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Abnormal growth hormone secretion : clinical aspects

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Chapter 6

Six-months of recombinant human GH therapy in patients with Ischemic Cardiac failure

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Abstract

Growth hormone therapy in patients with idiopathic dilated cardiomyopathy and ischemic cardiac failure has revealed varying effects on systolic function, probably related to the response in serum insulin like growth factor I levels. As diastolic function has not been studied thoroughly, we studied the effects of 6 months of recombinant human growth hormone treatment on systolic *and* diastolic function in patients with ischemic cardiac failure, using cardiovascular Magnetic Resonance imaging.

Nineteen patients with ischemic cardiac failure (left ventricular ejection fraction < 40 %) were studied in a randomized trial. Ten patients received during 6 months treatment with growth hormone (2 IU/d), 9 served as controls. Systolic and diastolic function were assessed at baseline and after 26 weeks by cardiovascular Magnetic Resonance imaging. No differences were found in systolic and diastolic function between rh GH treated patients and controls. No change was observed in left ventricular mass index, end-diastolic volume, end-systolic-volume and ejection fraction. The treated patients showed no clinical improvement. Six months of treatment with growth hormone therapy in ischemic cardiac failure has no favorable effects on left ventricular mass index, on systolic and diastolic function.

Introduction

Chronic heart failure still has a poor prognosis despite advances in pharmacological therapy.¹ Therefore, new strategies are warranted to improve structural myocardial problems such as tissue growth, repair, and fibrosis, the hallmarks of left ventricular remodeling.² In this context, the use of anabolic agents is worthwhile to explore. Experimental data revealed favorable effects of growth hormone and insulin-like growth factor (IGF-I) in vitro and in experimental myocardial infarction in rats.³⁻⁸ However, the experimental treatment with recombinant human growth hormone (rh GH) in patients with cardiac failure of various origins has revealed discrepant results. Although some non-randomized studies revealed favorable effects in idiopathic dilated cardiomyopathy⁹ and ischemic cardiac failure,¹⁰ these favorable effects could not be confirmed by randomized controlled studies in idiopathic dilated cardiac failure^{11,12} or randomized¹³ and non-randomized studies in ischemic cardiac failure.¹⁴

Although the majority of patients with cardiac failure have diastolic dysfunction,¹⁵ randomized studies on the effects of growth hormone in cardiac failure have only focused on systolic function.¹¹⁻¹³ It is not known, whether growth hormone therapy has a positive effect on diastolic function. Therefore, the aim was to investigate in a randomized study the effects of 6 months therapy with rh GH on systolic and diastolic function in patients with ischemic cardiac failure using cardiovascular Magnetic Resonance (MR) imaging.

Materials and Methods

Patients

Inclusion criteria were the presence of ischemic cardiac disease proven by prior myocardial infarction and/or coronary angiography, a left ventricular ejection fraction less than 40% assessed by gated-SPECT imaging or echocardiography, a stable clinical condition for at least 3 months, and stable medical therapy with ACE-inhibitors, diuretics, digoxin, nitrates or β -blocking agents for at least 3 months. Exclusion criteria were myocardial infarction within 3 months before the study, the presence of a pacemaker or implantable defibrillator, arrhythmias, chronic renal and liver disease, diabetes mellitus, pregnancy and malignant disease. The ethical committee of the Leiden University Medical Center approved the protocol, and all patients gave written informed consent.

Protocol

Baseline measurements included a physical examination, a 12-lead ECG, cardiovascular MR imaging and biochemical tests. After baseline measurements, 22 patients were randomly allocated to treatment with recombinant human growth hormone (Zomacton^R, Ferring Pharmaceuticals, Hoofddorp, The Netherlands), or 'non-treatment'. Except for rh GH treatment, the study protocol was identical for the two groups. rh GH treatment started with 0.5 IU/day, self-administered subcutaneously. The dose was increased after two weeks to 1.0 IU/day. Four weeks after entering the study, the final dose of 2.0 IU/day was initiated and continued until the end of the study at 26 weeks. Safety visits were performed at 2, 4, 8 and 16 weeks after initiation. At 26 weeks, cardiovascular MR was performed again. At each visit, weight, waist-hip ratio, blood pressure and heart rate were recorded, and growth hormone vials were collected to assess compliance.

