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Effects of Growth Hormone on Exercise Capacity and Cardiopulmonary Performance in Patients with Chronic Heart Failure

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Background: Because GH exerted beneficial effects in various experimental models of heart failure, we investigated the effects of GH on physical exercise capacity and cardiopulmonary performance in patients with dilated cardiomyopathy and chronic heart failure (CHF).

Methods: Twenty-two patients with CHF (New York Heart Association functional class II-III) underwent spirometry and a symptom-limited, cardiopulmonary exercise testing before and after 3 months of GH (n = 11; seven males; seven idiopathic; 57 ± 11 yr; 4 IU sc every other day) or placebo (n = 11; eight males; six idiopathic; 54 ± 10 yr) administration, in a randomized, double-blind trial. Background CHF therapy remained unchanged.

Results: GH, but not placebo, increased IGF-I serum concentration (from 144 ± 35 to 293 ± 58 ng/ml; $P < 0.005$) and improved New York Heart Association functional class (from 2.4 ± 0.5 to 1.8 ± 0.4; $P < 0.005$), exercise duration (from 831 ± 273 to 925 ± 266 sec; $P < 0.005$), peak power output (from 245 ± 127 to 280 ± 132 W; $P < 0.05$), peak minute ventilation (from 52.5 ± 16.1 to 61.3 ± 17.3 liters/min; $P < 0.05$), peak oxygen consumption (from 19.8 ± 5.6 to 25.1 ± 5.6 ml/kg·min; $P < 0.005$), and anaerobic threshold (from 14.9 ± 4.8 to 20.0 ± 4.5 ml/kg·min; $P < 0.005$) without affecting lung function parameters. Furthermore, the slope of the relationship between minute ventilation and pulmonary carbon dioxide production (ventilatory efficiency) decreased from 34.7 ± 5.1 to 31.7 ± 5.3 ($P < 0.005$), whereas the slope of the relation between percent predicted heart rate reserve used and percent observed metabolic reserve used (chronotropic index) rose from 0.57 ± 0.20 to 0.69 ± 0.18 ($P < 0.005$).

Conclusion: Given the predictive value of physical exercise capacity and cardiopulmonary performance in CHF progression, these data provide additional insights into the mechanisms by which GH may potentially benefit CHF patients. **(*J Clin Endocrinol Metab* 92: 4218–4223, 2007)**

GH AND ITS TISSUE effector IGF-I have been proposed as adjunctive therapy in the treatment of chronic heart failure (CHF). The rationale of this approach stems from the observation that GH and IGF-I induce physiological cardiac growth, which may potentially translate into functional advantage (1, 2). Studies conducted with a variety of experimental models of heart failure have almost invariably demonstrated that GH and IGF-I are beneficial to the failing heart (3–10). Despite these encouraging experimental data, the results of clinical studies of GH administration to patients with CHF are equivocal. In some studies, GH greatly benefited patients with idiopathic or postischemic dilated cardiomyopathy, whereas in others it exerted little or no effect (11–20). Indeed, as suggested by a recent subgroup analysis and metaregression from the available clinical trials, this discrepancy could well be explained by the heterogeneity in the circulating IGF-I increase in response to the different GH treatment regimens tested in CHF patients, likely attributable to the wide spectrum of GH/IGF-I axis abnormalities in CHF, ranging from severe GH deficiency to acquired GH resistance (21). In no instance, however, did GH deteriorate cardiac function or promoted clinically relevant arrhythmias, and the treatment was in general well tolerated. For this reason, we decided to explore further the effects of GH in patients with CHF.

Hitherto, clinical studies have focused on the effects of GH on left ventricular (LV) function and hemodynamics. Little is known about the impact of GH on cardiopulmonary performance and exercise capacity (12, 16, 17). Such data would be relevant, given the well-recognized importance of cardiopulmonary performance and exercise capacity as markers of disease progression and predictors of mortality in patients with CHF (22, 23). Consequently, we conducted a randomized, double-blind, placebo-controlled study to investigate the effects of a 3-month course of GH, adjunctive to background therapy, on cardiopulmonary performance and physical exercise capacity in patients with dilated cardiomyopathy and CHF.

