean concentration of GH in plasma, calculated from continuous or repetitive blood sampling over a 24-hour period, is 2 to 4 ng/ml in young adults and 5 to 8 ng/ml in children and adolescent boys and girls. On the basis of the mean plasma GH level and its metabolic clearance, the 24-hour secretion rate in young men is about 1 to 2 mg/day.

Actions. Direct effects of GH can be demonstrated in a number of isolated tissues and organs⁴. GH receptors are present in human liver membranes, adipocytes, fibroblasts, and lymphocytes. In each case, binding is specific for human GH and occurs via dimerization of the receptor and by activating a JAK-STAT transcription. The actions of GH include stimulation of skeletal and muscle growth, promotion of cellular uptake of amino acids, and regulation of lipolysis. GH also has anti-insulin effects. Some of the growth-promoting and metabolic effects of GH are mediated by the generation of insulin-like growth factor (IGF)-1. Most of the IGF-1 is synthesized in the liver and kidney and circulates in plasma bound to protein carriers (IGFBPs), although locally synthesized IGF-1 in other tissues also appears to be important in mediating GH effects. IGF-1 is structurally homologous to proinsulin, which may explain many of its insulin-like effects. IGF-1 is a single-chain protein with 70 amino acids coded for by a gene on chromosome 12. IGF-1 stimulates proliferation of cartilage and synthesis of cartilage matrix chondroitin sulfate. IGF-1 has much longer serum half-life than GH and therefore may facilitate tissue growth by acting in concert with GH and other growth factors. The IGFBPs are a family of recently characterized proteins that bind IGF-1 and modulate its action at the tissue level⁵. IGFBP-3 is the major circulating form of IGFBP and its main physiological role is the binding of free IGF-1 and thereby increasing its circulating half-life and biological activity. Because IGFBP-3 is GH-dependent, but has a prolonged half-life compared to GH and does not exhibit pulsatility or a circadian pattern, it is an integrated marker of somatotroph function.

Physiological regulation of growth hormone secretion.

GH secretion is under the control of two hypothalamic peptides⁶: GH-releasing hormone (GHRH), a peptide of 44 amino acids, which stimulates GH release; somato-

statin, which can exist both as 14 and 28 amino acid peptides, and inhibits GH secretion. GH secretion is regulated by negative feedback and neural control mechanisms. Both GH and IGF-1 inhibit GH secretion after intraventricular injection by promoting hypothalamic somatostatin release. Presumably, physiological concentrations of GH and IGF-1 reaching the hypothalamus in the bloodstream act in the same way (increase in somatostatin tone). In addition, IGF-1 may act directly on the pituitary to inhibit GHRH-stimulated secretion of GH. GH secretion can be augmented or inhibited by a number of neurogenic, metabolic, and hormonal influences⁷. In adults, the diurnal pattern of GH secretion has been characterized by obtaining blood samples every 20 or 30 min throughout a 24-hour period under non-stressful conditions. During most of the day, plasma GH levels of normal adults are < 5 ng/ml, with one or two sharp spikes 3 to 4 hours after meals. The most consistent period of GH secretion for both children and young adults occurs about 1 hour after the onset of deep sleep⁷.

Growth hormone and cardiac function. Basic studies.

GH exerts its effects on myocardial tissue via direct and indirect mechanisms. Most of the indirect effects are mediated by IGF-1⁸. The concept has emerged that GH acts by stimulating the local production of IGF-1, which in turn promotes tissue growth by paracrine or autocrine mechanisms. Evidence is also accumulating that IGF-1 is specifically involved in the control of cardiac tissue growth. The GH receptor gene is expressed in the myocardium to a greater extent than many other tissues⁹. Furthermore, cardiac myocytes of rats express the IGF-1 receptor and more importantly, IGF-1 increases the size of cultured cardiomyocytes and simultaneously induces muscle specific gene expression¹⁰. Recent data strongly suggest that IGF-1 promotes cardiac hypertrophy. IGF-1 mRNA expression is increased in the rat myocardium after pressure overload, secondary to either banding of the ascending aorta or to experimental renal hypertension. Interestingly, IGF-1 expression is more pronounced in those segments of the myocardium that are particularly subjected to mechanical stress¹¹. It is noteworthy that IGF-1 is the principal but not the only mediator of GH action on cardiac tissue. For instance, GH stimulates induction of the proto-oncogene *c-myc* in various tissues and of the platelet-derived growth factor in the heart. The role of these and other growth factors mediating the GH effect on the myocardium is still obscure¹². GH may also exert direct effects on the myocardium as well as on the blood vessels influencing the calcium-dependent contractile reserve¹³.

