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A placebo-controlled study of growth hormone in patients with congestive heart failure

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Aim Experimental data in heart failure models and an open trial of seven patients with idiopathic dilated cardiomyopathy have suggested beneficial effects of growth hormone on cardiac function. The aim of the present study was to evaluate growth hormone effects on cardiac function in a placebo-controlled study.

Methods Twenty two patients with congestive heart failure of different aetiologies in NYHA II and III and an echocardiographic ejection fraction <0·45 were studied in a 3 month double-blind placebo-controlled study with growth hormone added to optimal heart failure therapy. Patients received either placebo (n=11) or recombinant human growth hormone (n=11) in an initial dose of 0·1 IU . kg^{-1} $week^{-1}$ for 1 week, and thereafter 0·25 IU . kg^{-1} $week^{-1}$ for the rest of the treatment period. Cardiac function was assessed by equilibrium radionuclide angiography and Doppler echocardiography. Functional capacity was evaluated by computerized bicycle exercise electrocardiography.

Results Recombinant human growth hormone had no significant effect on systolic or diastolic cardiac function, exercise capacity or neuroendocrine activation. In addition, there was no overall improvement in functional class or dyspnoea grade. Insulin-like growth factor-I significantly increased demonstrating that the growth hormone had an endocrine effect.

Conclusion This is the first double-blind and placebo-controlled study of the administration, over 3 months, of recombinant human growth hormone in patients with congestive heart failure of different aetiologies. The treatment was safe and without serious side effects. However, no beneficial effects on cardiac function or structure could be detected.
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Key Words: Congestive heart failure, Doppler echocardiography, growth hormone, insulin-like growth factor-I, radionuclide angiography.

See page 1605 for the Editorial comment on this article

Introduction

Despite the introduction of angiotensin converting enzyme (ACE) inhibitors and beta-blockers, which have improved the treatment of congestive heart failure, the prognosis is still poor and there is a need for alternative or additional treatment strategies. Current therapy is based on afterload reduction by agents such as ACE inhibitors and by reduction of fluid retention by diuretics. Drugs that enhance myocardial contractility have so far been disappointing since different studies have showed an increase in mortality[1].

A number of experimental and clinical studies suggest a potential role for growth hormone, in addition to conventional therapy, for the treatment of congestive heart failure. Several studies in rats have shown beneficial effects of growth hormone, insulin-like growth factor-I or a combination of both agents on cardiac function after experimental myocardial infarction[2–5]. The precise mechanisms of actions are unclear, although it has been suggested that growth hormone increases the responsiveness of the myofilaments to Ca^{2+} and increases Ca^{2+} influx[6,7]. In growth hormone-deficient adults who receive growth hormone substitution therapy, an improvement in systolic function and normalization of left ventricular mass have been found[8,9]. Case reports of patients with growth hormone-deficiency and heart failure show the dramatic effects of the addition of growth hormone on heart function[10–12].

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Recently, heart failure in patients resulting from idiopathic dilated cardiomyopathy showed a positive response to the addition of growth hormone[13]. Infusion of growth hormone over 24 h was found to improve cardiac performance in an open study of 12 patients with congestive heart failure as a result of ischaemic heart disease or idiopathic dilated cardiomyopathy[14]. However, so far no placebo-controlled study with the addition of growth hormone to standard optimal therapy in patients with congestive heart failure has been published. The aim of the present study was to evaluate the effect of the addition of recombinant human growth hormone to optimal standard therapy for heart failure, in a double-blind, placebo-controlled study, of 3 months duration, in patients with congestive heart failure of different aetiologies.

