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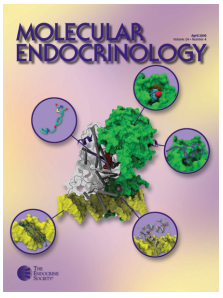

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Cardiac Effects of Growth Hormone Treatment in Chronic Heart Failure: A Meta-Analysis

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Context: Experimental studies suggest that GH treatment may improve cardiovascular parameters in chronic heart failure (CHF). However, clinical trials involved small numbers of patients and did not allow a conclusion to be drawn on the effect of this treatment in humans.

Objective: We systematically reviewed and analyzed all randomized controlled trials and open studies of sustained GH treatment in CHF.

Study Selection: Twelve trials were identified in three databases. We conducted a combined analysis of GH effects on cardiovascular parameters using the overall effect size to evaluate significance and computing the weighted mean differences with and without treatment to assess effect size.

Data Synthesis: GH treatment significantly modified morphological cardiovascular parameters [interventricular septum thickness, +0.55 (SD, 0.43) mm ($P < 0.001$); posterior wall thickness, +1.01 (0.44) mm ($P < 0.01$); left ventricle (LV) end-diastolic diameter, −2.02 (1.22) mm ($P < 0.01$); and LV end-systolic diameter, −5.30 (2.33) mm ($P < 0.05$)]; LV and systemic hemodynamics [LV end-systolic wall stress, −38.9 (13.3) dynes/cm^2 ($P < 0.001$); LV ejection fraction, +5.10 (1.74)% ($P < 0.05$); and systemic vascular resistance, +195.0 (204.5) dyn·sec^{-1}·cm^{-5} ($P < 0.01$)]; and functional parameters [New York Heart Association class, −0.97 (0.23) ($P < 0.01$); exercise duration, +103.7 (37.6) sec ($P < 0.001$); and maximal oxygen uptake, +2.48 (1.76) ml/kg·min ($P < 0.01$)]. Subgroup analysis and meta-regression showed significant relationships between the IGF-I response and GH treatment effects.

Conclusion: Our meta-analysis suggests that GH treatment improves several relevant cardiovascular parameters in patients with CHF. However, these results must be confirmed by a large randomized placebo-controlled trial on hemodynamic, morphological, and functional parameters during long-term high-dose GH treatment of patients with CHF. **(*J Clin Endocrinol Metab* 92: 180–185, 2007)**

CHRONIC HEART FAILURE (CHF) is characterized by a deleterious activation of several neurohormonal systems, and drugs blocking the sympathetic or renin-angiotensin-aldosterone system improve survival in patients with CHF (1–3). Nevertheless, the prognosis of CHF remains poor, most notably in New York Heart Association (NYHA) class III–IV patients. Clearly, new treatment strategies are needed (4).

Epidemiological studies have shown that GH deficiency is associated with increased cardiovascular mortality (5–7). A recent review of clinical trials of GH treatment in patients with GH deficiency suggests beneficial effects of GH on reduced left ventricular (LV) mass (LVM) and LV systolic function (8). In addition, GH treatment reduces cardiovascular risk factors in these patients (9). In contrast, GH excess contributes to increase cardiovascular mortality in acromegaly (10).

Numerous experimental and clinical studies suggest that GH and its effector IGF-I may contribute to regulate the cardiovascular system (11–17). In experimental studies, GH or a GH-releasing peptide had beneficial effects on cardiac function, peripheral resistance, and survival in animals with postischemic heart failure (12, 15–17). In addition, the anabolic effects of IGF-I are well established, together with its role in regulating heart function. IGF-I directly causes cardiomyocyte hypertrophy (14), augmented myocardial contractility via myofilament sensitization to Ca^{2+} (13), and retardation of cardiomyocyte apoptosis (11). Taken in concert, these data suggest that GH administration may have marked trophic and contractile effects on the heart.

