

Beneficial Effects of Growth Hormone in Patients With Chagas Cardiomyopathy and Dilated Cardiomyopathy of Unknown Etiology

Clinical Trial and Review of the Literature

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To date, experience with GH treatment in adults who have cardiovascular disease but no GHD is very limited. An important recent study has shown that administration of GH for 3 months to patients with moderately severe heart failure due to idiopathic dilated cardiomyopathy can increase myocardial mass and decrease the size of the left ventricular chamber, thereby improving haemodynamics, myocardial energy metabolism, and clinical status.¹

Volterrani² reported the acute effects of a short term continuous intravenous infusion of recombinant GH in 12 men with chronic heart failure (8 ischemic, 4 idiopathic), New York Heart Association Class II in 2, Class III in 5, and Class IV in 5; mean ejection fraction 20.7 (6.6%), mean peak exercise VO_2 10.2(3.1) ml/Kg/min, who were taking digoxin, diuretics and vasodilators, and were in sinus rhythm. After 24 hours of infusion, mean CI increased from 2.1 ± 0.6 to 3.3 ± 1.2 L/min/m² ($p=0.01$). Ten patients had a CI ≥ 2.5 L/min/m² at the end of GH infusion; one patient had a worsening of CI. In 10 of the 11 patients who responded the CI continued to increase for the whole period of infusion. After 24 hours of GH infusion, there was approximately a 25% drop in mean PAP. At the same time, O'Driscoll³ reported the use of GH in two patients with terminal heart disease and was

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ABBREVIATIONS AND ACRONYMS

ACE	Angiotensin converting enzyme
CHF	Congestive heart failure
CI	Cardiac index
GH	Growth hormone
GHD	Growth hormone deficiency
HDL	High density lipoprotein
IGF-1	Insulin-like growth factor
LDL	Low density lipoprotein
mRNA	Messenger RNA

able to demonstrate an improvement in exercise performance and VO_2 max.

We recently reported our experience with the use of GH in Chagas disease.⁴ Chagas disease is caused by the protozoan *Trypanosoma cruzi*. The major cardiovascular manifestation is an extensive myocarditis that typically becomes evident years after the initial infection. The disease is prevalent in Central and South America, particularly in Brazil, Argentina, Venezuela, and Chile. Pathological cardiac findings during the chronic phase include cardiac enlargement with dilatation and hypertrophy of all cardiac chambers. The left ventricular apex is often thin and bulging resembling an aneurysm. We used recombinant human growth hormone in patients with chronic congestive heart failure due to Chagas disease as well as idiopathic cardiomyopathy. Patients with severe congestive heart failure due to either Chagas disease or dilated cardiomyopathy of unknown etiology were the subject of the study.

Methods

The study involved 10 patients with chronic heart failure. Five of these patients had Chagas cardiomyopathy and 5 had dilated cardiomyopathy of unknown etiology. Their mean age was 54 ± 15 ; there were 8 men and 2 women with a mean New York Heart Association Clinical Class of III. All patients had clinical evidence of heart failure despite conventional therapy; and a left ventricular diastolic dimension greater than 60 mm, as measured by M-mode echocardiography; a left ventricular ejection fraction below 35% as assessed by two-dimensional echocardiography. Patients were excluded if they had active myocarditis, substantial coronary artery

disease, systemic hypertension, hypertrophic cardiomyopathy, diabetes mellitus, or chronic alcoholism. Patients were treated with digoxin, ACE inhibitors, and diuretics.

After obtaining informed consent the following protocol was performed. All the patients were studied at baseline, every 6 weeks, and after the end of the treatment period with recombinant human growth hormone (Genotropin, Pharmacia, Upjohn). GH was administered subcutaneously at a daily dose of 2 I.U. Standard medical therapy was continued throughout the study.

Procedures

M-mode, two-dimensional, and Doppler echocardiographic measurements were performed with an ultrasonographic system equipped with a 3.5 MHz transducer (Hewlett Packard 1500, MA) according to the recommendations of the American Society of Echocardiography.

Results

Effects of Growth Hormone Therapy. All patients completed the 3-month course of hormone treatment with no reported side effects. Heart rate and blood pressure did not change during the treatment period.

IGF-1 levels: Patients with CHF had a slightly (but not significantly) decreased level of the hormone compared to a group of normal controls at baseline. During treatment there was a three-fold increment of circulating IGF-1.

GH stimulation decreased left ventricular chamber volume and improved systolic performance of the left ventricle. There was no increment in wall thickness or myocardial mass (Table).