Growth hormone excess. Acromegaly is a clinical condition characterized by chronic GH hypersecretion which is characterized by high prevalence of cardiovascular complications that account, in part, for the increased mortality associated with this disease¹⁴. The most frequent cardiovascular abnormality observed in

acromegaly is concentric heart hypertrophy. Several cellular and subcellular changes including the induction of apoptosis¹⁵ have been described in acromegalic cardiomyopathy. In addition to cardiomegaly, another frequent cardiovascular abnormality is arterial hypertension, which affects approximately one third of acromegalic patients¹⁶. Coronary artery disease, ventricular arrhythmias, and congestive heart failure may be observed. Enough data have been presented on heart morphology and function to suggest the existence of a specific acromegalic heart disease and they include: 1) increased ventricular mass and wall thickness of both ventricles; 2) impaired diastolic filling with normal systolic function at rest; and 3) impaired cardiac performance under stress due to diastolic and systolic dysfunction. A frequent observation made in acromegaly is the poor correlation of heart hypertrophy with circulating levels of GH or IGF-1¹⁷. Conversely, the degree of hypertrophy is related to the duration of the disease¹⁸. The hemodynamic consequences of GH excess on the heart may be mediated by direct as well as indirect mechanisms. The effects on cardiac dysfunction of GH suppression with the first clinically used somatostatin analogue octreotide have now been extensively studied, and data available indicate a clearly favorable effect of octreotide¹⁹. Lim et al.²⁰ found that suppression of GH hypersecretion achieved with octreotide was followed by a significant and surprisingly rapid (7 days) reduction in left ventricular mass in acromegaly patients with left ventricular hypertrophy. Recently, we have shown that 24-hour continuous subcutaneous infusion of octreotide in patients with acromegaly and ventricular hypertrophy was able to improve several parameters of left ventricular function at rest (without any influence on ventricular mass) and work capacity at both anaerobic threshold and during maximal exercise²¹. The use of slow-release (SR) formulations of somatostatin analogues, such as SR lanreotide, could overcome the scarce compliance associated with either repeated subcutaneous injection or continuous pump administration that was necessary for the use of octreotide in the treatment of patients with acromegaly. Recently, it has been demonstrated a significant decrease in mean GH values during SR lanreotide treatment²². Our data show that the administration of SR lanreotide causes a decrease in circulating GH levels as well as beneficial and persistent effects on cardiopulmonary function after 7 and 14 days from the injection²³. Our work confirms that GH excess may not only have structural but also functional deleterious effects on the hypertrophic acromegalic heart. Moreover, we observed that SR lanreotide is rapidly effective in both reducing circulating GH and improving cardiac function in patients with acromegaly and could have, *per se*, positive acute functional effects on the hypertrophic acromegalic heart.

Growth hormone deficiency. GH deficiency produces different clinical effects, depending on the age of onset²⁴.

In children, the syndrome is characterized by short stature with normal body proportions, and reduced growth rate. The consequences of decreased GH production in adult life have been appreciated only recently: in fact, also in adults GH is essential for several physiological processes. Indeed, adult-onset GH deficiency is usually accompanied by excessive adiposity with an upper-body (abdominal) pattern, reduced muscle mass, reduced body water, decreased bone mineral density, psychological disorders, and increased incidence of cardiovascular mortality²⁵. Impaired cardiac function in GH-deficient patients, at baseline and during physical exercise, is due to the presence of a hypokinetic cardiac syndrome which can be corrected by specific treatment: this indicates that GH plays an important role in the physiological maintenance of a normal cardiac structure and function²⁶. GH deficiency is responsible for a reduced growth rate of cardiac muscle and cardiac performance is impaired because of a reduced myocardial mass and/or because of a direct effect of GH on myocardial contractility. GH deficiency may also reduce cardiac mass and function through activation of indirect mechanisms. The mechanism responsible for this phenomenon is not known. One possibility is that GH interacts with catecholamine release or action. In fact, data have demonstrated that GH increases tissue sensitivity to epinephrine²⁷. Furthermore, GH-deficient patients may have elevated total peripheral vascular resistances²⁸. Finally, GH-deficient patients are known to be at risk of early atherosclerotic lesions which can be prevented by substitutive treatment²⁹.