Based on these experimental observations, several clinical studies have been performed to evaluate the effects of GH given to patients with CHF in addition to conventional therapy (18–30). However, the results are inconclusive. For instance, LV ejection fraction (LVEF) improved significantly in some studies (21, 22, 25, 28) but not in others (18, 20, 23, 24, 29, 30). Similarly, only some of these studies showed increases in the thickness of the interventricular septum (IVS) (20, 21, 25, 27) or LV posterior wall (LVPW) (19–21, 23, 25). Conflicting results were obtained for other cardiac param-

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Abbreviations: CHF, Chronic heart failure; HR, heart rate; IVS, interventricular septum; LV, left ventricular; LVEDD, LV end-diastolic diameter; LVEF, LV ejection fraction; LVESD, LV end-systolic diameter; LVESWS, LV end-systolic wall stress; LVM, LV mass; LVPW, left ventricular posterior wall; NYHA, New York Heart Association; SVR, systemic vascular resistance; VO_2max, maximal oxygen uptake.

eters such as LV end-diastolic diameter (LVEDD), systemic vascular resistance, and LV end-systolic wall stress (LVESWS). However, most of these trials included small numbers of patients, raising the possibility that nonsignificant results were related in part to inadequate statistical power. We therefore conducted a meta-analysis to obtain a more reliable picture of the effect of sustained GH administration in patients with CHF.

Materials and Methods

Identification of relevant trials

The medical literature was searched for reports on the effect of sustained GH administration to adults with CHF in the absence of GH deficiency. We searched three electronic databases—MEDLINE (Ovid), BIOSIS, and Experta Medica (EMBASE)—from their years of inception to June 2005. We used the following keywords: growth hormone, GH, somatotropin, IGF-I, cardiac function, heart failure, cardiac failure, cardiomyopathy, vascular function, and vasodilatation. The search strategy was not limited by study design or language. GH manufacturers and authors of published studies were contacted, and abstracts from major cardiology meetings were reviewed, in an attempt to identify unpublished trials and to reduce the risk of publication bias.

Inclusion criteria

We included all open studies and randomized, blind, placebo-controlled trials of sustained (treatment duration >1 month) GH administration to adults with CHF but without GH deficiency. The selected publications reported at least one of the following outcome measures: heart rate (HR), IVS, LVPW, LVEDD, LV end-systolic diameter (LVESD), LVM, LVESWS, LVEF, ratio of early to late mitral diastolic flow, isovolumic relaxation time, systemic vascular resistance (SVR), NYHA class, exercise duration, and maximal oxygen uptake (VO_2max).

Data extraction

Data were extracted from published reports onto standardized forms by two meta-analysts (P.L.C. and P.M.). Discrepancies were resolved by discussion among the authors of the present paper. The following data were extracted: mean age, sex, number of patients included, etiology of heart failure, conventional heart failure therapy, target GH dose, treatment duration, increase in IGF-I concentration, study quality (design, blindness, statistical methods), losses to follow-up for each outcome measure, and baseline and follow-up values in both groups (means and SD or SEM). The authors of selected reports were contacted to obtain unpublished data and to verify extracted data when necessary.

Statistical methods

For primary analyses of continuous outcome measures, we calculated standardized effect sizes for each trial and global effect sizes for each outcome. In the study by Acevedo *et al.* (18), the values had to be estimated from the figures. The effect size was calculated differently for parallel-group, cross-over, and open study designs, to reflect the intergroup and intragroup variances (31). For parallel groups, the effect size was computed using the mean difference (GH minus placebo) in the changes (follow-up minus baseline) for each outcome measure divided by the estimated variance of changes in the two groups. Effect sizes in crossover trials were calculated using the mean difference between the ends of each period divided by the variance in the placebo group at follow-up. For open studies, effect sizes were calculated using the mean difference between baseline and follow-up divided by the variance. A positive effect size is an increase with GH treatment and a negative effect size is a decrease. To calculate the global effect size, each study was weighted by the reciprocal of its variance. When the variance of changes was not stated, it was calculated from the confidence intervals (variances, SEM) (31). We report the overall effect sizes with their 95% confidence intervals.

We explored heterogeneity across studies using the Q test. When the effect size was significant in a fixed model but the Q test was significant, causes were investigated and the analyses were repeated using a random-effects model. In these cases, the effect sizes according to the random-effects model are reported.