Methods

Patients

The study involved 22 patients (14 men and 8 women) with chronic heart failure as a result of idiopathic dilated cardiomyopathy (n=13), ischaemic heart disease (n=8) or heart failure after valvular surgery (n=1). Their mean age was 60·0 ± 2·4 years (60·1 ± 3·6 and 59·9 ± 3·4 years) in the placebo and growth hormone-treated group, respectively), and their mean New York Heart Association (NYHA) functional class was 3·0 ± 0·40 (3·1 ± 0·30 and 2·9 ± 0·45) in the placebo and growth hormone-treated group, respectively. Patients of either sex were eligible for the study if they were less than 75 years of age with a clinical diagnosis of congestive heart failure in NYHA functional class II–III, had an ejection fraction less than 0·45 by two-dimensional echocardiography, and were in a clinically stable condition with standard optimal treatment for congestive heart failure of at least 4 weeks' duration. If the patients were receiving beta-blockers they should have had this treatment for at least 6 months in a stable dose. Twenty patients were being treated with ACE inhibitors (enalapril, n=16, mean dose 15·3 ± 1·6 mg; or captopril, n=4, mean dose 90·6 ± 23·6 mg) and one patient was on an angiotensin II receptor blocker (losartan). Seven patients (four in the placebo group and three in the active treatment group) were being treated with beta-blockers (metoprolol n=5; atenolol n=1; sotalol n=1) for hypertension, arrhythmias or congestive heart failure. One patient was on amiodarone. Nineteen patients were treated with diuretics (furosemide n=18; amiloride n=1).

The exclusion criteria involved: active myocarditis, constrictive pericarditis, clinically significant valvular heart disease, hypertrophic cardiomyopathy, life threatening arrhythmias, percutaneous transluminal coronary angioplasty or coronary artery bypass grafting within 3 months prior to the study, myocardial infarction within 3 months prior to the study, planned or already performed heart transplantation, pregnancy, diabetes mellitus, alcohol or drug abuse, severe kidney (creatinine above 200 mmol . l^{-1}) or liver disease (transaminases more than three times the normal limit), uncontrolled hypertension (diastolic blood pressure above 105 mmHg), malignancy or other severe systemic disease. Written informed consent was obtained from all patients and the study was approved by the Ethics Committee at the Medical Faculty of the University of Göteborg and also by the Swedish Medical Products Agency.

Study protocol

The study was a randomized, double-blind and placebo-controlled trial of 3 months' duration. Patients were hospitalized for 2–3 days at baseline, after 2 weeks of treatment, and at completion, in order to perform the investigations. For reasons of safety, the patients were also seen 1, 4, 6 and 8 weeks after enrolment. Recombinant human growth hormone (Genotropin®, Pharmacia & Upjohn) in a dose of 0·1 IU . kg^{-1} . $week^{-1}$, or a corresponding placebo, was administered during the first week of treatment. After one week the dose was increased to 0·25 IU . kg^{-1} . $week^{-1}$, or to a maximum daily dose of 4 IU, and this dose was maintained during the remaining study period. The growth hormone was given subcutaneously in the thigh every evening.

The primary efficacy variable was ejection fraction determined by equilibrium radionuclide angiography at rest, while its measurement during exercise was a secondary efficacy variable. Other secondary variables included Doppler echocardiographic measurements of cardiac dimensions and function, changes in symptoms, functional capacity and neuroendocrine activation.

New York Heart Association functional class and dyspnoea score

Subjects were classified into New York Heart Association (NYHA) functional classes I–IV[15]. The dyspnoea grade was also determined, following the World Health Organisation (WHO) guidelines[16], with grade 1 as 'no shortness of breath', grade 2 'shortness of breath when hurrying on level ground or walking up a slight hill', grade 3 'having to stop for breath when walking at own pace on level ground' and grade 4 'shortness of breath when washing or dressing'.

Blood pressure and electrocardiography

Systolic and diastolic blood pressure were measured using the sphygmomanometric cuff method after 10 min of supine rest. Heart rate was calculated from an electrocardiographic recording of lead II at 100 mm . s^{-1}, together with the M-mode echocardiogram. Twelve-lead

electrocardiographic recordings at 50 mm . s^{-1} (Siemens-Elema) were evaluated for the presence of abnormal Q-waves, left ventricular hypertrophy, ST-T abnormalities, bundle branch block and cardiac rhythm.