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Abbreviations: ACE, Angiotensin-converting enzyme; AT, anaerobic threshold; CHF, chronic heart failure; FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity; LV, left ventricular; NYHA, New York Heart Association; %OMR, percent observed metabolic reserve used; %PHRR, percent predicted heart rate reserve used; %PMR, percent predicted metabolic reserve used; %PPO, percent of peak power output; VCO_2, pulmonary carbon dioxide production; VE, minute ventilation; VO_2, pulmonary oxygen consumption.

Patients and Methods

Patients and experimental design

Twenty-two patients with CHF due to idiopathic or ischemic dilated cardiomyopathy entered the study (Table 1). Inclusion criteria were: 1)

TABLE 1. Clinical, biochemical, and lung function parameters

	Placebo (n = 11)		GH (n = 11)		Treatment effect (%)
	Baseline	End of study	Baseline	End of study	
Gender (male/female)	7/4		8/3		
Age (yr)	57 ± 11		54 ± 10		
Etiology (ID/PI)	7/4		6/5		
NYHA functional class	2.4 ± 0.5	2.5 ± 0.5	2.4 ± 0.5	1.8 ± 0.4[a]	−26 ± 7[b]
Body weight (kg)	70 ± 12	71 ± 12	74 ± 14	73 ± 13	−1 ± 1
BMI (kg/m^2)	26 ± 3	26 ± 3	27 ± 4	27 ± 3	−1 ± 1
HR (bpm)	64 ± 6	63 ± 6	69 ± 11	71 ± 8	3 ± 4
SBP (mm Hg)	126 ± 12	120 ± 7	128 ± 14	117 ± 4[c]	−4 ± 4
DBP (mm Hg)	73 ± 8	73 ± 6	74 ± 6	69 ± 4[c]	−7 ± 5
MAP (mm Hg)	90 ± 7	88 ± 7	92 ± 8	85 ± 3[a]	−5 ± 3
Hemoglobin (g/dl)	13.2 ± 1.7	13.3 ± 1.7	13.8 ± 1.2	14.1 ± 1.6	1 ± 3
IGF-I (ng/ml)	149 ± 54	156 ± 49	144 ± 35	293 ± 58[a]	101 ± 18[b]
FVC (liters)	3.23 ± 0.79	3.30 ± 0.63	3.27 ± 0.84	3.34 ± 0.77	3 ± 2
FEV_1 (liters)	3.08 ± 0.64	3.11 ± 0.59	3.13 ± 0.67	3.20 ± 0.65	2 ± 4
FEV_1/FVC (%)	96 ± 4	94 ± 2	97 ± 11	97 ± 6	1 ± 6

ID, Idiopathic; PI, postischemic; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; Treatment effect, Δ% change in GH group − Δ% change in placebo group.

[a] $P < 0.005$ *vs.* baseline.

[b] $P < 0.005$ *vs.* placebo.

[c] $P < 0.05$ *vs.* baseline.

echocardiographic evidence of LV ejection fraction less than 40% and LV internal dimension greater than 58 mm; 2) clinical evidence of CHF despite conventional therapy; 3) stable hemodynamic conditions and treatment during the previous 3 months; and 4) sinus rhythm. Twelve patients were in New York Heart Association (NYHA) class II and 10 in NYHA class III. Exclusion criteria were myocardial infarction or treatment of coronary artery disease by interventional procedures during the previous 6 months, unstable angina, major arrhythmias (Lown class > IV), systemic hypertension, significant valvular heart disease, hypertrophic cardiomyopathy, active myocarditis, peripheral vascular disease, insulin-treated diabetes mellitus, obstructive pulmonary disease, chronic alcoholism, and skeletal muscle or bone diseases limiting exercise capacity. Eleven patients were treated for 3 months with recombinant human GH (4 IU sc every second day), whereas 11 patients received placebo, according to a randomized, double-blind design. In the treatment of the patients, ramipril was the only angiotensin-converting enzyme (ACE) inhibitor used (6.1 ± 2.6 and 6.3 ± 2.8 mg/daily in GH and placebo-treated group, respectively) and bisoprololo was the only β-blocker (4.5 ± 1.3 and 4.4 ± 1.4 mg/daily in GH and placebo-treated group, respectively). Individual medical therapy for CHF was left unchanged throughout the study. GH (Humatrope), placebo, and the injection system (Humatro-Pen II) were provided by Eli Lilly (Florence, Italy). Written informed consent was obtained from each patient and the study was approved by the Ethics Committee of the University of Naples Federico II. The trial was registered on ClinicalTrial.gov (NCT00501514).