Funnel plots were drawn, and their asymmetry was measured to assess the possible influence of publication and location biases (32). The intercept of linear regression, where the effect size divided by the SE is regressed against the reciprocal of the SE, provides a measure of asymmetry. To assess sensitivity, when the effect size was dependent on one or two trials (*e.g.* a large trial), these trials were dropped from the analysis.

To quantify effect size, we calculated the weighted mean (and SD) of the change between the groups or periods, for each outcome measure, when data were available.

The effects of the GH dose, IGF-I increase, treatment duration, age of patients, etiology of heart failure, and degree of LV dysfunction on the overall estimates were assessed by stratification or meta-regression. Weighted least squares regression was used for meta-regression, with individual study effects weighted by the inverse of the estimated variance. The β coefficient and its significance are reported, along with the adjusted R^2 to show the overall variability explained by the model.

Analyses were conducted using the SPSS 12.0 (SPSS Inc., Chicago, IL) package for Windows.

Results

The combined search strategy identified 12 publications, four open studies, and eight blinded, randomized, placebo-controlled trials, including a total of 195 patients (Table 1). Patient characteristics (age, sex), treatment (dose, duration), and baseline parameters were not different between randomized controlled trials and open studies (data not shown). Most of the patients included in these studies were treated with conventional drugs: diuretics (88.1%), angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists (94.3%), and β-blockers (42.4%). Mean baseline NYHA (n = 5 studies) and LVEF (n = 10) were, respectively, 2.8% (0.3) and 25.1% (9.5). The studies were generally of good quality, estimated with: lost to follow-up, intention-to-treat analysis, adequate statistical methods. Subjects were lost in only four trials (24, 27, 29, 30) (Table 1).

A search for potential bias in the meta-analysis showed significant heterogeneity for LVPW, LVM, and LVEF (Table 2). Funnel plot and linear regression did not suggest selection bias (data not shown), except for LVEF and exercise duration (β = 5.3, P = 0.003; and β = 17.3, P = 0.022, respectively).

A significant overall effect size was found with GH treatment (Table 2) for IVS (0.47 [0.18; 0.77]), LVPW (0.58 [0.20; 0.96]), LVEDD (−0.43 [−0.71; −0.16]), LVESD (−0.48 [-0.93; −0.04]), LVESWS (−0.80 [−1.43; −0.17]), LVEF (0.57 [0.18; 0.97]), SVR (−0.45 [−0.77; −0.13]), NYHA class (−0.93 [−1.75; −0.12]), exercise duration (0.79 [0.35; 1.23]), and VO_2max (0.68 [0.27; 1.09]). A trend was noted for isovolemic relaxation time (−0.52 [−1.05; 0.01]), which was measured in only three studies. Overall effect sizes were not significant for HR (0.02 [−0.24; 0.29]), LVM (0.65 [−0.40; 1.7]), or ratio of early to late mitral diastolic flow (E/A ratio) (0.15 [−0.31; 0.61]) (Table 2). When the analysis was confined to randomized controlled trials, the significant effect sizes were confirmed for IVS (0.43 [0.08; 0.77]), LVESWS (−0.69 [−1.37; −0.02]), and VO_2max (0.62 [0.16; 1.09]). Because selection bias was suspected for LVEF and exercise duration, effect sizes were recalculated after exclusion of studies responsible for asymmetry (Osterziel *et al*. (27) for LVEF and Spallarossa *et al.* (30) for exercise duration). The effect sizes remained