Cardiovascular MR

Cardiovascular MR imaging was performed on a Philips 1.5-T ACS-NT15 MR system with Power Trak 6000 (Philips Medical Systems International, Best, The Netherlands) using ECG triggering. A stack of short-axis images consisting of 2 to 12 slices (depending on heart size), with a thickness of 8 mm and an intersection gap of 1 mm was acquired using breath hold multishot echo planar imaging. Images encompassed the entire left ventricle. The imaging protocol was similar as reported previously.¹⁶

Phase contrast flow velocity measurements across the mitral valve orifice were acquired using a gradient echo acquisition sequence with retrospective gating. Velocity maps were acquired across the mitral orifice using a flip angle of 20° and an echo time of 10-12 ms. The image section had a thickness of 8 mm, a field of view of 350 mm, and consisted of 2 measurements of a 128×128 acquisition which was interpolated to a display matrix of 256×256 pixels. Depending on the actual heart rate, between 30 and 45 time frames were evenly distributed over the cardiac cycle, resulting in a temporal resolution of 35 to 39 ms. Total acquisition time was about 3 min. The maximum phase shift of 180° was set to occur at a velocity of 100 cm/s.

Cardiovascular MR Analysis

The MR images and velocity maps were analyzed on a remote workstation (Sun Microsystems Computer Corp., Mountain View, California). The left ventricular short axis acquisitions were used to assess LV dimensions, wall mass, ejection fraction. The endocardial, epicardial and papillary muscle borders of the end-diastolic and end-systolic images from each short-axis slice were manually traced using a MR analytical software system developed at our institution.¹⁷ Myocardial borders were detected as previously reported.¹⁸ The left-ventricular mass index (LVMI) and left ventricular ejection fraction (LVEF) were calculated as described before.¹⁶

Volumetric flow across the mitral valve was calculated by manually tracing the borders of the mitral valve in all time frames of the velocity map series, using flow analytical software package (MEDIS Medical

Imaging Systems, Leiden, The Netherlands)¹⁹. An experienced observer who was blinded for the treatment modality performed contour tracings. Flow curves were automatically analyzed following a manual indication of the start of early filling, peak early filling, peak atrial contribution to filling, and the end of filling as described previously.²⁰

Laboratory tests

At baseline and after completion of the study, fasting blood samples were taken between 0800-0900 h for growth hormone, IGF-I and IGF binding protein-3 (IGFBP-3) measurements. Serum growth hormone was measured with the Delfia human growth hormone assay (Wallac, Turku, Finland). Serum IGF-I was measured by RIA (INCSTAR CORP., Stillwater, MN), intra-assay variability was < 11 %; the detection limit was 1.5 nmol/liter. Normal values are 9-34 nmol/liter for subjects aged 30-50 yr and 8-26 nmol/liter for 50-70 yr. IGFBP-3 was measured by RIA (Nichols Institute Diagnostics, Wychen, The Netherlands) with a detection limit of 0.03 mg/liter and the intra-assay variability of < 8 %. IGF-I and growth hormone determinations of all subjects were measured in one assay. Safety laboratory measurements included serum levels of urea, creatinine, glucose, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase and hematological profile. Other measurements were performed using routine laboratory methods.

Statistics

Continuous variables are expressed as the mean $\pm$ SD. Paired or unpaired Student t-tests were used, when appropriate. To analyze treatment effects, the differences in treatment response (post-therapy divided by pre-therapy values) were compared between the groups. A P value of less than 0.5 was considered significant. SPSS 10.0 (SPSS, Inc., Chicago, IL) was used for all statistical calculations.

Results

Baseline measurements

Three patients left the study prematurely for various reasons, not related to the study. Data from these patients were not included in any analysis. The baseline characteristics of the 19 patients who completed the study are shown in Table 1.

