Growth Hormone for Optimization of Refractory Heart Failure Treatment

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It has been reported that growth hormone may benefit selected patients with congestive heart failure. A 63-year-old man with refractory congestive heart failure waiting for heart transplantation, depending on intravenous drugs (dobutamine) and presenting with progressive worsening of the clinical status and cachexia, despite standard treatment, received growth hormone replacement (8 units per day) for optimization of congestive heart failure management. Increase in both serum growth hormone levels (from 0.3 to 0.8 µg/l) and serum IGF-1 levels (from 130 to 300ng/ml) was noted, in association with clinical status improvement, better optimization of heart failure treatment and discontinuation of dobutamine infusion. Left ventricular ejection fraction (by MUGA) increased from 13 % to 18 % and to 28 % later, in association with reduction of pulmonary pressures and increase in exercise capacity (rise in peak VO_2 to 13.4 and to 16.2ml/kg/min later). The patient was "de-listed" for heart transplantation. Growth hormone may benefit selected patients with refractory heart failure.

Heart failure remains a high mortality and morbidity syndrome despite advances in management [1]. Besides its relative effectiveness, the clinical use of conventional or newer drugs is sometimes limited by clinical status of the patient, pharmacological intolerance or because the drug is under investigation [2]. The use of surgical procedures, such as heart transplantation, cardiomyoplasty, partial left ventriculectomy and cardiac pacemakers, is limited by donor scarcity, rigid selection criteria, graft degeneration or by lack of knowledge of accurate criteria to select patients who have chance of benefiting from a given modality of treatment [1,3,4].

Among neurohormonal changes in congestive heart failure, fall or elevation in growth hormone levels and changes in IGF-1 (somatomedin C) hormonal axis have been described, with inappropriate (low/normal) IGF-1 level in relation to growth hormone level [5-8]. Growth hormone has a widespread metabolic effect and influences the control of heart stress and performance, through activation of somatomedins, especially IGF-1 [6]. It has been suggested that resistance to growth hormone might occur in heart failure [9]. It was proposed that growth hormone might be useful in patients with heart failure, and the purpose of this report is to describe its effect optimizing the therapy of refractory heart failure, in a patient receiving intravenous inotropic drugs.

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Case report

A 63-year-old white man, referred to heart transplantation due to refractory heart failure, was admitted into the hospital in July 23, 1998. He had suffered an acute myocardial infarction in 1988 and underwent coronary artery bypass surgery in October 1988. He had already been submitted to prostatectomy in July 10, 1997, due to prostate adenocarcinoma. He had been asymptomatic until January 1998, when he began to complain of exertional dyspnea. Coronary arteriography was performed in April 09, 1998 and showed total occlusion of both left anterior descending and left circumflex arteries, a proximal 70 % stenosis of a left marginal branch, a severe proximal stenosis of the right coronary artery, total ostial occlusion of two saphenous vein grafts (from the aorta to a marginal branch and from the aorta to the right coronary artery) and another saphenous vein graft, to the anterior descending artery, free of significant narrowing, with a satisfactory aspect. The patient underwent a successful percutaneous transluminal coronary angioplasty of the right coronary artery with stent implantation, but his symptoms did not improve. Laboratory evaluation showed total cholesterol of 154 mg/dl, HDL-cholesterol of 51 mg/dl and LDL-cholesterol of 90 mg/dl. The patient continued complaining of dyspnea and was treated with digitalis, angiotensin II receptor (AT1) antagonist and high doses of loop diuretic with potassium replacement, in association with dietetic advice and physical activity. Thallium myocardium perfusion scintigraphy showed no signs of ischemia. The patient tolerated neither angiotensin-converting enzyme inhibitor nor aldosterone antagonist. There was a progressive worsening of clinical status and the patient was hospitalized at Intensive Care Unit six times in two months, when a fast improvement was achieved with intravenous inotropic drugs. When he was admitted into Heart Institute, he presented with anasarca, pleural effusion, ascites, hepatomegaly, poor peripheral perfusion with