TABLE 1. Characteristics of studies included in the meta-analysis

Author (Ref.)	Year of publication	Study design	Patients included	No. lost[a]	Ischemic (%)	Women (%)	Age (mean ± SD)	Target dose (unit per week)	Increase of IGF-I (%)	Treatment duration (months)	Outcomes
Fazio (21)	1996	Open	7	0	0	29	46 ± 9	14	105.1	3	HR, IVS, PW, LVM, LVEDD, LVESD, ESWS, EF, E/A, IRT, SVR, ED, NYHA
Frustaci (22)	1996	Open	4	0	0	75	32 ± 8.1	28	NA	3	IVS, LVEDD, EF
Isgaard (24)	1998	Parallel	22	2	36	36	60 ± 11.3	0.25 U/kg·wk up to 28	137.1	3	HR, IVS, PW, LVM, LVEDD, LVESD, ESWS, EF, E/A, IRT, SVR, ED, NYHA
Osterziel (27, 28)	1998, 2001	Parallel	50	4	0	14	54 ± 10	14	78.8	3	HR, IVS, PW, LVM, LVEDD, ESWS, EF, SVR, NYHA
Genth-Zotz (23)	1999	Open	7	0	100	0	55 ± 9	14	110.1	3	HR, PW, LVEDD, LVESD, EF, SVR, VO_2max, ED, NYHA
Jose (25)	1999	Open	6	0	0	NA	NA	7	NA	6	IVS, PW, LVEDD, LVESD, EF, ED, NYHA
Spallarossa (30)	1999	Parallel	20	5	100	0	62.1 ± 8	0.14 U/kg·wk	89	6	IVS, PW, LVM, LVEDD, EF, E/A, IRT, ED, NYHA
Smit (29)	2001	Parallel	22	3	100	16	65.5 ± 8.5	14	36.7	6	HR, LVM, EF, ESWS
Napoli (26)	2002	Parallel	16	0	31	25	54.5 ± 11.3	14	85.5	3	HR, VO_2max
Acevedo (18)	2003	Parallel	19	0	35	10	57.7 ± 4.5	0.245 U/kg·wk	40.1	2	EF, VO_2max
Adamopoulos (19)	2003	Crossover	12	0	0	33	50 ± 13.8	14	NA	3	PW, ESWS, VO_2max
Cittadini (20)	2003	Parallel	10	0	0	NA	38.9 ± 10.6	0.21 U/kg·wk	NA	3	HR, IVS, PW, EF, E/A, SVR, ESWS

NA, Not available; E/A, ratio between early and late mitral diastolic flow; IRT, isovolumetric relaxation time; PW, posterior wall; ESWS, end-systolic wall stress; EF, ejection fraction; ED, exercise duration.

[a] Maximum lost (varying with outcome).

significant for both parameters (0.59 [0.25; 0.93] and 0.67 [0.22; 1.14], respectively).

The mean difference (and SD) between the GH treatment and control groups weighted were determined for each outcome to quantify the size of the effect (Table 2).

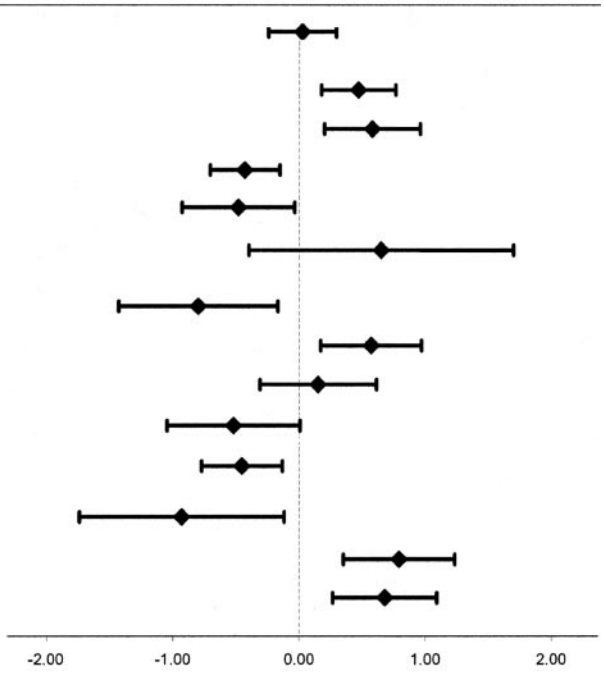
In the subgroup analysis according to the target dose, high-dose GH therapy (14 IU/wk) was associated with significant overall effect sizes for IVS (0.43 [0.12; 0.74]), LVPW (0.65 [0.22; 1.08]), LVEDD (−0.46 [−0.77, −0.16], LVESWS (−0.80 [−1.43; −0.17]), SVR (−0.45 [−0.77; −0.13]), exercise duration (0.64 [0.16; 1.12]), and VO_2max (0.68 [0.27; 1.09]). With low-dose therapy (7 IU/week, n = 2 studies), effect sizes were significant only for exercise duration (1.32 [0.52; 2.13]) and NYHA (−2.06 [−1.13; −3.00]). Although these results suggest a dose/effect relationship, definitive conclusions cannot be drawn because of the small number of studies using the low dose. The analysis of subgroups defined by GH treatment duration led to similar conclusions, because short studies (2 or 3 months) used high-dose GH, whereas two of the three 6-month studies used low-dose GH. Therefore, our results suggest that GH may induce an effect as early as 3 months after treatment initiation, but they cannot be used to determine whether the effect is increased after 6 months.

