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Acquired Growth Hormone Resistance in Patients With Chronic Heart Failure: Implications for Therapy With Growth Hormone

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OBJECTIVES	We aimed to determine whether growth hormone (GH) resistance is present in patients with chronic heart failure (CHF) and whether it may be linked to the biochemical response to GH treatment.
BACKGROUND	Acquired GH resistance is a feature of severe illness, in particular, cachexia. In patients with CHF, the response to GH therapy appears to be variable.
METHODS	Biochemical markers of the GH-insulin-like growth factor-I (IGF-I) axis were compared in 21 cachectic patients with CHF, 51 noncachectic patients and 26 healthy control subjects. In separate studies, the predictive value of baseline biochemical variables for the IGF-I response to GH treatment was analyzed.
RESULTS	Cachectic patients showed an increase of total GH and immunologically intact GH ($p \leq 0.0002$) and a decrease of GH-binding protein (BP) ($p = 0.005$), IGF-BP3 ($p = 0.01$) and IGF-I ($p = 0.06$), compared with noncachectic patients. Similar changes were found when the cachectic group was compared with the control group. No differences were found between noncachectic patients and control subjects. Levels of GH-BP correlated with the IGF-I/GH ratio in all subgroups (all $p \leq 0.002$). Baseline GH-BP levels were related to the increase of IGF-I levels in response to GH treatment in patients with CHF after 24 h ($r = 0.83$, $p = 0.005$; $n = 9$; study 2), 44 days ($r = 0.52$, $p = 0.007$; $n = 25$; study 3) and 96 days ($r = 0.54$, $p = 0.006$; $n = 24$; study 3).
CONCLUSIONS	Most cachectic and some noncachectic patients with CHF show features of acquired GH resistance. The principal predictors of the biochemical features of GH resistance and of the poor biochemical response to short-term and longer-term GH treatment are GH-BP plasma levels. The presence of GH resistance is potentially a major factor determining the response to GH therapy in patients with CHF. (J Am Coll Cardiol 2001;38:443-52) © 2001 by the American College of Cardiology

Chronic heart failure (CHF) is a complex disease affecting many body systems. Cachexia is known to occur in CHF, and several metabolic pathways are involved in this syndrome, causing a catabolic/anabolic imbalance, including the growth hormone (GH)-insulin-like growth factor-I (IGF-I) system (1). Growth hormone is secreted from the pituitary gland in a pulsatile manner and exerts direct

lipolytic effects, but its major mode of action is indirect and anabolic through activation of the somatomedins (2). The main GH-dependent somatomedin is IGF-I. Acquired GH resistance is a feature of severe catabolism and malnutrition in conditions of sepsis, surgery and critical illness (reviewed in [3,4]). Biochemically, it is defined as the presence of high GH but low IGF-I levels. The GH-IGF axis, in particular, the presence of GH resistance, has not been studied in detail in patients with CHF.

Pilot studies of the treatment of patients with CHF due to dilated cardiomyopathy (5) or ischemic cardiomyopathy (6) with recombinant human GH have shown favorable effects, but another pilot study (7) reported no benefit. Recently, randomized, controlled trials of GH treatment in patients with CHF have not shown clinical benefit (8,9). In these studies, the IGF-I response to GH was highly variable, and the degree of IGF-I increase during GH treatment was directly related to the increase of the left ventricular mass (8).

A lack of GH receptors could cause GH resistance, and its presence may prevent a beneficial response to GH therapy. Growth hormone-binding protein (BP) is structurally identical to the GH receptor ectodomain and is thought

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Abbreviations and Acronyms

BMI	=	body mass index
BP	=	binding protein
CHF	=	chronic heart failure
DEXA	=	dual-energy X-ray absorptiometric
GH	=	growth hormone
IGF-I	=	insulin-like growth factor-I
IRMA	=	immunoradiometric assay
LVEF	=	left ventricular ejection fraction
NYHA	=	New York Heart Association
RIA	=	radioimmunoassay
SC	=	standardized coefficient

to reflect the cellular GH receptor status (10,11). It has not been studied whether GH-BP plasma levels could predict the IGF-I response to GH treatment.