Biometric, biochemical aspects at baseline between the two groups are shown in Table 2. No differences in blood pressure and heart rate were found between both groups at the start of the study. Baseline IGF-1 levels were within the normal age-adjusted range in all patients (12-35 nmol/l). The rh GH treatment group showed a significant lower level of IGF-BP3 at baseline compared with the control group ($+2.1 \pm 0.95$ mg/l resp. $+2.93 \pm 0.45$ mg/l; $P=0.02$).

Cardiac function data measured by cardiovascular MR at baseline are summarized in Table 2. End-diastolic volume, end-systolic volume, stroke volume, LVEF and LVMI were not different between the two groups. In addition, no significant changes were observed in diastolic function between the groups.

Table 1. Baseline Characteristics

	Control <i>n</i> = 10	rh GH <i>n</i> = 9
Age(yrs)	64	67
Gender (M/F)	9/1	7/2
History of MI ^a	10	9
History of cardiac surgery or PTCA	6	6
NYHA class ^b		
I	1	0
II	4	3
III	5	5
IV	0	1
Treatment		
ACE inhibitors	9	11
Diuretics	6	9
β-Blocking agents	5	3
HMG-CoA reductase inhibitors	9	6
Platelet aggregation inhibitors	5	2
Coumarin derivatives	4	7
Fasting serum GH $\pm$ SE (mU/liter)	2.60 ± 1.29	2.61 ± 1.43

^a Number of subjects

^b New York heart Association Classification

Effects of rh GH treatment on biochemical and biometric aspects

The effects of rh GH therapy on biochemical and biometric aspects are shown in Table 3. Systolic blood pressure decreased slightly in the treatment group as compared with the control group (+15.8 %; $P = 0.05$). Diastolic blood pressure and heart rate did not change after therapy.

rh GH therapy induced a significant increase in serum IGF-1 levels in

Table 2. Biochemical and cardiac parameters at baseline between groups

	Control	rh GH treatment	<i>P</i> -value
	<i>N</i> =10	<i>N</i> =9	
Biometric aspects			
Systolic blood pressure (mmHg)	141 ± 26	138 ± 12	0.75
Diastolic blood pressure (mm Hg)	83 ± 11	80 ± 11	0.51
Heart rate (min ⁻¹)	63 ± 5.8	63 ± 14	0.97
Biochemical aspects			
IGF-1 (nmol/l)	19.7 ± 5.4	18.4 ± 6.1	0.64
IGFBP-3 (mg/l)	2.93 ± 0.45	2.1 ± 0.95	0.02
LV Dimensions and Systolic function			
EDV (ml)	278 ± 90	327 ± 179	0.46
ESV (ml)	204 ± 79	242 ± 151	0.50
SV (ml)	74 ± 18	85 ± 35	0.41
EF (%)	28 ± 7.4	28 ± 7.2	0.97
AO acc peak ((ml/s ²)10 ⁻³)	6.08 ± 1.9	5.03 ± 1.7	0.23
AO PER (ml/s)	381 ± 83	383 ± 114	0.98
AO dec peak ((ml/s ²)10 ⁻³)	-3.66 ± 1.1	-3.17 ± 0.74	0.28
LVMl (g/m ²)	99.8 ± 22.5	94.2 ± 29.3	0.65
LV Diastolic function			
E acc peak ((ml/s ²)10 ⁻³)	5.71 ± 3.0	4.54 ± 3.5	0.45
E PFR (ml/s)	358 ± 144	307 ± 190	0.52
E dec peak ((ml/s ²)10 ⁻³)	-3.31 ± 2.1	-2.98 ± 2.42	0.77
A acc peak ((ml/s ²)10 ⁻³)	6.88 ± 2.0	4.69 ± 2.76	0.07
A PFR (ml/s)	410 ± 86	349 ± 135	0.28
A dec peak ((ml/s ²)10 ⁻³)	-6.44 ± 2	-5.24 ± 2.36	0.26
E/A peak flow	0.87 ± 0.52	1.17 ± 1.12	0.48