Ambulatory electrocardiography

A 24 h ambulatory electrocardiogram was performed in all patients at baseline, after 2 weeks and after study completion at 3 months. The electrocardiograms were analysed with Pathfinder® (Reynolds Medical, Hertford, England) or Delmar® (DelMar Avionics, Irvine, CA, U.S.A.) equipment. Ventricular tachycardia was defined as the occurrence of three or more consecutive premature ventricular complexes, of a duration exceeding 120 ms, and with an ST-T vector in a direction opposite to the major QRS deflection[17].

Exercise electrocardiography

Maximal exercise capacity was determined by a symptom-limited maximal sitting bicycle exercise test. This was carried out at screening about 2 weeks before randomization so that subjects could familiarize themselves with the equipment, at baseline, after 2 weeks and at study completion after 3 months. The starting load was 30 W and there was a 10-W increment per min. Pulse rate, blood pressure, symptoms, arrhythmias and ST deflection were registered at each level. The given value of maximal exercise capacity represents the work load maintained for at least 45 s.

Doppler echocardiography

Doppler echocardiography was performed using an Acuson-128 computed sonograph equipped with a 2 or 3·5 MHz transducer (Acuson, Mountain View, CA, U.S.A.). Two-dimensional echocardiography was performed in standard parasternal and apical projections to evaluate valvular abnormalities and rule out regional wall motion disturbances. M-mode echocardiography was used for the evaluation of left atrial end-systolic dimensions, left ventricular end-diastolic and end-systolic dimensions, and left ventricular walls at end-diastole and end-systole, respectively. Measurements were made according to the recommendations of the American Society of Echocardiography[18] where end-diastole was defined by the electrocardiographic Q-wave and end-systole as the minimum left ventricular dimension or, for left atrial measurement, as aortic valve closure. Left ventricular fractional shortening was calculated as: (end-diastolic–end-systolic)/end-diastolic dimensions. End-systolic wall stress was calculated as earlier described[19]. Stroke volume was measured by Doppler echocardiography by multiplying the left ventricular outflow tract area by the velocity time integral of the Doppler flow. The area was calculated from the left ventricular outflow diameter in the parasternal long-axis view. Cardiac output was obtained by multiplying stroke volume by heart rate.

The left ventricular mass was calculated by two-dimensional echocardiography as previously described[20]. Isovolumic relaxation time was measured from M-mode strip-chart recordings (100 mm . s^{-1}) as the distance in time from the initial phase of the second heart sound to mitral valve opening. The atrial emptying index was measured from the aortic root motion, as an index of left ventricular filling properties[21]. Left and right atrial areas were measured in the four-chamber view. The mitral Doppler flow spectrum was categorized into four types: normal (type 1), impaired relaxation with a high late (A, atrial contribution to left ventricular filling) wave and prolonged deceleration (type 2), pseudonormalized (type 3) and restrictive filling (type 4).

The pulsed mitral Doppler spectrum of flow velocities, midway between the mitral leaflets in the apical four-chamber view, was recorded on paper printouts at 100 mm . s^{-1}. The A-wave and early (E-wave) peak velocities of the mitral flow profile were measured, and the A/E ratio calculated as a measure of the relative atrial contribution to left ventricular filling. Important valvular leakage was ruled out by colour and continuous wave Doppler, the degree estimated from 0 to 4 where grade 1 represented mild and grade 2 moderate regurgitation.

Equilibrium radionuclide angiography

Equilibrium radionuclide angiography was performed at rest and during exercise in the supine position. The patient's red blood cells were labelled with 925 MBq Tc-99m pertechnetate using an in vivo/in vitro technique[22]. Acquisition was conducted using a single-crystal gamma camera with a general all purpose collimator placed with a 20° caudal tilt to give the best separation of the right and left ventricles from the left anterior oblique position The images were obtained in frame mode. Time/frame was 50 ms at a heart rate <90/min and 40 ms at a heart rate >90/min. Acquisition at rest was stopped when the mean left ventricular count density was approximately 130/pixel (frame size: 64 × 64, regular field of view camera).