When enough studies were available, trials were separated in two groups according to the median of IGF-I increase (89%) observed for all studies. In trials with large IGF-I increases (>89%), a significant overall effect size was found for LVPW (0.78 [0.02; 1.55]), LVEDD (−0.49 [−0.95; −0.04]), NYHA (−1.22 [−2.24; −0.20]), and exercise duration (0.67 [0.19; 1.14]) (all parameters were evaluated except VO_2max). By contrast, trials with smaller IGF-I increases (<89%) showed no effect; the following parameters were evaluated: HR (n = 3), FE (n = 3), LVM (n = 2), VO_2max (n = 2), and ESWS (n = 2). The meta-regression model confirmed a relationship between the change in IGF-I concentration and the treatment effects, with significant results on NYHA ($\beta = 0.96$, $P = 0.04$, $R^2 = 0.89$) and VO_2max ($\beta = 1.0$, $P = 0.008$, $R^2 = 1.0$). No significant relationship was found with patient age or HF treatment. A significant relationship between sex and PW ($\beta = -0.96$, $P = 0.003$, $R^2 = 0.92$) independently to the cause suggests a more favorable effect in men. A significant relationship between the cause and LVEF ($\beta = 0.73$, $P = 0.04$, $R^2 = 0.53$) independent of sex suggests a more favorable effect in ischemic etiology.

No difference was observed in the frequency of major adverse events between GH and placebo treatments: deaths (2.8 vs. 2.1%, not significant), worsening of heart failure (6.1

TABLE 2. Global effect sizes by outcomes

Factor	Number of trials	Number of patients		Q test (p value)	Weighted mean differences (SD)	Global effect size (95% CI)
		GH	Control			
HR	7	72	71	ns	0.98 beats/min (4.27)	
IVS	7	65	64	ns	0.55 mm (0.43)	
LVPW	8	80	79	<0.05	1.01 mm (0.44)	
LVEDD	7	66	67	ns	-2.02 mm (1.22)	
LVESD	4	30	30	ns	-5.30 mm (2.33)	
LVM	5	58	60	<0.05	26.5 g (9.5)	
LVESWS	6	69	68	ns	-38.9 dynes/cm² (13.3)	
LVEF	10	91	89	<0.05	5.10 % (1.74)	
E/A ratio	4	30	29	ns	0.08 (0.37)	
IRT	3	24	25	ns	-18.5 msec (17.5)	
SVR	4	45	43	ns	-195.0 dyn.sec^{-1}.cm^{-5} (204.5)	
NYHA	6	59	60	ns	-0.85 (0.21)	
ExD	5	37	38	ns	103.7 sec (37.6)	
VO_2max	4	36	36	ns	2.48 ml/kg/min (1.76)	



E/A, Ratio between early and late mitral diastolic flow; IRT, isovolumic relaxation time; ExD, exercise duration; ns, not significant.

vs. 9.3%, not significant), or ventricular arrhythmias (2.0 vs. 0.0%, not significant).

Discussion

Experimental studies showed potentially beneficial effects of GH treatment in different heart failure models (12, 15–17). However, the small clinical trials performed to date produced conflicting results (18–30). The present systematic review demonstrates that sustained GH treatment improves several cardiovascular parameters in patients with CHF.

As with all systematic reviews, the possibility of publication bias is of major concern, because trials with positive and significant results are more likely to be published than those with neutral or negative results (32). However, in the present meta-analysis, an effect of publication bias is unlikely because statistically significant parameters were rarely identical across the selected trials and because results for nonsignificant parameters were reported also. Meta-analysis is also limited by study quality. One third of the studies are open, but the results were confirmed in sub-group analysis of randomized controlled trials.