Abbreviations: rh GH=recombinant human growth hormone, IGF-1: insulin like growth factor 1, IGFBP-3: insulin like growth factor binding protein, EDV=End-diastolic volume, ESV=End-systolic volume, SV=Stroke volume, EF=Ejection fraction, AO acc peak=Aortic acceleration peak, AO PER=Aortic peak ejection rate, AO dec peak=Aortic deceleration peak, LVMl=Left ventricular mass indexed to body-surface area, E acc peak=Early acceleration peak, E PFR=Early peak filling rate, E dec peak=Early deceleration peak, A acc peak=Atrial acceleration peak, A PFR=Atrial peak filling rate, A dec peak=Atrial deceleration peak, E/A peak=E PFR /A PFR

the treatment group, whereas the control group showed a small decrease ($+23.6 \pm 51$ % resp. -14.0 ± 21.2 %; $P = 0.05$). Serum IGF-BP3 showed a significant change in the treated group as compared with the control group ($+58.2 \pm 68.7$ % resp. $+4.6 \pm 27.8$ %; $P = 0.04$).

Serum cholesterol, HDL and triglycerides were not affected by GH therapy (data not shown). Safety parameters were unchanged.

Effect of rh GH therapy on systolic and diastolic function

Table 4 describes the results of systolic and diastolic function assessed by cardiovascular MR after 26 weeks treatment. rh GH therapy had no effect on systolic function. There was no treatment effect observed in left ventricular dimensions, ejection fraction and left ventricular mass index.

The early peak filling rate showed a positive change in the treatment group ($+31.5 \pm 37.5$ % versus -0.2 ± 17.9 %; $P = 0.03$). No change was observed in atrial peak filling rate, and as a result the E/A ratio increased slightly after 26 weeks in the treatment group ($+43.5 \pm 59.7$ % versus $+5.0 \pm 22.6$ %; $P = 0.09$). Other diastolic function parameters were not affected by rh GH therapy.

Table 3. Biometric and biochemical aspects after 26 weeks between control group and rh GH treatment group

	Control group		% Change	rhGH Treatment group		% Change	P value
	T=0	T=26		T=0	T=26		
Biometric aspects							
Systolic blood pressure (mmHg)	141 $\pm$ 26	131 $\pm$ 17	-5.8 $\pm$ 11.2	135 $\pm$ 12	116 $\pm$ 9	-15.8 $\pm$ 4.6	0.05
Diastolic blood pressure (mm Hg)	83 $\pm$ 11	82 $\pm$ 10	-0.5 $\pm$ 14.3	80 $\pm$ 10	73 $\pm$ 9	-8.6 $\pm$ 8.6	0.22
Heart rate (min ⁻¹)	68 $\pm$ 5.7	75 $\pm$ 9.9	9.5 $\pm$ 14.8	63 $\pm$ 14	62 $\pm$ 14	8.3 $\pm$ 8.7	0.85
Biochemical aspects							
IGF-1 (nmol/l)	19.7 $\pm$ 5.4	16.6 $\pm$ 5.0	-14.0 $\pm$ 21.2	18.4 $\pm$ 6.1	21 $\pm$ 5.3	23.6 $\pm$ 51	0.05
IGFBP-3 (mg/l)	2.93 $\pm$ 0.45	3.1 $\pm$ 1.07	4.6 $\pm$ 27.8	2.1 $\pm$ 0.95	2.84 $\pm$ 1.05	58.2 $\pm$ 68.7	0.04

Abbreviations: IGF-1: insulin like growth factor 1, IGFBP-3: insulin like growth factor binding protein 3

Table 4. Left ventricular dimensions, systolic and diastolic function after 26 weeks between control group and treatment group