arterial hypotension (80x60mmHg), tachycardia (heart rate of 110bpm) and persistent third sound. Electrocardiogram demonstrated normal sinus rhythm and signs of left atrium enlargement and anterior wall fibrosis. Chest roentgenogram showed moderate enlargement of cardiac silhouette and signs of pulmonary venous congestion and pleural effusion. Laboratory results were: serum sodium 129 mEq/l (reference range: 136-145 mEq/l), creatinine 1.2 mg/dl (reference range: 0.6-1.4 µg/dl), AST (aspartate aminotransferase) 17 U/l (reference range: up to 18 U/l), ALT (alanine aminotransferase) 15 U/l (reference range: up to 22 U/l), serum albumin 3.6g/dl (reference range: 3.3-5.2g/dl), CEA (carcinoembryonic antigen) 3.4ng/ml, free PSA (prostate-specific antigen) 0.01 mg/l, total PSA 0.05 µg/l, TSH (thyroid-stimulating hormone) 14.5 mU/l (reference range: 0.3-4.0 mU/l), reverse T3 0.82nmol/l (reference range: 0.18-0.51nmol/l), free T3 0.26 (reference range: 0.3-0.5), free T4 1.2 (reference range: 0.7-1.4), and high levels of antithyroid antibodies. Twenty-four hour electrocardiogram (Holter monitoring) showed normal sinus rhythm, 8001 premature ventricular complexes, 298 premature supraventricular complexes, 50 episodes of nonsustained ventricular tachycardia and 1 run of supraventricular tachycardia. Clinical conditions did not allow an ergospirometric test to be performed, in order to measure maximal oxygen consumption during exercise. Other laboratory findings and cardiovascular assessment are presented in table I. The following diagnoses were established: refractory, progressive heart failure (New York Heart Association - NYHA - functional class IV), receiving intravenous drugs, ischemic cardiomyopathy, previous prostate neoplasm, hypothyroidism and panic disorder. The treatment was optimized with intravenous furosemide, oral amiloride-hydrochlorothiazide combination, T4 replacement (normalizing TSH level), intravenous dobutamine and maintenance of angiotensin II receptor (AT1) antagonist. Congestive manifestations were reduced but the patient continued presenting with anorexia, frequent nausea, signs of inadequate perfusion and hemodynamic instability, depending on intravenous dobutamine infusion, with no change after reduction of digoxin dose. There was no improvement after introduction of pentoxifylline (1200mg/d), a TNF-a inhibitor, and shift of diuretic regimen to furosemide in association with spironolactone (100mg/d) and hydrochlorothiazide (100mg/d). The patient did not tolerate carvedilol. Angiotensin II receptor (AT 1) antagonist was changed by angiotensin-converting enzyme inhibitor, which was not tolerated due to hemodynamic instability. The patient was then included in the waiting list for heart transplantation. Due to progressive heart failure, with hyponatremia, progressive weight loss and cachexia, growth hormone (8 U/d intramuscularly) was introduced after family and patient agreement. Rise of both growth hormone and

Table I - Laboratory findings before and after introduction of growth hormone (GH)

	Before	Optimization - GH	Optimization - GH
NYHA functional	IV-C / drug	II-III	I
BMI (kg/m²)	21.93	23.04	24,1
Echocardiogram			
LVEDD (mm)	74	74	73
ST (mm)	7	8	7
PWT (mm)	8	9	8
Mitral regurg.	Moderate	Moderate	Mild/moderate
Tricuspid regurg	Mild	Mild	Mild
Radionuclide			
LVEF (%)	13%	18%	28%
RVEF (%)	12%	-	29%
Peak VO_2 (ml/kg/min)	Not possible	13,4	16,2
IGF-1 (70-290ng/ml)	130	300	-
GH (0-2.5 µg/l)	0,3	0,8	-
Pressures measurements			
Right atrium	22	14	-
Pulmonary artery (systole)	54	33	-
Pulmonary artery (diastole)	45	20	-
Pulmonary capillary wedge	30	24	-
Systemic (systole)	120	100	90
Systemic (diastole)	80	60	70
Cardiac index (l/min/m²)	2,54	2,20	-
PVR (Wood units)	3,91	-	-
SVR (Wood units)	15,5	-	-
Drugs			-
Carvedilol (mg)	-	6,25	47,5
Captopril (mg)	-	-	75 150
Digoxin (mg)	0,25	0,125	0,125
Dobutamine	4,6 (µg/kg/min)	-	-

New York Heart Association functional class; BMI- body mass index; LVEDD- left ventricular end diastolic diameter; EF- ejection fraction; LV- left ventricle; RV- right ventricle; peak VO_2- maximal oxygen uptake during exercise; IGF-1- somatomedin C; PVR- pulmonary vascular resistance; SVR- systemic vascular resistance; optimization-GH- 30 days after introduction of carvedilol; late optimization-GH- 80 days after introduction of carvedilol.

IGF-1 levels was noted (table I). The hemodynamic status began to improve progressively after 3–4 days on growth hormone use. The patient could then tolerate angiotensin-converting enzyme inhibitors. Anorexia was resolved and there was a progressive rise of body mass index. After this improvement, carvedilol was introduced and tolerated. It was also noted reduction of right atrial and pulmonary pressures and better exercise capacity. The patient was discharged on T4 150 mm/d, carvedilol 9.375mg/d, digoxin 0.125mg/d, furosemide 320mg/d, amiloride-hydrochlorothiazide combination and captopril 75mg/d and received dietetic counseling. The patient was in NYHA class II heart failure in September 28, 1998, maintained on carvedilol 37.5mg/d, captopril 150mg/d, furosemide 80mg/d, hydrochlorothiazide-amiloride combination, digoxin 0.125mg/d and B vitamins. In November 19, 1998, the patient was in NYHA class I and was "de-listed" for heart transplantation. At the same time, carvedilol dose was increased to 50mg/d.

Discussion

Our report shows that growth hormone may be useful for optimization of heart failure management, when added to conventional drugs in patients presenting with cardiac cachexia. This hormone may allow the use of drugs previously not tolerated, such as carvedilol, which can significantly improve left ventricular function [2].