Procedures and calculations

Each patient was studied at baseline and immediately after the 3-month treatment period. Evaluations consisted of a general physical examination, routine laboratory tests, measurement of IGF-I serum concentration by RIA, routine spirometry, cardiopulmonary exercise testing, and complete Doppler echocardiography

Forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV_1), was assessed with a computerized system (Benchmark exercise test system; Morgan, Bologna, Italy), according to European Respiratory Society recommendations. Maximal voluntary ventilation in 1 min was calculated as: $FEV_1 \times 41$ (24). Patients underwent cardiopulmonary exercise testing before 1200 h and without interrupting medical treatment according to the Cornell-modified treadmill protocol (2-min step increments). All patients performed the test before entering the study to get used to the procedure. Breath-by-breath respiratory gases analysis was recorded on a commercially available metabolic chart (Benchmark exercise test system; Morgan). Pulmonary oxygen consumption (VO_2), pulmonary carbon dioxide production (VCO_2), and minute ventilation (VE) were measured at rest and during exercise using a moving average of eight breaths. During each stage of exercise, heart rate and rhythm data and blood pressure were recorded. All patients were encouraged to exercise until they felt unable to continue because of dyspnea and/or fatigue.

The upper limit of VO_2 from VO_2-work rate relationship was identified as the highest VO_2 achieved by the patient and was defined as peak VO_2. This was always observed just before the patient exhausted, independent of whether a flattening of the VO_2-work rate relationship was seen. Anaerobic threshold (AT), defined as the level of exercise VO_2 above which aerobic energy production was supplemented by anaerobic mechanisms, was determined by placing a 45° right triangle on the VCO_2-VO_2 relationship (plotted on equal scales) and by identifying the VO_2 at which the data points started to increase at an angle greater than 45° (V slope method). In each case, the attainment of AT was confirmed by the simultaneous visual inspection of the ventilatory equivalent for O_2 (VE/VO_2) and CO_2 (VE/VCO_2) *vs.* work-rate plot (ventilatory equivalent method). The breathing reserve was calculated as: (1 − peak VE/maximal voluntary ventilation in 1 min) × 100, where the peak VE is the maximum minute ventilation measured during exercise (25). The ventilatory efficiency (VE-VCO_2 slope) was measured as the angular coefficient of the linear relationship between VE and VCO_2 below AT, *i.e.* up to a respiratory gas exchange ratio (VO_2 to VCO_2) of 1, thus excluding the nonlinear part of the relationship reflecting the ventilatory compensation for the metabolic acidosis of exercise (26). The chronotropic index (%PHRR-%OMR) was measured as the slope of the linear relationship between the percent predicted heart rate reserve used (%PHRR) and the percent observed metabolic reserve used (%OMR) at any stage of exercise (27). The aerobic work efficiency (%PMR-%PPO) was measured as the slope of the linear relationship between the percent predicted metabolic reserve used (%PMR) and the percent of peak power output (%PPO) at any stage of exercise (28). The mechanical work efficiency during exercise was estimated as the ratio of total power output to total O_2 required to develop it, after calculating the respective caloric equivalents as follows: 1 liter VO_2/min = 4.96 calories, assuming a respiratory exchange ratio of 0.95, and 1 W/min = 0.014 calories. Reproducibility of cardiopulmonary exercise parameters in our laboratory was very high with a correlation coefficient for peak VO_2 of 0.992 ($P < 0.001$).