Exercise was performed using a bicycle ergometer with the patient supine. Exercise was started at a work-load of 25 W with an increment of 25 W every 4 min. Equilibrium radionuclide angiographic acquisition was conducted during the last 3 min of each stage. The 12-lead electrocardiogram was monitored throughout the examination. Criteria for terminating exercise were severe angina pectoris, severe fatigue, shortness of breath, a decrease in systolic blood pressure, complex ventricular arrhythmias or marked ST-segment changes.

Left ventricular ejection fraction was calculated using automatically derived left ventricular regions of interest. Each study was evaluated on a blinded basis by

two experienced observers, independent of each other. Whenever necessary, regions of interest were corrected manually. Different results between the observers were resolved by consensus. Left ventricular end-systolic and end-diastolic volumes were calculated using the count proportional method[23].

Biochemical assays

Blood samples for assessment of hormone levels were taken at randomization, after 2 weeks and at study completion after 3 months. Serum free thyroxine was determined using a luminometric labelled antibody-immunoassay (MAB free T4, Ortho-Clinical Diagnostics, Amersham, U.K.). The serum concentration of insulin-like growth factor-I was determined using a hydrochloric acid–ethanol extraction radio-immunoassay and authentic insulin-like growth factor-I for labelling (Nichols Institute Diagnostics, San Juan Capistrano, CA, U.S.A.). Insulin-like growth factor-binding protein-3 concentrations in serum were also determined using a radio-immunoassay (Nichols Institute Diagnostics, San Juan Capistrano, CA, U.S.A.). Adrenaline and noradrenaline were measured by a high pressure liquid chromatography technique. Aldosterone was measured by radio-immunoassay (Aldosterone MAIA, Serono, Biodata S.p.A., Rome, Italy) and plasma renin activity using a radio-immunoassay for angiotensin I (Renin-RIA bead, Abbot Diagnostics Division, CA, U.S.A.). Angiotensin II was also analysed by radio-immunoassay. Safety blood samples including blood sugar, lipoproteins, and electrolytes were measured at randomization, after 2, 4, 6 and 8 weeks and at study completion after 3 months.

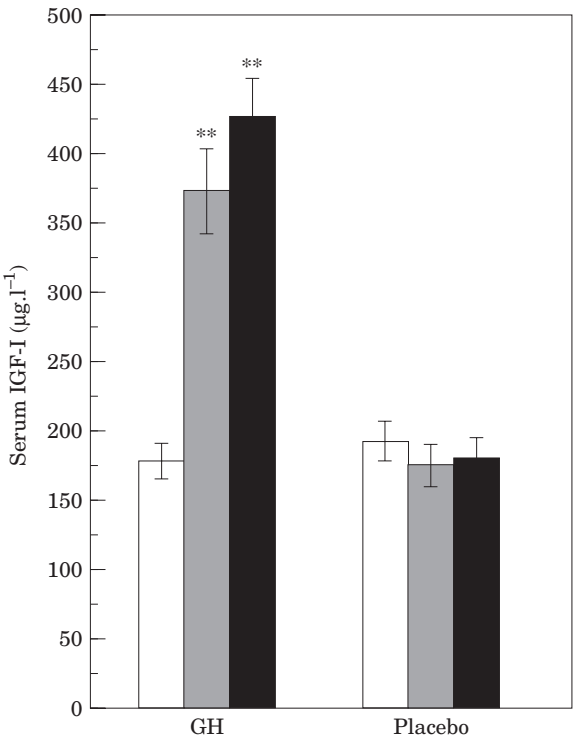

Figure 1 **Serum concentration of insulin-like growth factor-I (serum IGF-I). Patients were treated with recombinant human growth hormone in a dose of 0·1 IU . week^{-1} . kg^{-1} body weight for one week and then 0·25 IU . week^{-1} . kg body weight^{-1} for the rest of the study. Serum concentration of insulin-like growth factor-I is expressed in μg . l^{-1}. Levels are mean ± SE. **P<0·01 growth hormone vs placebo group. □=baseline; ▨=after 2 weeks of treatment; ■=after 3 months of treatment.**