Our meta-analysis shows that sustained GH treatment in CHF patients leads to an increase in LVEF and a reduction in SVR, suggesting an improvement in systemic hemodynamics. This last effect may be ascribable to an improvement in endothelium-dependent vasodilatation (33) that occurs within hours after treatment onset, as shown by reports of similar results after short-term (<24 h) iv GH infusion in healthy individuals or patients with heart failure (34–36). The improvement in LV systolic function may be related to GH-induced modifications in loading conditions (12, 21, 34, 36) or, as suggested by experimental studies, to a direct positive effect of GH on intrinsic myocardial contractility mediated by a shift in sarcolemmal calcium affinity (13) and/or by preservation of cardiac sarcoplasmic reticulum Ca^{2+} release channels (37). In addition, sustained GH treatment induces long-term modifications in cardiac morphology, *i.e.* a reduction in LVEDD and an increase in left ventricular wall thickness (IVS and LVPW), resulting in reduced LVESWS. These cardiovascular effects of GH may explain the improvement in functional capacity of patients with CHF, which manifested as improvements in NYHA class, exercise duration, or VO_2max, although an effect of GH on peripheral muscle wasting cannot be excluded (38). It is interesting to note that, recently, similar results on LVEF, LVM, and exercise capacity were reported after treatment with the growth hormone-releasing factor ghrelin in patients with CHF (38).

Beneficial effects of GH treatment on cardiac parameters in patients with GH deficiency caused by hypopituitarism have been shown in several clinical trials and in recent a meta-analysis by our group (8). Interestingly, striking similarities exist between patients with GH deficiency and those with CHF regarding abnormalities in cardiac parameters, as well as the effects of GH treatment on cardiovascular parameters. GH deficiency is characterized by a specific cardiac phenotype that includes alterations in endothelium-dependent vasodilatation (39), diminished LV wall thickness (40,

41) resulting in increased LVESWS (42), and a reduction in LVEF correlated with the severity of GH deficiency (40, 41, 43). Similar to patients with CHF, patients with GH deficiency respond to GH treatment by increases in LV wall thickness and stroke volume (8) and by improvement in endothelium-dependent vasodilatation that cause a reduction in SVR (39, 44).

CHF occurred mainly in the elderly, and functional GH deficiency (somatopause) is generally reported in this population (45). In CHF patients, modification of the GH-IGF-I axis has been reported only in patients with cachexia with a relative increase in GH plasma concentration associated with an unchanged (46) or even decreased IGF-I level (47), suggesting an acquired endogenous GH resistance in these patients (46–47). In addition, the magnitude of the IGF-I increase in response to GH in patients with CHF is inversely correlated with disease severity (48). Conceivably, differences in the degree of GH resistance across patients or studies may explain the variability of the results obtained with GH treatment. Interestingly, the Osterziel's study (28) has been reanalyzed and the authors reported that increase in IGF-I (expressed as a relative change during GH treatment) determined the magnitude of increases in LVEF and LVM. Our meta-analysis supports these results and suggests a dose/effect relationship and a correlation between the IGF-I response and the improvements in cardiovascular parameters in patients with CHF. Failure to use high doses to overcome GH resistance might explain the lack of efficacy in some studies.

Finally, our meta-analysis suggests that the effect of GH treatment could be more favorable in men. This gender effect could be related to differences in IGF-I release sensibility (49).

Conclusion

Our meta-analysis suggests that GH treatment improves several relevant cardiovascular parameters in patients with CHF. However these results must be confirmed by a large randomized placebo-controlled trial on hemodynamic, morphological, and functional parameters during long-term high-dose GH treatment of patients with CHF.

Acknowledgments

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Conflict of Interest Statement: Pr. P. Chanson has been an investigator in clinical trials sponsored by manufacturers (Pfizer, Serono, Novo Nordisk), has received funds for organizing education, and is a member of the International Advisory Board of HYPOCCS (Hypopituitary Control and Complication Study), which is sponsored by Eli Lilly.

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