M-mode, two-dimensional, and Doppler-echocardiographic analysis was performed with an ultrasonographic system equipped with a 3.5-mHz transducer (Toshiba Aplio SSA-770A; Tochigi, Japan), according to the recommendations of the American Society of Echocardiography (29). Intraobserver and interobserver variability was 9.2 and 16.4% for left ventricular mass, 2.4 and 3.1% for left ventricular dimensions, and 3.9

and 4.6% for ejection fraction. Details of the variability coefficients of the measurements of diastolic function are reported elsewhere (30).

Statistical analysis

The results are expressed as means ± SD. The comparison between groups at baseline was performed with the two-sided, unpaired Student's *t* test. The treatment effect within groups was evaluated with the two-sided, paired Student's *t* test. Treatment effect between groups (Δ% change in GH group-Δ% change in placebo group) was evaluated with the two-sided, unpaired Student's *t* test. Correlation analysis was performed by Spearman test. $P < 0.05$ was considered statistically significant.

Results

The patients' clinical, biochemical, and lung function parameters were comparable before treatment (Table 1). Nine of the patients in placebo arm were in treatment with ACE inhibitors, whereas seven of them where on β-blockers; in the GH group instead, eight patient were on ACE inhibitors and nine on β-blocker treatment. All patients completed the 3-month course of treatment; those in the GH group did not report side effects. There was no change in body weight, body composition, or hemoglobin concentration after GH or placebo. The serum IGF-I level significantly increased (near doubled) in all patients treated with GH and remained stable in the placebo group. The clinical status improved after GH, as indicated by the significantly decreased NYHA functional class, whereas it remained stable in the placebo group. GH did not affect the resting heart rate; the mean arterial pressure was significantly lower due to a reduction in both systolic and diastolic arterial pressure. There was no change in heart rate or in arterial blood pressure after placebo. At baseline, patients in the GH and placebo groups showed a mild and comparable restrictive-like pattern of lung function, which was not substantially affected by GH or placebo.

Placebo and GH did not alter the resting cardiopulmonary parameters (Table 2). In contrast, GH significantly improved exercise capacity and cardiopulmonary performance. In particular, exercise duration, peak power output, peak VE, peak VO_2, and VO_2 AT were significantly increased. At maximum effort, the breathing reserve and mean arterial pressure was significantly reduced by GH, whereas heart rate was significantly increased and mean arterial pressure was significantly reduced. In addition, GH improved ventilatory efficiency, the chronotropic index and the aerobic work efficiency, as demonstrated by the significant reduction in the slope of the VE-VCO_2 relationship and the significant increase in the slopes of the %PHRR-%OMR and %PMR-%PPO relationships, respectively. A positive significant correlation was present between individual percent variation of IGF-I and peak VO_2 in the whole study population (Fig. 1). No change in the mechanical work efficiency occurred after GH. None of the above parameters were affected by placebo.

The LV mass index and relative wall thickness significantly increased after GH because of LV wall thickening without a change in LV dimension (Table 3). GH also improved the indices of systolic and diastolic function, as demonstrated by the significant increase in LV ejection fraction and early to late peak velocities ratio of transmitral inflow and the significant reduction in end-systolic wall stress and heart rate-corrected isovolumic relaxation time. No parameter of LV morphology and function was affected by placebo. Finally, GH, but not placebo, significantly improved resting hemodynamics, as indicated by