We present the results of three parallel studies from three heart failure centers. The first study analyzed the biochemical characteristics of acquired GH resistance in prospectively defined cachectic patients with CHF, compared with noncachectic patients and healthy subjects (London, study 1). To validate the use of single blood samples to assess GH and IGF-I, we investigated the relationship between fasting and overnight blood samples in patients with CHF and control subjects (Brescia, study 2). Finally, we investigated the predictive value of baseline biochemical variables for the IGF-I response to GH treatment in patients with CHF. The periods of GH treatment were 24 h in study 2 (Brescia) and three months in study 3 (Berlin).

METHODS

Study 1. PATIENTS AND CLINICAL CHARACTERISTICS. Between March 1992 and December 1996, 26 healthy control subjects and 72 stable patients with CHF were investigated (Table 1). The patients had a mean peak oxygen consumption (treadmill exercise test [12]) of 16.5 ± 0.7 ml/kg body weight/min, compared with 36.1 ± 1.4 ml/kg/min in control subjects ($p < 0.0001$). The patients with CHF were

receiving stable drug treatment consisting of furosemide or other diuretics (n = 66), an angiotensin-converting enzyme inhibitor (n = 62), warfarin (n = 27), digoxin (n = 26), aspirin (n = 25), amiodarone (n = 25) and nitrates (n = 21). No patient had severe renal failure (all serum creatinine levels $< 255 \mu\text{mol/l}$) or diabetes mellitus.

Twenty-one patients with CHF were defined as cachectic (13), based on a history of ≥ 6 months of nonedematous, weight loss $> 7.5\%$ of their previous normal weight (weight loss 12.5 ± 1.5 kg [range 5.5 to 30]) over 2.8 ± 0.6 years (i.e., 6.4 ± 1.0 kg/year and $16.2 \pm 1.7\%$ of previous normal weight; body mass index [BMI] 21.1 ± 0.4 kg/m²). No patient had clinical signs of an acute infection or other primary cachectic states, such as cancer, severe liver or thyroid disease. The remaining 51 noncachectic patients (BMI 26.6 ± 0.5 kg/m², $p < 0.0001$ vs. cachectic patients) had no history of significant weight loss in the two years before this study. The maximal weight gain in this period was 12 kg. When comparing cachectic with noncachectic patients, peak oxygen consumption (15.1 ± 1.4 vs. 17.1 ± 0.9 ml/kg/min, $p = 0.23$), left ventricular ejection fraction (LVEF) ($27 \pm 3\%$ vs. $27 \pm 2\%$, $p = 0.93$), treatment and mean New York Heart Association (NYHA) functional class (2.6 ± 0.1 vs. 2.8 ± 0.1 , $p = 0.45$) were not found to be significantly different. This study group includes 16 control subjects and 53 patients in whom total GH and IGF-I results were presented previously (1).

HUMORAL MEASUREMENTS. Venous blood samples (30 ml) were collected in the morning, between 9 and 10 AM, after a fasting period of ≥ 12 h and with the patient in the supine position at rest for ≥ 20 min. After centrifugation, aliquots were stored at -80°C until analysis. In all subjects, IGF-I (Medgenix, Fleurus, Belgium; sensitivity 0.25 ng/ml by radioimmunoassay [RIA]) and GH (Nichols Institute Diagnostics, San Juan Capistrano, California; sensitivity 0.02 ng/ml by immunoradiometric assay [IRMA]) were measured. The GH results measured by IRMA are presented in the figures and tables, except where otherwise

Table 1. Clinical Details and Absolute Ratio of IGF-I to GH of Control Subjects (Study 1) and Patients With CHF in Studies 1 to 3

	Control Subjects (n = 26)	Patients With CHF		
		Study 1 (n = 72)	Study 2 (n = 10)	Study 3 (n = 24)
Age (yr)	56 ± 2	61 ± 1*	62 ± 3	54 ± 2
Weight (kg)	81 ± 2	75 ± 2	64 ± 3	83 ± 3
Height (cm)	176 ± 1	173 ± 1†	168 ± 2	174 ± 2
Body mass index (kg/m ²)	26 ± 1	25 ± 0.5	24 ± 1	27 ± 1
Etiology: CAD/DCM (n)	—	50/22	7/3	0/24
NYHA functional class	—	2.7 ± 0.1	3.0 ± 0.2	2.3 ± 0.6
LVEF (%)	—	27 ± 2	23 ± 2	26 ± 2
Log IGF-I/GH ratio	2.72 ± 0.19	2.47 ± 0.12	2.19 ± 0.20	2.38 ± 0.06
Absolute IGF-I/GH ratio	525 (+288; -186)	295 (+94; -71)	155 (+91; -57)	240 (+36; -31)

*p = 0.07 vs. control subjects (in study 1). †p < 0.05 vs. control subjects (in study 1). Data are presented as the mean value ± SEM, except for etiology and absolute IGF-I/GH ratio.