	Control group		% Change	
	<i>T=0</i>	<i>T=26</i>		<i>T=0</i>
LV Dimensions and Systolic function				
EDV (ml)	278 ± 90	298 ± 86	9.1±13.4	327 ± 179
ESV (ml)	204 ± 79	21 ± 78	7.9±10.6	242 ± 151
SV (ml)	74 ± 18	82 ± 18	13.2±25.7	85 ± 35
EF (%)	28 ± 7.4	29 ± 7.5	2.7±11	27 ± 6.5
AO acc peak ((ml/s ²)10 ⁻³)	6.08 ± 1.9	6.43 ± 1.6	14.4±37.5	5.03 ± 1.7
AO PER (ml/s)	381 ± 83	378 ± 83	1.9±23.6	383 ± 114
AO dec peak ((ml/s ²)10 ⁻³)	-3.66 ± 1.1	-3.74 ± 1.36	6.4±33	-3.17 ± 0.1
LVMl (g/m ²)	99.8 ± 22.5	99.4 ± 22.4	-0.4±6.9	94.2 ± 29.1
LV Diastolic function				
E acc peak ((ml/s ²)10 ⁻³)	5.71 ± 3.0	5.38 ± 2.7	0.1±25.7	4.54 ± 3.5
E PFR (ml/s)	358 ± 144	348 ± 126	-0.2±17.9	307 ± 190
E dec peak ((ml/s ²)10 ⁻³)	-3.31 ± 2.1	-3.2 ± 2.37	-5±17.9	-2.98 ± 2.1
A acc peak ((ml/s ²)10 ⁻³)	6.88 ± 2.0	6.78±1.86	3.6±29.4	4.69 ± 2.7
A PFR (ml/s)	410 ± 86	397 ± 94	-2.8±13.3	349 ± 135
A dec peak ((ml/s ²)10 ⁻³)	-6.44 ± 2	-6.82 ± 1.63	11.1±26	-5.24 ± 2.1
E/A peak flow	0.87 ± 0.52	0.89 ± 0.52	5.0±22.6	1.17 ± 1.1

Abbreviations: rh GH treatment=recombinant human growth hormone, EDV=End-diastolic volume, ESV=End-systolic volume, SV=Stroke volume, AO acc peak=Aortic acceleration peak, AO PER=Aortic peak ejection rate, AO dec peak=Aortic deceleration peak, LVMl=Left ventricular mass index, E acc peak=Early acceleration peak, E PFR=Early peak filling rate, E dec peak=Early deceleration peak, A acc peak=Atrial acceleration peak, A dec peak=Atrial deceleration peak, E/A peak= E PFR /A PFR

Discussion

In the present randomised study, we evaluated the systolic and diastolic function in patients with ischemic cardiac failure after 26 weeks with rh GH therapy, using cardiovascular MR. No beneficial effects of rh Gh therapy were observed on systolic and diastolic function. Left ventricular mass index also remained unchanged.

Chronic heart failure results in increased mortality, despite the developments in pharmacological therapy.¹ Modern drug treatment is based on the prevention of the progression of heart failure, with ACE inhibitors, b-adrenergic blockers, spironolactone, digoxin and diuretics.^{1,2} In the near future strategies may be designed to improve the structural myocardial problems like tissue growth, repair and fibrosis (the hallmarks of LV remodeling).² In this framework, the use of anabolic agents to improve the remodeling and therefore the cardiac function is a worthwhile option to explore. One of these agents, growth hormone showed promising results in animal studies. Experimental data with adult cardiomyocytes in rats revealed that IGF-1 enhanced myofibril development and, concomitantly, down regulates α -actin, a protein that forms stressfiberlike structures.⁴

Administration of IGF-1 given to normal rats leads to hypertrophy of the heart.⁵ In animals with experimental myocardial infarction, GH therapy leads to an improvement or preservation of cardiac function and induced an increase in myocardial energy reserves.^{6,7,8} These observations have led to the assumption that rh GH therapy may result in improvement of cardiac function in patients with cardiac failure of various origins without underlying GH deficiency. Experimental studies with idiopathic dilated cardiomyopathy have shown contradictory results. In an open study, Fazio et al. found an increased myocardial mass, reduced left chamber size and improved hemodynamic parameters in patients with idiopathic dilated cardiomyopathy after 3 months of human Growth hormone administration.⁹ In contrast, two randomized studies that focused on dilated cardiomyopathy, demonstrated that administration of rh GH for at least 12 weeks had no effect on cardiac function.^{11,12} In addition, Osterziel et al. demonstrated an increase in LV

mass which was not accompanied by a clinical benefit.¹¹

Studies in ischemic heart failure revealed similar results. Spallarossa et al. found in a non-randomized study an increase in exercise duration and well-being, but no effect on cardiac function.¹⁴ Genth-Zotz et al. observed in a non-randomised study an improvement in clinical well being, and a decrease in end-diastolic and end-systolic indexes.¹⁰