Chronic heart failure and growth hormone

Chronic heart failure (CHF) is a clinical syndrome with an overall poor prognosis, despite the advances in drug treatment. The only effective treatment for end-stage heart failure remains heart transplantation, which is limited by a shortage of donor organs, therefore new therapeutic strategies are under investigation. CHF is characterized by left ventricular impairment which leads to secondary changes in other organs with consequent symptoms like dyspnea, muscular fatigue, and exercise intolerance. While in the past heart failure has been considered mainly a hemodynamic disorder, in the last decade the attention has focused on the muscular and hormonal changes in this condition. Pituitary GH has recently been indicated as a key factor in the neuroendocrine responses observed in heart failure. Whether the GH response is a primary effect of heart failure or a secondary feature of the sympathetic renin-angiotensin-aldosterone and cytokine system activation remains to be established.

Endocrine studies. GH secretion is pulsatile and is modified by external stimuli and endogenous neural

rhythms, and by the feedback effects of GH itself³⁰. Moreover, plasma half-life of GH is relatively short. Therefore, an adequate schedule of repetitive and prolonged blood sampling must be implemented to obtain significant and useful quantitative information concerning pulsatile GH release³¹. Conversely, since IGF-1 has a much longer half-life than GH and circulating IGF-1 levels do not significantly change through the day, a single sample assay may give a reliable measure of IGF-1³². The limitations of the clinical use of the IGF-1 assay as a marker of GH secretion are mainly two: first, IGF-1 synthesis is not only regulated by GH but also by nutrient supply and by other hormones³³; second, it has been reported that low IGF-1 levels in the presence of high-normal GH synthesis may reflect a peripheral resistance to GH action³⁴. In 12 male patients with CHF (ischemic or idiopathic), we studied GH and IGF-1 profile at baseline and after acute (24 hours) human recombinant GH intravenous infusion³⁵. The results are reported in table I. In our patients, baseline mean nocturnal GH levels were higher than in normal subjects and it was possible to notice that the 7 patients (subgroup B) with higher mean spontaneous GH levels ($> 2 \mu\text{g/l}$) tended to have lower circulating IGF-1 levels as compared to the 5 patients (subgroup A) with apparently lower spontaneous GH secretory activity. Interestingly, the highest IGF-1 levels after GH infusion were obtained in those patients with higher IGF-1 levels at baseline independently of the serum GH levels obtained during the infusion. The observed effects of GH were marginally dependent on the baseline hemodynamic picture of the subjects (weak correlation between baseline and post-GH hemodynamic parameters). Conversely, the baseline endocrine picture appeared to be of some importance in determining the cardiovascular responsiveness to GH infusion. In fact, patients with low circulating IGF-1 levels and spontaneously high GH levels (i.e. those characterized by a certain degree of "GH resistance") had less dramatic endocrine (increase in IGF-1) and hemodynamic responses to GH infusion. It seems unlikely that other factors may have contributed to the different IGF-1 response to GH infusion observed. In fact, nutritional and external conditions were maintained constant throughout the study. In those subjects with low baseline IGF-1 a more compromised liver function, likely consequent to CHF, was found: baseline IGF-1 levels correlated negatively with serum total bilirubin and

positively with serum pseudo-cholinesterase. It could be hypothesized either that impaired IGF-1 response to GH may be a biological marker of generalized tissue resistance to GH (and therefore that the cardiovascular tissue may be less responsive to the direct action of GH) or that the hepatic or cardiovascular synthesis of IGF-1 in response to GH could be reduced (and therefore the cardiovascular response to circulating or locally produced IGF-1 is impaired). In clinical practice pathological conditions characterized by genetic (Laron dwarfism)³⁴ or acquired (type 1 diabetes mellitus, renal insufficiency, starvation)^{36,37} GH resistance are well known. All these conditions with impaired IGF-1 synthesis have been demonstrated to decrease the biological effect of GH at the tissue levels.