TABLE 2. Physical exercise capacity and cardiopulmonary performance

	Placebo (n = 11)		GH (n = 11)		Treatment effect (%)
	Baseline	End of study	Baseline	End of study	
Exercise duration (sec)	775 ± 272	805 ± 308	831 ± 273	925 ± 266[a]	12 ± 5[b]
Peak power output (W)	219 ± 119	231 ± 117	245 ± 127	280 ± 132[c]	11 ± 7
HR (bpm)					
Rest	80 ± 14	74 ± 14	75 ± 7	75 ± 7	5 ± 7
Peak	134 ± 31	129 ± 28	133 ± 20	141 ± 18[c]	8 ± 4
MAP (mm Hg)					
Rest	86 ± 6	86 ± 6	90 ± 6	85 ± 7[c]	−6 ± 2[b]
Peak	101 ± 21	106 ± 10	111 ± 11	106 ± 10[c]	−13 ± 5[b]
VE (liters/min)					
Rest	13.7 ± 4.3	13.4 ± 3.5	11.4 ± 4.1	12.0 ± 4.1	5 ± 11
Peak	54.8 ± 14.9	57.7 ± 15.5	52.5 ± 16.1	61.3 ± 17.3[c]	13 ± 8
VO_2 (ml/kg·min)					
Rest	4.9 ± 0.9	5.4 ± 0.5	4.7 ± 1.2	5.2 ± 1.1	−1 ± 11
AT	16.4 ± 3.7	17.1 ± 3.9	14.9 ± 4.8	20.0 ± 4.5[a]	37 ± 12[b]
Peak	21.2 ± 5.3	22.6 ± 5.4	19.8 ± 5.6	25.1 ± 5.6[a]	23 ± 10[b]
RER					
Rest	0.89 ± 0.07	0.86 ± 0.05	0.87 ± 0.08	0.86 ± 0.07	2 ± 3
Peak	0.98 ± 0.13	0.98 ± 0.10	0.99 ± 0.09	0.99 ± 0.04	−1 ± 4
Chronotropic index	0.64 ± 0.25	0.56 ± 0.24	0.57 ± 0.20	0.69 ± 0.18[a]	38 ± 11[d]
Breathing reserve (%)	56 ± 11	54 ± 12	58 ± 12	52 ± 12[c]	−6 ± 4
VE-VCO_2 slope	33.7 ± 5.5	33.3 ± 4.4	34.7 ± 5.1	31.7 ± 5.3[a]	−8 ± 3[b]
Aerobic work efficiency index	0.57 ± 0.15	0.63 ± 0.18	0.55 ± 0.22	0.73 ± 0.23[a]	30 ± 17
Mechanical work efficiency (%)	25 ± 10	24 ± 8	28 ± 9	26 ± 6	−7 ± 11

HR, Heart rate; MAP, mean arterial pressure; RER, respiratory exchange ratio; Treatment effect, Δ% change in GH group − Δ% change in placebo group.[a] $P < 0.005$ *vs.* baseline.
[b] $P < 0.05$ *vs.* placebo.
[c] $P < 0.05$ *vs.* baseline.
[d] $P < 0.005$ *vs.* placebo.

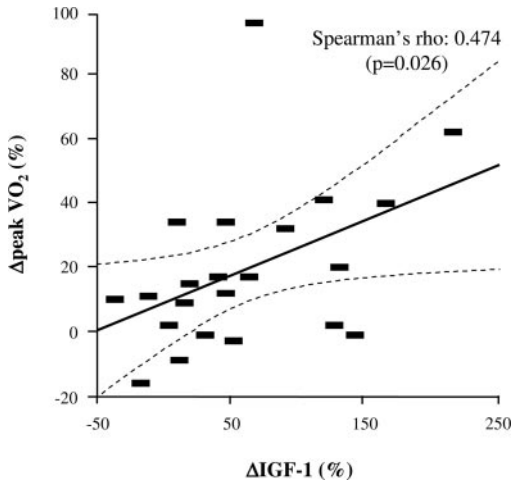

FIG. 1. Correlation analysis between individual percent variations of IGF-I and peak VO_2 in subjects studied before and after GH or placebo treatment.

an increased cardiac index and decreased peripheral vascular resistance.

Discussion

This double-blind and placebo-controlled trial study shows that a 3-month course of GH improves exercise capacity and cardiopulmonary performance of patients with idiopathic and postischemic dilated cardiomyopathy and mild CHF, as indicated by a consistent increase in exercise duration, peak power output, peak VO_2, and peak VE. The fact that GH therapy did not affect lung function at rest or hemoglobin concentration suggests that the enhanced exercise capacity consequent to GH resulted from improved cardiovascular adaptation to exercise. This interpretation is supported by three lines of evidence. The first is that GH attenuated LV remodeling and improved LV function indices at rest, including the cardiac index. The second is that heart rate response to exercise improved after GH, as demonstrated by the mild increase in peak heart rate and the significant increase in the chronotropic index, which reflects the higher percentage of the predicted heart rate reserve used at any given metabolic work load. Finally, GH improved the aerobic work capacity and efficiency, indicating greater O_2 uptake by muscle at any given increase in power output. Because mechanical work efficiency was unchanged, it is conceivable that GH enhanced the contribution of energy supply from aerobic metabolism, *i.e.* the rate of aerobic ATP generation, probably by improving O_2 delivery to the exercising muscle. Consistent with this line of reasoning is the remarkable decrease in peripheral vascular resistance observed in our patients after GH treatment, a finding that is compatible with increased vasodilatation capacity. In this context, it is pertinent to recall that GH also corrects endothelial dysfunction and improves the nonendothelial component of vasodilation (31).