Although the treatment group showed a significant change of serum IGF-1, it was observed only in 4 of 9 (44%) patients (Figure 1). Several explanations for the absence of an effect of growth hormone may apply, for instance the advanced stage of cardiac failure^{21,22} or the concomitant use of α -blockers.²³ In our opinion, the third and most important explanation may be the existence of growth hormone resistance in chronic cardiac failure, like in many other chronic diseases.²⁴ Indeed in

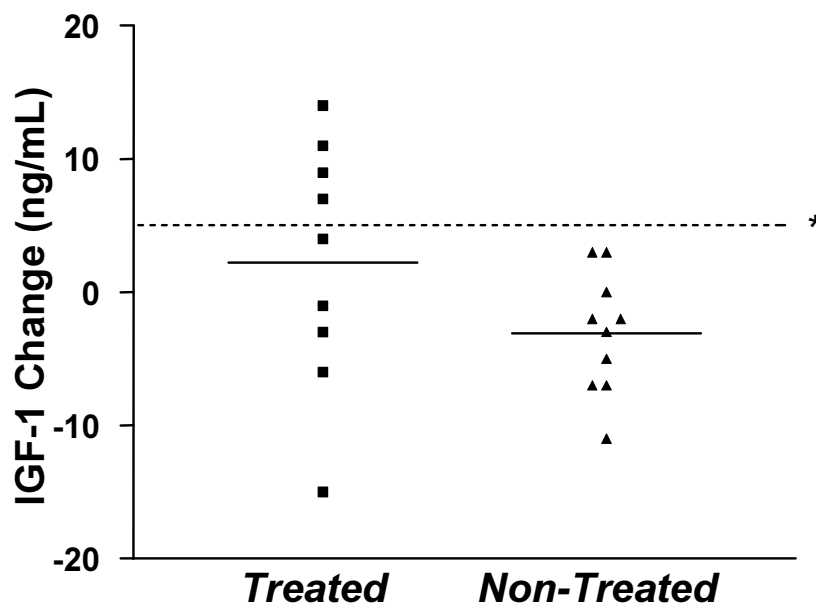


Figure 1. Changes in serum IGF-I in patients with ischemic cardiac failure after 26 weeks of treatment with recombinant human growth hormone (2 IU/d) or non-treatment. The dotted line at 5.8 nmol/l represents the mean IGF-I change of non-treated patients + 2 SD; * $P < 0.05$.

chronic cardiac failure, decreased sensitivity to growth hormone has been observed.²⁵⁻²⁷ The moderate increase in serum IGF-I concentration in only 4 of 9 patients in our study as compared with other studies may be in line with this assumption.^{10,12,13}

Osterziel *et al.* observed an effect of growth hormone therapy on cardiac output in patients with idiopathic dilated cardiomyopathy who showed an IGF-I response above the median response.²⁸ In addition, they demonstrated a dose-effect relation between short-term growth hormone application and left ventricular function in ischemic cardiac failure.²⁹ The IGF-I response to growth hormone was related to the severity of cardiac failure.^{28,29} In our study, the patients who responded to rh GH therapy had a comparable LVEF as observed in non-responders; moreover, the responders did not improve their systolic or diastolic function after treatment. The existence of a threshold for growth hormone therapy, could explain why in this study no effect was found of growth hormone on cardiac function. Future studies require a distinct increase in circulating IGF-I by giving each patient an individual dose.

The present study showed, that 26 weeks of 2 IU/day rh GH had no beneficial effect on systolic and diastolic function. Further studies are warranted to evaluate the application of growth hormone in earlier stages of ischemic cardiac disease and regarding individual dose adjustment depending on the IGF-I response.