Therefore, it may be possible that low baseline circulating IGF-1 levels could represent a good predictor of a weak hemodynamic response to exogenous GH infusion: impaired cardiovascular response to exogenous GH may be due to an impaired hepatic (as suggested by the correlation between IGF-1 levels and liver function) or cardiac production of IGF-1 (it implicates a role for systemic or local IGF-1 in cardiovascular response to GH)³⁸ or to an impaired GH action at the cardiac level (it implicates a direct effect of GH on heart function)³⁹.

Clinical studies and growth hormone treatment. It has been found that neurohormonal activation is closely related to a poor outcome of CHF⁴⁰⁻⁴³; moreover, drugs that interfere with the neurohormonal changes occurring in CHF (such as ACE-inhibitors and beta-blockers) can positively influence the natural history of the disease^{44,45}. Like other hormones in CHF, GH axis has also been found to be significantly altered⁴⁶. Furthermore, in patients with GH deficiency, left ventricular function is reduced and GH administration normalizes cardiac performance⁴⁷. Studies of various models of experimental heart failure suggest that GH may induce myocyte hypertrophy, improve myocardial contractility and change the distribution of myosin isoforms that improve the metabolic efficiency of the heart⁴⁸⁻⁵¹. Beneficial effects of GH therapy in patients with CHF have now been reported in a series of controlled and uncontrolled studies (Table II)^{39,52-57}. Fazio et al.⁵² reported that GH administered every second day for 3 months increased septal thickness and left ventricular mass, improved

Table I. Growth hormone (GH, nocturnal mean and peak) and insulin-like growth factor-1 (IGF-1, $\mu\text{g/l}$) in the control group and patients (subgroup A and B).

	Control	Patients	Subgroup A	Subgroup B
Mean GH	1.46 ± 0.66	2.5 ± 1.3	1.40 ± 0.8	3.3 ± 1.1
Peak GH	7.2 ± 3.2	8.6 ± 7.2	4.4 ± 2.4	11.5 ± 8.2
IGF-1	155.5 ± 47.14	166.3 ± 79.8	236.8 ± 35.9	119.3 ± 63

Subgroup A: GH levels $< 2 \mu\text{g/l}$ (n = 5); Subgroup B: GH levels $> 2 \mu\text{g/l}$ (n = 7).

Table II. Summary of published studies on growth hormone treatment in patients with congestive heart failure.

Author	No. patients	Randomized controlled	Dose	Treatment time
Cuneo et al. ⁵³	1	No	12 IU/day	3 months
Fazio et al. ⁵²	7	No	4 IU 3/week	3 months
Frustaci et al. ⁵⁵	5	No	4 IU/day	3 months
Volterrani et al. ³⁹	12	No	0.1 IU/kg/24 hours	24 hours
O'Driscoll et al. ⁵⁴	2	No	> 10 IU/day	1-7 weeks
Osterziel et al. ⁵⁶	50	Yes	2 IU/day	3 months
Isgaard et al. ⁵⁷	22	Yes	2.5 IU/day	3 months

clinical symptoms, exercise capacity and reduced chamber size and end-systolic wall-stress while biochemically inducing a marked increase in IGF-1 levels in 7 patients with CHF. A 57% improvement in the cardiac index and a 25% decrease in mean pulmonary artery pressure were by us shown after a 24-hour infusion of GH (0.1 IU/kg) in 12 CHF patients³⁹ (Fig. 1). Beneficial clinical responses to GH have also been reported in small groups of CHF patients with increases in body weight, improved functional capacity and exercise tolerance^{53,54}. However, a study by Frustaci et al.⁵⁵ on 5 patients with severe CHF, showed only a mild reduction in left ventricular diameters and minor improvement in left ventricular ejection fraction after 3 months of GH administration (4 IU/day). These initial studies have all been open and uncontrolled. More recently, two placebo-controlled studies of GH therapy in CHF patients have been published^{56,58}. In Isgaard's study, GH was given daily at a dose of 0.25 IU/kg/week to 22 CHF patients. No significant effects on hemodynamic parameters, clinical symptoms, left ventricular mass or exercise tolerance were reported⁵⁸. Similarly, a second randomized controlled trial of GH therapy in CHF patients did not show any significant benefits on NYHA functional class or on the 6-min walking distance⁵⁶.