Interestingly, the GH-induced enhanced exercise capacity was associated with improved ventilatory efficiency, as demonstrated by the blunted increase in VE relative to VCO_2, and it was paralleled by a significant reduction in NYHA functional class. Given the key pathophysiological role of abnormally high ventilatory response to exercise in the exertional dyspnea of patients affected by CHF (32), and hence in the allocation of patients' NYHA functional class, the present finding that GH improved ventilatory efficiency provides a novel potential mechanism by which GH may help patients with CHF to perform ordinary physical activity with less discomfort.

The improvement in NYHA class and exercise capacity observed in the present double-blind and placebo-controlled trial is in agreement with several previous studies of patients with CHF treated with GH (11–13, 16–19). However, in other controlled studies, GH produced little, if any, improvement (14, 15, 20). The explanation for the variable response to GH is probably 2-fold. First, it is becoming clear that some patients with CHF, particularly those with wasting or frank cachexia, enter a state of GH resistance (33). In this setting, the endocrine and clinical response to exogenous GH administration may be seriously hindered. Indeed, the rise in IGF-I after GH treatment in some studies reporting little or no clinical improvement was very modest (14). In other patients with CHF, a state of GH secretory defect has been documented (33). Obviously, exogenous GH administration to these patients works mostly as simple replacement therapy rather than pharmacological treatment. Second, although the weekly dosage of GH was comparable in all studies (~14 IU/wk) (11–15), the different dosage regimen used, 4 IU every second day (11) or 2 IU/d (12–15), may have determined different patterns of GH action, with important consequences in terms of IGF-I generation in peripheral tissues, although circulating plasma levels of IGF-I might not be affected by the different distribution of the GH administration (34). We decided to administer GH every other day, instead of every day because with this approach the patients receive a reduced number of injections with improvement in compliance and discomfort. On the other hand, an increase in the levels of circulating IGF-I appears to be of critical importance in determining the improvement of the cardiopulmonary response, as demonstrated clearly in Fig. 1. Some experimental studies indicated that a pulsatile pattern of plasma GH concentration (intermittent injections) is optimal for induction of IGF-I in peripheral tissues as opposed to the liver, which is more prone to respond to continuous GH stimulation (35). Interestingly, in mice with IGF-I gene knockout only in the liver, which results in significantly reduced serum IGF-I levels, cardiac development and growth were normal, as compared with wild-type littermates. This is direct evidence of the importance of the autocrine/paracrine role of IGF-I in cardiovascular physiology (36).

The mechanism(s) by which GH improved heart rate and ventilatory response to exercise remains speculative. Chronotropic incompetence in patients with CHF is thought to reflect underlying abnormalities of neurohormonal regulation sustained by impaired cardiac output and baroreceptor desensitization (23). In addition, the most important cause of ventilatory inefficiency in patients with CHF, despite normal arterial blood gases, is the increase in physiological dead space by alveolar hypoperfusion of the well-ventilated lung (high ventilation to perfusion ratio mismatching), resulting