Statistical analysis

Data are presented as means ± SE. Differences between the active treatment and the placebo group were evaluated by one-way analysis of variance (ANOVA) followed by the Student–Newman–Keuls multiple test between individual groups.

Results

All patients but two (10 patients in the placebo and the active treatment groups, respectively) completed the 3-month treatment trial. Two patients were excluded from further participation in the study after 2 weeks. The mean dose of growth hormone was 2·6 ± 0·14 IU daily. All patients who received growth hormone showed a significant increase in serum insulin-like growth factor-I (Fig. 1) and insulin-like growth factor-binding protein-3 (Fig. 2). Patient characteristics are presented in Table 1. There were no changes in body weight in either treatment group during the study period. NYHA functional class, heart rate, diastolic and systolic blood pressure remained unchanged in both groups during the study. All patients were in sinus rhythm. Growth hormone had no significant effect on maximal work-load or exercise duration compared to the placebo group. There were no significant changes in plasma levels of free thyroxine, aldosterone, renin activity, angiotensin II or catecholamines after growth hormone treatment.

Growth hormone had no significant effect on ejection fraction at rest or maximal work-load as demonstrated by equilibrium radionuclide angiography. There were no changes in end-diastolic or end-systolic volumes in patients given growth hormone compared to those who received placebo (Table 2). Cardiac geometry, and systolic and diastolic function measured with Doppler echocardiography are shown in Table 3(a) and (b), respectively. There were no significant changes in wall thickness or left ventricular mass in either group. No significant changes in systolic or diastolic function were observed in the growth hormone group compared to the placebo group.

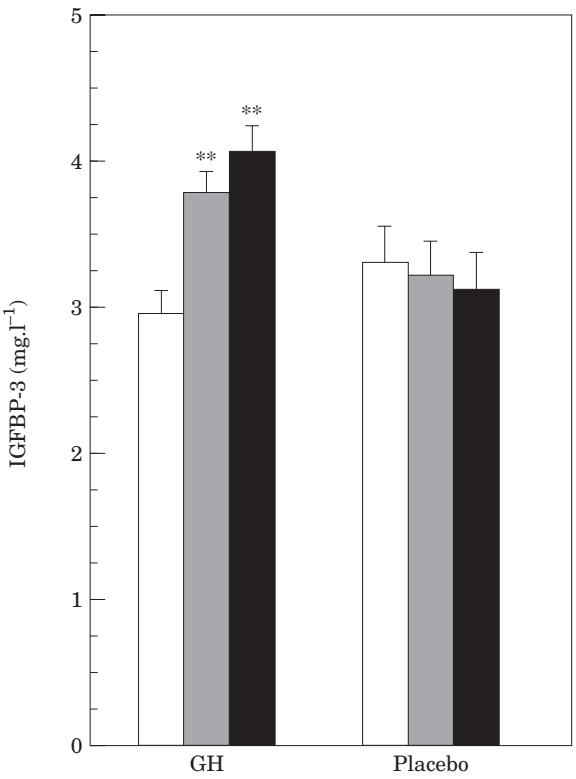

Figure 2 **Serum concentration of insulin-like growth factor-binding protein-3 (IGFBP-3). Patients were treated with recombinant human growth hormone in a dose of 0·1 IU . week^{-1} . kg body weight^{-1} for one week and the dose was then 0·25 IU . week^{-1} . kg body weight^{-1} for the rest of the study. Serum concentration of IGFBP-3 is expressed in mg . l^{-1}. Levels are mean ± SE. **$P<0·01$ growth hormone vs placebo group. □ = baseline; ▨ = after 2 weeks of treatment; ■ = after 3 months of treatment.**

No serious side effects were seen during the study. One woman in the placebo group was excluded due to worsening congestive heart failure. Another woman in the active treatment group, with a history of intermittent glucose intolerance, was excluded due to permanent hyperglycaemia. Her glucose levels normalized after withdrawal. No other significant side effects were reported or observed among the remaining patients in the study. There was no significant increase in the number of patients with ventricular tachycardia or number of ventricular tachycardia episodes during growth hormone treatment compared to placebo.