CAD = coronary artery disease; CHF = chronic heart failure; DCM = dilated cardiomyopathy; GH = growth hormone; IGF-I = insulin-like growth factor-I; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

indicated. In 83 subjects (24 control subjects and 59 patients), measurement of the immunofunctionally intact form of GH was performed by using an immunofunctional assay, as previously published (14). This test has a lower detection limit of 0.1 ng/ml. In 81 subjects (24 control subjects and 57 patients), IGF-BP3 and GH-BP were measured. For quantitative measurement of IGF-BP3, a nonisotopic sandwich immunoassay was used (15). The assay has a lower detection limit of 2.18 pg/tube. For analysis of biologically intact GH-BP, a ligand immunofunctional assay (16) that has a lower detection limit of 19.9 pM/l (0.5 fmol/well) was used: intra-assay coefficients of variation were 3.4% at 115 pM/l and 5.9% at 1550 pM/l; the inter-assay coefficients of variation were 8.5% and 10.9%, respectively.

BODY COMPOSITION. To assess whether potential alterations of GH, IGF-I and, in particular, GH-BP, are a reflection of fat tissue differences between cachectic and noncachectic patients, we evaluated body composition using dual-energy X-ray absorptiometric (DEXA) scanning (17). In 58 patients (18 cachectic and 40 noncachectic), DEXA scans were obtained (effective dose equivalent 0.002 mSv; Lunar model DPX total body scanner, Lunar Radiation Company, Madison, Wisconsin).

Study 2. OVERNIGHT PROFILES. In 10 patients with CHF (2 cachectic) (Table 1) (18) and 9 healthy control subjects (age 60 ± 2 years, BMI 26 ± 2 kg/m², $p = 0.09$), venous blood samples were collected every 20 min between 10 PM and 6 AM using an indwelling catheter in the brachial artery (kept open through a saline infusion). Retrospectively, the blood samples were used to study GH levels (at each time point) and IGF-I levels (at three time points, every 4 h). To validate the use of single blood samples for the assessment of GH and IGF-I, the results of the overnight assessments were compared with the hormone level results obtained in a fasting blood sample taken between 7 and 8 AM after at least 20 min of supine rest after the end of the overnight sampling procedure. After centrifugation, aliquots were stored at -80°C until analysis. Growth hormone and IGF-I were measured as described elsewhere (19). In 9 of the 10 patients with CHF, it was also possible to relate the increase of IGF-I levels after a continuous intravenous infusion of 0.1 IU/kg GH over 24 h (Humatrope, Eli Lilly, Italy) (18,19) with baseline GH-BP levels. Growth hormone-BP was determined as described in study 1.

Study 3. RESPONSE OF IGF-I TO GH TREATMENT. The 25 patients with CHF in this study comprise the group of actively treated patients described in detail previously (8). None of these patients was cachectic. The clinical details of these patients are compared with those of the patients in studies 1 and 2 (Table 1). The patients in study 3 received 2 IU of GH daily (subcutaneous injections in the evening; Genotropin, Pharmacia & Upjohn, Erlangen, Germany). Venous fasting blood samples were collected in the morning, between 7 and 9 AM, after the patient rested in the

supine position for at least 20 min, on the day of randomization, after 44 ± 1 days of treatment and at the end of the treatment phase (mean 96 ± 1 days). After centrifugation, aliquots were stored at -80°C until analysis. Levels of IGF-I, GH and GH-BP were determined as described previously (8,20,21). The GH-BP RIA (tracer and standard; human recombinant GH-BP; batch 1070, kindly provided by Pharmacia & Upjohn, Stockholm, Sweden) has an intra-assay coefficient of variation of 9%.