Growth hormone is synthesized by the pituitary gland and its secretion is enhanced by hypothalamus growth hormone releasing factor, and inhibited by somatostatin (hypothalamus), IGF-1 (somatomedin C) and by growth hormone itself. Growth hormone secretion is also enhanced by α_2 stimulus, physical conditioning, anorexia and desnutrition and inhibited by α_1 and β agonists. Its secretion also reduces with aging [10]. Some tests can stimulate its release, such as the insulin tolerance test, pharmacological tests (glucagon, arginine, clonidine and growth hormone releasing factor) and physiologic stimulus (sleep, fasting and physical activity, specially when vigorous). An association between growth hormone synthesis and heart failure severity has been described [11] and a significant reduction in growth hormone levels was not found in patients without cachexia [12]. Patients with heart failure and cachexia (body mass index $<24kg/m^2$ and unintentional fall of dry weight $\geq 5kg$ in the previous six months) show a decrease in growth hormone levels in association with an increase in catecholamines, TNF-α, cortisol, hyponatremia and insulin resistance, when compared to normal and noncachetic subjects [7]. Other authors have reported an increase in growth hormone, TNF-α and norepinephrine levels in heart failure, in association with low IGF-1 levels, indicating growth hormone resistance through reduced IGF-1/growth hormone ratio [6]. The positive effect of growth hormone has also been noted in most, but not all experimental models of heart failure [13-15]. Growth hormone also reduced the chance of aneurysm development in experimental models of myocardial infarction [16].

The beneficial effect of growth hormone that we noted corroborates some findings in humans described by some authors. However, this report is the first one to describe the effect of growth hormone in NYHA class IV patients, depending on intravenous inotropic drug. The beneficial effect of growth hormone replacement was first reported in postpartum hypopituitarism with cardiomyopathy and in cardiomyopathy in association with hypophysectomy [17]. Other beneficial effects of growth hormone on hemodynamic conditions, ventricular stress, symptoms, exercise capacity and quality of life were reported in a small number of patients [18-21]. Otherwise, only an increase in left ventricular mass and no beneficial effect on functional class, left ventricular ejection fraction, hemodynamic pattern or exercise capacity were reported in a recent double-blind randomized study [22]. These conflicting results may have been caused by differences in patient selection, functional class, cachexia condition, duration of symptoms, concomitant drugs and growth hormone dose (2 to 14 U/day). It seems that there are patients who benefit from growth hormone replacement and others who do not. The anabolic and trophic effect of growth hormone and IGF-1 might be particularly desirable and effective for patients who present with weight loss and muscle atrophy.

Several mechanisms have been proposed to explain the beneficial effects of growth hormone. This hormone has a positive inotropic effect in normal subjects and its deficiency is associated with an abnormal body composition and reduction of muscle capacity, cardiac mass, exercise tolerance and sense of well being [23]. Growth hormone replacement can increase left ventricular mass, systolic volume and fractional shortening, and can sometimes reduce peripheral vascular resistance through synthesis of nitric oxide. Some authors suggested that growth hormone administration could cause acute effects similar to those provoked by dobutamine and phosphodiesterase inhibitors [20]. In the heart, growth hormone replacement increases IGF-1 mRNA expression, contractility and myocyte size, and shifts heavy myosin chain to V3 isoform. Therefore, growth hormone influences hemodynamic conditions and left ventricular remodeling [24]. Inhibition of apoptosis and reduction of sympathetic activity and aldosterone levels might be other possible effects [25,26].

Growth hormone replacement is beneficial and safe in children; however, its administration must be carefully monitored in adults [27]. Patients with acromegaly might present with myocardium hyperkinesis, high contractility, cardiac output and peripheral vascular resistance in the early stages of the disease. There might be development of ventricular hypertrophy and signs of heart failure later on. The risks of long-term growth hormone replacement must be carefully investigated, once IGF-1 can promote tumor growth through the IGF-1 receptor. A higher chance of developing colonic polyps and tumors was described in acromegalic patients [28]. Rise in growth hormone levels has been reported to be a risk factor for the development of neoplasms, although this was not observed in subjects receiving growth hormone replacement. Reduction in the number of IGF-1 re-

ceptors, antibodies against IGF-1 receptor and the induction of a mutant for IGF-1 receptor all inhibit tumor growth, in contrast to elevation in IGF-1 receptors, which protects tumor cells from apoptosis [29-34]. Other possible effects are: activation of the renin-angiotensin system, retention of sodium and water (in the beginning of the use), arthralgia, carpal tunnel syndrome, tinnitus, increase in serum glucose, arterial hypertension, increase in aldosterone and insulin levels, positive nitrogen balance, decrease in LDL-cholesterol and HDL-cholesterol levels and a higher conversion rate of T4 to T3 [10,35].

In conclusion, despite possible undesirable effects and possible loss of long-term efficacy, growth hormone replacement might be considered in patients presenting with cachexia for optimization of refractory heart failure treatment.

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