TABLE. VENTRICULAR SIZE AND SHAPE

WALL THICKNESS	PRE-GH	POST-GH	PAIRED T TEST
Septum (cm)	0.8 ± 0.2	0.9 ± 0.1	NS
Posterior wall (cm)	0.9 ± 0.1	1.0 ± 0.1	NS
	PRE-GH	POST-GH	PAIRED T TEST
LVESd (cm)	6.4 ± 0.1	5.2 ± 0.8	$p < 0.005$
LVEDd (cm)	7.4 ± 0.8	6.5 ± 1.0	$p < 0.005$
LVmass (g)	270 ± 61.1	260.5 ± 69.8	NS
LVEF (%)	25 ± 6	42 ± 1	$p < 0.005$

Discussion

In this study we attempted to induce cardiac hypertrophy with recombinant growth hormone in an effort to improve wall stress. We could not demonstrate an improvement in wall thickness but there was a clear improvement in the volumes and dimensions of the left ventricle. Ejection fraction as an index of left ventricular contractility increased significantly.⁵

Review of Relevant Literature

It has been well recognized that the myocardium undergoes structural changes in response to cardiovascular disease. Irrespective of the initial etiology, myocardial damage may result in reduced power output of the heart, which occurs over a varying time frame, depending on the severity of disease and the etiology of myocardial damage. Severe impairment of left ventricular pump function leads to the syndrome of CHF. Initial myocardial damage induces a process of remodeling, which is a combination of dilatation and compensatory hypertrophy of the left ventricle. This hypertrophy is often inadequate to maintain normal hemodynamics.

Between 1986 and 1993, multiple clinical trials were conducted with vasodilators and positive inotropic agents to attempt to enhance systolic performance of the heart. With one exception, all of these trials resulted in worsening the natural history of chronic heart failure.⁶⁻⁹ In the latter part of the 1980s and early 1990s, evidence began to appear that certain ACE inhibitors and β -blockers might have beneficial effects on the natural history of left ventricular dysfunction or myocardial failure, despite having initial hemodynamic effects that were either unimpressive¹⁰⁻¹² or even adverse.¹³⁻¹⁵

Since the 1980s, there has been much work on neurohumoral systems and the pathophysiology of heart failure. Neurohormonal factors proved to be not only indicators of severity of heart failure, but also important determinants of the progression of this syndrome.

The clinical utility of ACE inhibitors to prolong survival in patients with heart failure and their reported ability to block in vivo hypertrophy in several experimental settings have led to the view that activation of cardiac hypertrophy is an unfavorable component of pathological remodeling of the ventricular chamber. As a result, the inhibition of ventricular chamber enlargement and hypertrophy has become one therapeutic target for new molecular strategies to improve or maintain cardiac function after myocardial injury.¹⁶⁻¹⁹

An alternate approach would be to stimulate the development of more adequate, physiological compensatory hypertrophy. Recent advances in the development of in vitro and in vivo systems for analyzing the signaling pathways for cardiac hypertrophy suggest that there may be distinct programs that dictate physiological and pathological forms of muscle hypertrophy.²⁰⁻²⁴ Therefore, appropriate biological targets for maintaining cardiac function in the setting of heart failure might not only include agents designed to block pathological forms of hypertrophy, such as ACE inhibitors, but also the development of new approaches to promote physiologic maintenance or improvement of cardiac function. Moreover, novel and/or known growth factors might mediate either pathological or physiological forms of hypertrophy through the activation of different subsets of cardiac muscle genes.

Several independent lines of evidence suggest that IGF-1 may be involved in mediating physiological forms of heart failure.

The advent of techniques to determine IGF-1 mRNA expression has shed further light on the interactions between tissue growth and GH and IGF-1. 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 in many other tissues,²⁵ and GH administration to hypophysectomized rats increases cardiac IGF-1 content²⁶ and induces IGF-1 mRNA expression.²⁷ Furthermore, cardiac myocytes of rats express IGF-1 receptors^{30,31} and more important, IGF-1 increases the size of cultured cardiomyocytes and simultaneously induces muscle specific gene expression.³²

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 aorta²⁵ or to experimental renal hypertension.²⁶ Moreover, IGF-1 mRNA expression is stimulated in the myocardium of volume-overloaded animals.³² Interestingly, IGF-1 expression is more pronounced in those segments of the myocardium that are particularly subjected to mechanical stress.²⁵⁻³²

The evaluation of the effects of GH on the heart comes from the animal model. There are several models, but the most specific is probably the transplanted pituitary tumor. The main observation with this preparation is an increase in total body weight and generalized splanchnomegaly. The increase in myocardial mass is slightly, if at all, out of proportion to the body weight.^{26,36,37} In this model there

are important alterations in the intrinsic contractility of the myocardium. This is defined as the ability of the myocardial fiber to develop force independent of other variables (loading conditions). Studies have been performed on cardiac papillary muscles and on the skinned cardiac fibers taken from rats with GH secreting tumors.^{33,34} These studies have demonstrated improved cardiac contractile performance and a significant increment in calcium sensitivity of the contractile proteins.^{33,34} Interestingly, GH excess also produced a prolonged action potential,³⁸ which in turn may facilitate Ca influx through calcium channels, thereby explaining in part the enhanced contractility.