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References

1. Gombert-Maitland M, Baran DA, Fuster V. Treatment of congestive heart failure: guidelines for the primary care physician and the heart failure specialist. *Arch Intern Med* 2001; 161:342-352
2. Francis GS. Pathophysiology of chronic heart failure. *Am J Med* 2001; 110 Suppl 7A:37S-46S.
3. Timsit J, Riou B, Bertherat J, Wisnewsky C, Kato NS, Weisberg AS, Lubetzki J, Lecarpentier Y, Winegrad S, Mercadier JJ. Effects of chronic growth hormone hypersecretion on intrinsic contractility, energetics, isomyosin pattern, and myosin adenosine triphosphatase activity of rat left ventricle. *J Clin Invest* 1990; 86:507-515
4. Donath MY, Zapf J, Eppenberger-Eberhardt M, Froesch ER, Eppenberger HM. Insulin-like growth factor I stimulates myofibril development and decreases smooth muscle alpha-actin of adult cardiomyocytes. *Proc Natl Acad Sci* 1994; 91:1686-1690
5. Duerr RL, Huang S, Miraliakbar HR, Clark R, Chien KR, Ross JJ. Insulin-like growth factor-1 enhances ventricular hypertrophy and function during the onset of experimental cardiac failure. *J Clin Invest* 1995; 95:619-627
6. Omerovic E, Bollano E, Mobini R, Kujacic V, Madhu B, Soussi B, Fu M, Hjalmarson A, Waagstein F, Isgaard J. Growth hormone improves bioenergetics and decreases catecholamines in post infarct rat hearts. *Endocrinology* 2000; 141:4592-4599
7. Cittadini A, Grossman JD, Napoli R, Katz SE, Stromer H, Smith RJ, Clark R, Morgan JP, Douglas PS. Growth hormone attenuates early left ventricular remodeling and improves cardiac function in rats with large myocardial infarction. *J Am Coll Cardiol* 1997; 29:1109-1116
8. Isgaard J, Kujacic V, Jennische E, Holmang A, Sun XY, Hedner T, Hjalmarson A, Bengtsson BA. Growth hormone improves cardiac function in rats with experimental myocardial infarction. *Eur J Clin Invest* 1997; 27:517-525
9. Fazio S, Sabatini D, Capaldo B, Vigorito C, Giordano A, Guida R, Pardo F, Biondi B, Sacca L. A preliminary study of growth hormone in the treatment of dilated cardiomyopathy. *N Engl J Med* 1996; 334:809-814
10. Genth-Zotz S, Zotz R, Geil S, Voigtlander T, Meyer J, Darius H. Recombinant growth hormone therapy in patients with ischemic cardiomyopathy : effects on hemodynamics, left ventricular function, and cardiopulmonary exercise capacity. *Circulation* 1999; 99:18-21
11. Osterziel KJ, Strohm O, Schuler J, Friedrich M, Hanlein D, Willenbrock R, Anker SD, Poole-Wilson PA, Ranke MB, Dietz R. Randomized, double blind, placebo-controlled trial of human recombinant growth hormone in patients with chronic heart failure due to dilated cardiomyopathy. *Lancet* 1998; 351:1233-1237