It is not easy to justify the discrepant results of the above-mentioned studies of GH administration in CHF patients. It has been previously shown that acquired GH resistance is closely related to CHF, particularly in patients with cardiac cachexia⁵⁹. The different responses to GH therapy might be related to the proportion of patients "resistant" to the effect of the hormone. GH resistance might be a major determinant of the response to GH treatment, as in this condition its administration would not be effective. Cardiac cachexia might be an important determinant of response to GH therapy, because of its close relationship with GH resistance. In most of the studies previously mentioned^{39,52,55,56,58}, it has not been stated whether the patients suffered from body wasting. The only two studies on cachectic patients^{53,54} showed significant clinical benefits in this subgroup of patients, but high doses were administered, to override possibly GH resistance. Another theoretical possibility of overcoming GH resistance might be the mode of GH administration as suggested by the same authors. In most studies GH was given daily, while it has been ob-

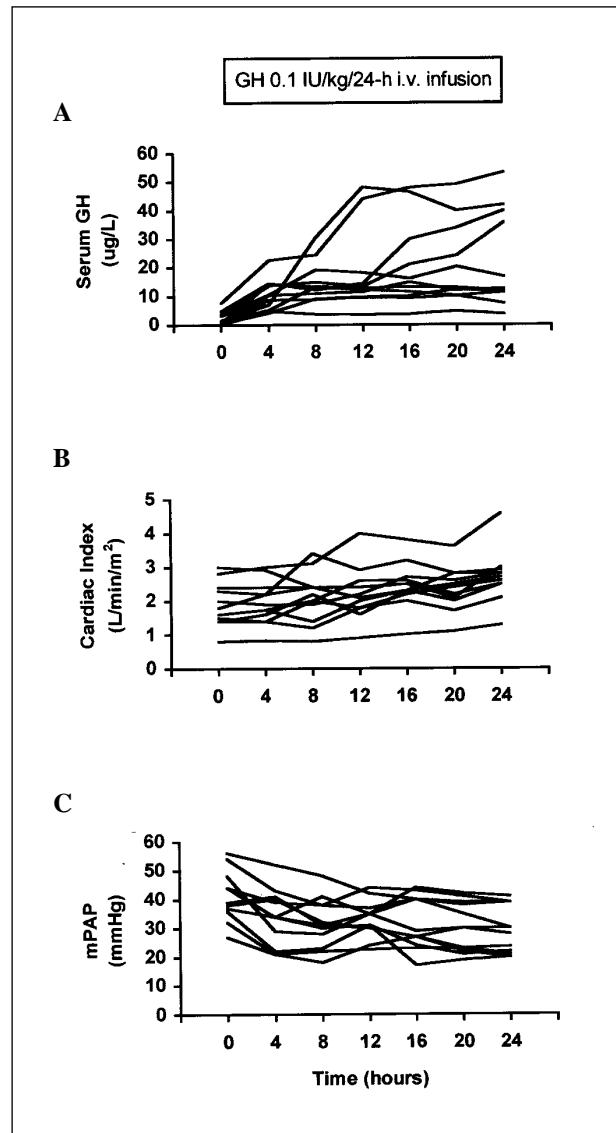


Figure 1. Individual serum growth hormone (GH) levels (A), cardiac index (B) and mean pulmonary artery pressure (mPAP) (C) profiles during exogenous GH infusion (0.1 IU/kg/24 hours) in 12 patients with congestive heart failure. Blood sampling for GH was possible only in 11 out of the 12 patients.

served that an intermittent administration is able to produce greater induction of IGF-1 mRNA in peripheral tissues⁵⁷. Only Fazio et al.⁵² used injections every second day, and they were the only ones who found significant clinical benefits of chronic GH therapy in CHF patients.

Conclusions

GH treatment in CHF patients is an exciting but still an open clinical research issue. Randomized, placebo-controlled studies with larger patient groups and different duration are required to assess safety, long-term results, and best dosage regimens. Moreover, on the basis of recent data giving some interesting insights into the possible determinants of the observed positive functional acute cardiovascular effects of GH, patient baseline endocrine picture should be carefully considered, to select those who might have more clinical benefits from this new therapeutic option.

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