TABLE 3. Doppler-echocardiographic data and hemodynamics at rest

	Placebo (n = 11)		GH (n = 11)		Treatment effect (%)
	Baseline	End of study	Baseline	End of study	
LVmWTi (mm/m^2)	5.6 ± 0.9	6.1 ± 1.1	5.9 ± 0.7	6.8 ± 0.7[a]	5 ± 7
LVEDVi (ml/m^2)	120 ± 30	112 ± 27	117 ± 28	115 ± 22	5 ± 6
LVMi (g/m^2)	160 ± 27	178 ± 39	178 ± 22	201 ± 28[b]	1 ± 10
RWT	0.29 ± 0.07	0.31 ± 0.05	0.32 ± 0.03	0.38 ± 0.04[a]	7 ± 7
EF (%)	34 ± 4	37 ± 7	32 ± 4	43 ± 9[a]	23 ± 10[c]
ESS ($kdyn \cdot cm^{-2}$)	126 ± 33	112 ± 28	119 ± 26	101 ± 18[b]	−18 ± 7[c]
E/A	0.95 ± 0.52	1.05 ± 0.51	0.76 ± 0.36	1.12 ± 0.40[b]	61 ± 32
IVRTc (msec)	127 ± 30	117 ± 15	128 ± 23	112 ± 18[b]	−9 ± 10
CI ($liters/min \cdot m^2$)	2.56 ± 0.74	2.61 ± 0.61	2.53 ± 0.56	3.41 ± 0.64[a]	38 ± 14[c]
SVRi ($dynes \cdot sec \cdot cm^{-5}/m^2$)	1016 ± 350	966 ± 376	976 ± 414	672 ± 272[a]	−27 ± 10[c]

LVmWTi, Left ventricular end-diastolic mean [(interventricular septum + posterior wall thickness)/2] wall thickness index; LVEDVi, left ventricular end-diastolic volume index; LVMi, left ventricular mass index; RWT, relative wall thickness; EF, ejection fraction; ESS, end-systolic wall stress; E/A, early to late peak velocities ratio of transmitral inflow; IVRTc, heart rate-corrected isovolumic relaxation time; CI, cardiac index; SVRi, systemic vascular resistance index; Treatment effect, Δ% change in GH group − Δ% change in placebo group.

[a] $P < 0.005$ *vs.* baseline.

[b] $P < 0.05$ *vs.* baseline.

[c] $P < 0.05$ *vs.* placebo.

from impaired endothelial vasodilatory capacity or neurohormonal activation (32, 37). In a previous study (38), GH administration to patients with CHF reduced the myocardial sympathetic drive during physical exercise and lowered the circulating aldosterone concentration. Noteworthy is evidence that aldosterone contributes to vascular dysfunction in patients with CHF (39) and that it may also depress the baroreceptor reflex (40). Thus, it is conceivable that GH, by promoting neurohormonal deactivation, affects the baroreceptor-mediated control of heart rate and pulmonary vasomotor tone, with a consequent improvement in the chronotropic response index and ventilatory efficiency.

The present observation that GH improves exercise capacity, chronotropic index, and ventilatory efficiency may be particularly relevant to the long-term outcome of GH treatment. Indeed, measurements of functional capacity, ventilatory and heart rate response to exercise, either alone or in combination, have emerged as sensitive markers of disease progression and the most consistent and powerful predictors of mortality in patients with CHF (22–26). Although the changes induced by GH were small, the fact that GH improved a variety of parameters simultaneously may be of clinical relevance, also considering the relatively short duration of treatment. Whether a longer treatment period or larger doses of GH would be more effective remains to be clarified.

Limitations of the study

In the analysis of the current data, a few limitations should be considered. First of all, this study evaluated a relatively small number of subjects. We think that a larger study including many more patients and adequately supported should be implemented to confirm and expand the conclusions of our study.

In addition, the results we obtained are relative to a short period of observation, and a longer period of therapy and evaluation should be performed. On the other hand, a 3-month treatment in patients with CHF should not be considered a very short period of time, given the unfavorable prognosis of the disease. Furthermore, we have no information on the relation between therapeutic effects and stage of the disease at which the therapy would be the most effective. Finally, a large survival study looking at the mortality would be necessary to support a large-scale treatment of CHF with GH.

Conclusions

Administration of GH to patients with idiopathic and postischemic dilated cardiomyopathy and mild CHF, as an addition to the standard therapy, improves their clinical status and cardiopulmonary adaptation to metabolic demand, resulting in increased physical exercise capacity and improved ventilatory efficiency. These data provide additional insights into the mechanisms by which GH interacts with CHF and may foster further investigation in this area.

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