Discussion

This is the first randomized, placebo-controlled study in which growth hormone is added to standard optimal congestive heart failure therapy in patients with congestive heart failure of different aetiologies. There was a significant increase in serum insulin-like growth factor-I and insulin-like growth factor-binding protein-3 after 2 weeks of growth hormone treatment which indicates a good overall response to growth hormone in the patients and excludes any severe growth hormone resistance. However, growth hormone did not affect any of the studied cardiac parameters, such as systolic and diastolic function or left ventricular dimensions. There was also no affect on exercise performance, neuroendocrine activation or NYHA classification.

A number of experimental studies both in normal rats[24] and in rats with experimental myocardial infarction[2,4,5] show that growth hormone and insulin-like growth factor-I, alone or in combination, improve cardiac function. However, the absence of positive effects of growth hormone on cardiac function has also been reported in rats with experimental myocardial infarction[25]. In patients with growth hormone-deficiency, growth hormone substitution improves myocardial function and exercise capacity[8,26,27]. Until

Table 1 Patient characteristics in the placebo and growth hormone treatment groups at baseline and after 3 months, respectively

Variable	Placebo		Growth hormone	
	Baseline (n=11)	After treatment (n=10)	Baseline (n=11)	After treatment (n=10)
Weight	86·9 ± 5·5	87·1 ± 5·5	75·8 ± 3·9	76·5 ± 4·1
NYHA functional classification	3·1 ± 0·30	2·4 ± 0·60	2·9 ± 0·45	2·6 ± 0·58
WHO dyspnoea grade	0·9 ± 0·20	1·0 ± 0·26	1·3 ± 0·24	1·1 ± 0·18
Heart rate at rest (beats . min^{-1})	84 ± 4	83 ± 4	69 ± 4	74 ± 6
Diastolic blood pressure at rest (mmHg)	80 ± 3	75 ± 4	74 ± 3	75 ± 3
Systolic blood pressure at rest (mmHg)	138 ± 7	127 ± 8	126 ± 4	124 ± 4
Peak work-load (W)	100 ± 10	102 ± 11	120 ± 11	118 ± 8
Exercise duration (s)	508 ± 61	523 ± 64	617 ± 56	598 ± 40
Serum-free thyroxine (pmol . l^{-1})	15 ± 0·75	15 ± 0·98	18 ± 0·98	17 ± 1·9
P-aldosterone (nmol . l^{-1})	0·4 ± 0·06	0·3 ± 0·06	0·4 ± 0·06	0·4 ± 0·07
P-renin activity (ng A l . ml^{-1} . h^{-1})	5·0 ± 1·6	3·8 ± 1·1	4·7 ± 3·1	3·0 ± 0·9
P-angiotensin II (pg . ml^{-1})	3·2 ± 1·74	5·3 ± 2·39	2·1 ± 1·14	6·0 ± 1·67
P-adrenaline (nmol . l^{-1})	0·2 ± 0·06	0·2 ± 0·03	0·2 ± 0·03	0·1 ± 0·03
P-noradrenaline (nmol . l^{-1})	2·9 ± 0·37	1·7 ± 0·33	2·0 ± 0·29	2·6 ± 0·29

Table 2 Equilibrium radionuclide angiography in patients in the placebo and growth hormone group at baseline and after 3 months of treatment