12. Isgaard J, Bergh CH, Caidahl K, Lomsky M, Hjalmarson A, Bengtsson BA. A placebo-controlled study of growth hormone in patients with congestive heart failure. *Eur Heart J* 1998; 19:1704-1711
13. Smit JW, Janssen YJ, Lamb HJ, van der Wall EE, Stokkel MP, Viergever E, Biermasz NR, Bax JJ, Vliegen HW, de Roos A, Romijn JA, Roelfsema F. Six months of recombinant human GH therapy in patients with ischemic cardiac failure does not influence left ventricular function and mass. *J Clin Endocrinol Metab* 2000; 86:4638-4643
14. Spallarossa P, Rossettin P, Minuto F, Caruso D, Cordera R, Battistini M, Barreca A, Masperone MA, Brunelli C. Evaluation of growth hormone administration in patients with chronic heart failure secondary to coronary artery disease. *Am J Cardiol* 1999; 84:430-433
15. Grossman W. Diastolic dysfunction in congestive heart failure. *N Engl J Med* 1991; 325:1557-1564.
16. Pattynama PM, Lamb HJ, van der Velde EA, van der Wall EE, de Roos A. Left ventricular measurements with cine and spin-echo MR imaging: a study of reproducibility with variance component analysis. *Radiology* 1993; 187:261-268
17. van der Geest RJ, Buller VG, Jansen E, Lamb HJ, Baur LH, van der Wall EE, de Roos A, Reiber JH. Comparison between manual and semiautomated analysis of left ventricular volume parameters from short-axis MR images. *J Comput Assist Tomogr* 1997; 21:756-765
18. Lamb HJ, Beyerbacht HP, van der Laarse A, Stoel BC, Doornbos J, van der Wall EE, de Roos A. Diastolic dysfunction in hypertensive heart disease is associated with altered myocardial metabolism. *Circulation* 1999; 99:2261-2270
19. van der Geest RJ Buller VG, Reiber JH. Automated quantification of flow velocity and volume in the ascending and descending aorta using MR flow velocity mapping. *Comput Cardiol* 1995; 29-32
20. Pluim BM, Lamb HJ, Kayser HW, Leujes F, Beyerbacht HP, Zwinderman AH, van der Laarse A, Vliegen HW, de Roos A, van der Wall EE. Functional and metabolic evaluation of the athlete's heart by magnetic resonance imaging and dobutamine stress magnetic resonance spectroscopy. *Circulation* 1998; 97:666-672
21. Jin H, Yang R, Gillett N, Clark RG, Ko A, Paoni NF. Beneficial effects of growth hormone and insulin-like growth factor-1 in experimental heart failure in rats treated with chronic ACE inhibition. *J Cardiovasc Pharmacol* 1995; 26:420-425
22. Ryoke T, Gu Y, Mao L, Hongo M, Clark RG, Peterson KL, Ross J Jr. Progressive cardiac dysfunction and fibrosis in the cardiomyopathic hamster and effects of growth hormone and angiotensin-converting enzyme inhibition. *Circulation* 1999; 100:1734-1743

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23. Stromer H, Cittadini A, Grossman JD, Douglas PS, Morgan JP. Intrinsic cardiac muscle function, calcium handling and beta -adrenergic responsiveness is impaired in rats with growth hormone deficiency. *Growth Horm IGF Res* 1999; 9:262-271
24. Van den Berghe G, Wouters P, Bowers CY, de Zegher F, Bouillon R, Veldhuis JD. Growth hormone-releasing peptide-2 infusion synchronizes growth hormone, thyrotrophin and prolactin release in prolonged critical illness. *Eur J Endocrinol* 1999; 140:17-22
25. Niebauer J, Pflaum CD, Clark AL, Strasburger CJ, Hooper J, Poole-Wilson PA, Coats AJ, Anker SD. Deficient insulin-like growth factor I in chronic heart failure predicts altered body composition, anabolic deficiency, cytokine and neurohormonal activation. *J Am Coll Cardiol* 1998; 32:393-397
26. Anker SD, Chua TP, Ponikowski P, Harrington D, Swan JW, Kox WJ, Poole-Wilson PA, Coats AJ. Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia . *Circulation* 1997; 96:526-534
27. Sacca L. Growth hormone: a new therapy for heart failure? *Baillieres Clin Endocrinol Metab* 1998; 12:217-23
28. Osterziel KJ, Ranke MB, Strohm O, Dietz R. The somatotrophic system in patients with dilated cardiomyopathy: relation of insulin-like growth factor-1 and its alterations during growth hormone therapy to cardiac function. *Clin Endocrinol* 2001; 53:61-68
29. Osterziel KJ, Blum WF, Strohm O, Dietz R.. The severity of chronic heart failure due to coronary artery disease predicts the endocrine effects of short-term growth hormone administration. *J Clin Endocrinol Metab* 2000; 85:1533-1539