GH excess also affects the phenotype of cardiac contractile proteins. Some exist in multiple isoforms that may undergo changes in the fetal post-natal transition and in response to environmental stimuli. The specific effect of GH excess is to induce a myosin phenoconversion consisting of a marked shift toward the low ATPase activity V3 isoform.^{33,34} Thus, GH excess would evoke a unique pattern of myocardial response with a simultaneous improvement in both force and economy of contraction.³⁵ In other words, the myocardium would function at a lower energy cost. This contrasts sharply with other forms of cardiac hypertrophy, such as that secondary to hemodynamic overload, where V3 phenoconversion occurs but is associated with depressed contractility.^{35,39}

GH can increase the size of myocytes without causing fibrosis,⁴¹ improve the efficiency with which these cells contract, and enhance their responsiveness to calcium and beta adrenergic stimulation.^{42,43} The improvement in efficiency is manifest as an increase in the maximal active force of contraction, and seems to result from a rise in the number of active myosin cross-bridges and a decrease in their cycling rate.³⁴ To determine whether additional hypertrophy would be beneficial or maladaptive in cardiac failure, the effects of IGF-1 were investigated in rats with left ventricular dysfunction. Stimulation by IGF-1 of the severely dysfunctional heart was capable of inducing additional hypertrophy with evidence of improved function.⁴⁴

Duer⁴⁵ provided evidence that the exogenous administration of GH-IGF-1 for 4 weeks beginning 1 month after myocardial infarction causes only minor remodeling of the failing left ventricle compared with controls, but substantially increases the CI in rats with large myocardial infarctions. The latter effect may have been largely due to an IGF-1/GH mediated decrease in peripheral resistance. Jin⁴⁶ studied the effects of GH and IGF-1 in rats after inducing myocardial infarction. A group of

these animals was treated with ACE inhibition and another with ACE inhibition + IGF-GH. There was a greater increment in the CI in the ACE inhibition + GH/IGF-1 animals than in those treated with ACE inhibitors alone. Systemic vascular resistance was lower in the combination group. The beneficial effect of captopril in reducing cardiac hypertrophy was preserved in the captopril + GH/IGF-1 group. Yang⁴⁷ demonstrated in the rat heart after ligation of the left coronary artery that the administration of GH increased CI, stroke volume index and left ventricular dP/dt, and reduced left ventricular end diastolic pressure and systemic vascular resistance, suggesting that in these failing hearts GH increased myocardial contractility and decreased peripheral resistance.

Cittadini⁴⁸ investigated the cardiac effects of GH administration during the early phase of pathologic remodeling in a rat model of large myocardial infarction. GH caused hypertrophy of the non-infarcted myocardium in a concentric pattern. Left ventricular dilation was reduced in the GH versus placebo group and cardiac function improved. Isgaard⁴⁹ used a similar model and demonstrated a 13% increment in ejection fraction and a 50% increment in CI after the administration of GH. There were no significant changes in the left ventricular or interventricular wall thickness, LV dimensions, heart rate, or diastolic function.

Conclusions

The results of recent basic research have demonstrated that GH has important effects on the heart. It improves haemodynamics, myocardial energy metabolism, and clinical status in patients with moderate to severe left ventricular dysfunction. Further evidence that GH has important effects on the cardiovascular system is provided by the results of studies in adults with GHD. It is well known that these patients suffer from reduced well-being and vitality, abnormal body composition, and decreased exercise capacity. Recent work indicates that they also have impaired cardiac performance and an increased prevalence of certain cardiovascular risk factors, including elevated plasma levels of total cholesterol and LDL cholesterol, reduced plasma levels of HDL cholesterol, impaired insulin sensitivity, and decreased fibrinolytic activity. In addition, GH may reverse cachexia in patients with CHF.

There is no doubt about the importance of the GH and IGF-1 system on cardiovascular integrity. A well documented GHD in children and adults is an indication for replacement therapy with recombinant human growth hormone. Review of the pub-

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lished research on clinical trials of recombinant growth hormone shows that there is considerable variability in the etiology of CHF, as well as the dosage and route of treatment. Fazio et al reported on 7 patients with CHF due to dilated cardiomyopathy, we studied 10 patients in NYHA Class III with great success.

End-stage dilated cardiomyopathy is the main indication for left ventricular reduction procedures and cardiac transplantation. Because of the high surgical risk for patients undergoing the so-called Batista (left ventricular reduction) procedure, plus the small supply of donor organs and excessive costs arising from cardiac transplantation, subcutaneous recombinant human growth hormone in conjunction with the widely accepted drugs for CHF—e.g., ACE inhibitors, diuretics, nitrates, calcium antagonists, digoxin—could become an alternative to cardiac surgery.

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