Variable	Placebo		Growth hormone	
	Baseline (n=11)	After treatment (n=10)	Baseline (n=11)	After treatment (n=10)
Ejection fraction at rest (%)	29·4 ± 3·3	28·4 ± 3·7	29·9 ± 3·2	29·3 ± 2·5
Ejection fraction at max work-load (%)	26·8 ± 2·6	26·8 ± 4·0	27·6 ± 2·8	28·3 ± 2·8
End-diastolic volume (ml)	175 ± 16	178 ± 18	170 ± 18	179 ± 17
End-systolic volume (ml)	120 ± 16	126 ± 18	112 ± 14·7	121 ± 11·8

Table 3(a) Doppler echocardiography data on dimensions and systolic function in patients in the placebo and growth hormone group at baseline and after 3 months of treatment

Variable	Placebo		Growth hormone	
	Baseline (n=11)	After treatment (n=10)	Baseline (n=11)	After treatment (n=10)
Left ventricular dimensions				
Left ventricular diastolic diameter (mm)	69·3 ± 3·1	70·3 ± 2·4	69·6 ± 2·4	71·3 ± 3·1
Left ventricular systolic diameter (mm)	60·3 ± 3·6	60·6 ± 2·9	58·5 ± 3·5	59·3 ± 3·5
Interventricular septum (mm)	11·6 ± 0·9	11·6 ± 0·9	12·4 ± 1·2	12·1 ± 1·5
Posterior wall (mm)	10·3 ± 0·6	10·5 ± 0·5	10·9 ± 0·7	10·9 ± 0·6
Left ventricular mass (g)	266 ± 17	286 ± 20	272 ± 14	270 ± 21
Left ventricular systolic function				
Fractional shortening (%)	13·4 ± 2·1	14·2 ± 1·8	16·2 ± 1·8	17·1 ± 2·0
Wall stress (kPa)	20·3 ± 0·6	18·8 ± 0·7	17·3 ± 1·5	17·4 ± 0·6
E-point septal separation (mm)	26·4 ± 1·9	25·6 ± 1·7	26·8 ± 2·2	26·4 ± 1·7
Stroke volume (ml)	54·5 ± 4·23	59·7 ± 6·37	66·6 ± 7·88	62·3 ± 3·82
Cardiac output ($l \cdot min^{-1}$)	4·5 ± 0·33	4·8 ± 0·37	4·4 ± 0·40	4·6 ± 0·39

Table 3(b) Doppler echocardiography data on diastolic function and valvular insufficiency in patients in the placebo and growth hormone group at baseline and after 3 months of treatment

Variable	Placebo		Growth hormone	
	Baseline (n=11)	After treatment (n=10)	Baseline (n=11)	After treatment (n=10)
Left ventricular diastolic function				
Atrial emptying index	0·25 ± 0·08	0·32 ± 0·09	0·76 ± 0·09	0·67 ± 0·10
Mitral flow patterns				
Type 1	1	1	1	2
Type 2	5	4	5	4
Type 3	0	1	2	1
Type 4	4	4	2	3
Mitral E/A (early/late) velocity	1·26 ± 0·38	1·52 ± 0·44	1·74 ± 0·56	2·52 ± 0·63
Deceleration time (ms)	168 ± 18	140 ± 18	199 ± 32	157 ± 19
Isovolumic relaxation time (ms)	77 ± 12	77 ± 10	80 ± 13	69 ± 15
Left atrial dimension (mm)	50·4 ± 1·9	48·9 ± 1·8	44·4 ± 2·5	45·4 ± 2·7
Left atrial area (cm^2)	26·1 ± 2·2	25·7 ± 2·3	21·0 ± 1·4	24·7 ± 1·2
Right atrial area (cm^2)	16·2 ± 1·8	15·9 ± 1·4	16·5 ± 1·6	16·8 ± 1·1
Atrioventricular leakage				
Mitral regurgitation (0–4)	0·44 ± 0·11	0·63 ± 0·15	0·63 ± 0·15	0·81 ± 0·21
Tricuspid regurgitation (0–4)	0·50 ± 0·08	0·57 ± 0·08	0·33 ± 0·08	0·41 ± 0·06
Tricuspid regurgitation gradient (mmHg)	31·6 ± 3·0	36·3 ± 3·3	27·5 ± 5·2	30·3 ± 5·0

recently, studies on growth hormone treatment in heart failure were limited to case reports in patients with growth hormone-deficiency[10,11] where growth hormone administration dramatically improved cardiac function. In a small open study of seven patients with idiopathic dilated cardiomyopathy and congestive heart failure

without growth hormone-deficiency, who received growth hormone treatment for 3 months, there was a dramatic improvement in cardiac function[13]. More recent studies have demonstrated beneficial effects in patients with congestive heart failure as a result of both ischaemic and idiopathic dilated cardiomyopathy. Improvements were seen in haemodynamics when growth hormone was added both as maintenance therapy and as a short-term infusion[14,28]. However, concern has been raised regarding increased levels of circulating insulin-like growth factor-I[29] and a possible worsening of arrhythmias[30].

The present study demonstrates that growth hormone treatment over 3 months in patients with congestive heart failure without growth hormone-deficiency is safe and without any major side effects such as an increased fluid retention or a worsening of arrhythmias. There was a substantial increase in serum insulin-like growth factor-I, which shows that it is necessary to perform studies on dose levels of growth hormone vs efficacy on cardiac function.

There are several possible explanations for the absence of significant effects of growth hormone on cardiovascular parameters in the present study. Although the study was double-blind and placebo-controlled, it was a small pilot study in patients with congestive heart failure of various aetiologies who, theoretically, may respond in a variety of ways to growth hormone. The statistical power was not sufficient to discover small improvements in the efficacy variable. This is in contrast to the study by Fazio and co-workers[13], which was open and included only patients with idiopathic dilated cardiomyopathy. However, preliminary data show that growth hormone may be effective in congestive heart failure of aetiologies other than idiopathic dilated cardiomyopathy[28]. Secondly, our patients were optimally treated for congestive heart failure, confirmed by neurohormonal pattern and exercise capacity, and received higher doses of ACE inhibitors than in the Italian study[13]. This might have limited the potential effects of growth hormone on cardiac structure and performance. However, experimental data suggest that the effects of growth hormone treatment are complementary to ACE inhibitors as regards cardiac function in rats with experimental myocardial infarction[3]. Thirdly, the duration of growth hormone treatment may influence the cardiac response. Growth hormone may have a positive short-term affect on haemodynamics[14], although it is unclear how long this effect is maintained. It is also possible that the treatment period in the present study was not long enough to yield possible results, although the duration of growth hormone treatment was comparable to that in the study by Fazio *et al.*[13]. The mode of growth hormone administration may also influence the present result. We administered growth hormone by daily subcutaneous injections, which has been the routine method for several years in growth hormone-deficient patients, and we achieved a pronounced increase in circulating insulin-like growth factor-I. However, a double dose of growth hormone every second day may be more favourable, with a more optimal plasma pattern of growth hormone, even if the total weekly dose is the same as with daily injections. Some experimental studies indicate that a pulsatile plasma concentration of growth hormone is more optimal for induction of insulin-like growth factor-I mRNA in peripheral tissues, as opposed to the liver which is more prone to respond to a continuous presence of growth hormone in plasma[31].

In conclusion, we found that the addition of growth hormone in patients with congestive heart failure and without growth hormone-deficiency is feasible and without major side effects, which is an important finding. The lack of a positive effect in this study was not an unexpected result, in view of the size and power of the study. Since an increased number of experimental studies clearly demonstrate beneficial effects of growth hormone on cardiac function, larger placebo-controlled trials have to be performed to further evaluate the effect of growth hormone, as an adjunct to standard therapy, in congestive heart failure of different aetiologies, and such studies are under way.

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