MEASUREMENT OF GH-BP. It is important to note that the two tests to measure GH-BP are based on different methods (i.e., a ligand immunofunctional assay was used by Pflaum et al. [16] and RIA was used as published by Blum and Breier [20,21]). The first test kit is thought to measure functionally intact GH-BP. The second test kit measures the absolute quantity of GH-BP. The latter test kit could be influenced by GH-BP fragments. It is difficult to directly compare the results of the two analyses. Therefore, we present the GH-BP data in their respective units, as originally reported. To make these results comparable, we performed a test kit validation for GH-BP with 65 subjects, including healthy control subjects, patients with CHF and patients with a GH deficiency (age 57 ± 3 years). It was found that the results of the two GH-BP assessments correlated very well ($r = 0.87$, $r^2 = 0.75$; GH-BP [pmol/l] = $-4,160 + 3,427 \times$ [GH-BP in ng/ml]). When transforming plasma levels of functionally intact GH-BP into equivalent absolute levels of GH-BP, we found that the coefficient of variance between the two methods was 13.8%.

ANALYSES. All results are presented as the mean value \pm SEM. The chi-square test, Student *t* test, analysis of variance and Fisher post hoc test were applied, as appropriate. Simple, multivariate and stepwise regression analyses were performed. A p value <0.05 was considered significant. Because of skewed distribution, log-transformed values were used for statistical analyses of the ratio of IGF-I to GH (log IGF-I/GH) and for calculation of the proportion of intact GH in percent total GH. All studies were approved by the respective ethics committees, and patients gave written, informed consent.

RESULTS

Study 1. REST MEASUREMENTS OF THE GH-IGF-I AXIS. The results are shown in Table 2. When the patients with CHF were subclassified according to the presence or absence of cachexia, major differences in the measures of the GH-IGF axis were found. Noncachectic patients with CHF and control subjects did not differ. The cachectic patients with CHF, as a group, presented with the biochemical characteristics of the syndrome of acquired GH resistance. Compared with noncachectic patients with CHF, they had increased GH levels (342%, $p < 0.0001$) and immunofunctionally intact GH (229%, $p = 0.0002$). The relative proportion of immunologically functional (i.e., intact) GH

Table 2. Variables of the GH/IGF-I Axis in Healthy Control Subjects and Patients With CHF

	Control Subjects	All Patients With CHF	Noncachectic Patients With CHF*	Cachectic Patients With CHF†
Total GH (ng/ml) (n = 26/72/51/21)	1.22 ± 0.31	2.40 ± 0.47	1.20 ± 0.28	5.31 ± 1.29§/§
Intact GH (ng/ml) (n = 24/59/38/21)	0.53 ± 0.12	1.05 ± 0.20	0.58 ± 0.14	1.91 ± 0.47 /
Percent intact/total GH	55.7 (+5.9; -5.3)	47.1 (+3.2; -3.0)	55.5 (+4.5; -4.2)	35.0 (+3.0; -2.8)¶/¶
IGF-I (ng/ml)‡ (n = 26/72/51/21)	151 ± 9	142 ± 6	150 ± 8	124 ± 9#/#
IGF-BP3 (μg/ml) (n = 24/57/36/21)	3.75 ± 0.14	3.49 ± 0.12	3.70 ± 0.13	3.13 ± 0.21**/**
GH-BP (pmol/liter) (n = 24/57/36/21)	852 ± 83	823 ± 62	950 ± 84	607 ± 64#/#
log IGF-I/GH ratio (n = 26/72/51/21)	2.72 ± 0.19	2.47 ± 0.12	2.80 ± 0.14	1.68 ± 0.16 /§

Data are from study 1 and are presented as the mean value ± SEM. *Noncachectic patients with CHF had no history of weight loss; †cachectic patients with CHF had a history of weight loss >7.5% compared with previous normal weight; ‡p = 0.13 by analysis of variance; #p < 0.10; **p < 0.05; ¶p < 0.01; ||p < 0.001; §p < 0.0001 vs. control subjects and noncachectic patients with CHF, respectively (logarithmic transformation of the ratio of intact to total growth hormone resulted in asymmetric standard errors).

BP = binding protein; other abbreviations as in Table 1.

(percent total GH [IRMA test]) was reduced in cachectic patients with CHF (p = 0.0005 vs. noncachectic patients; p = 0.0012 vs. control subjects), although the total concentration of intact GH remained highest in the cachectic subgroup (Table 2). The absolute IGF-I/GH ratio was 12-fold higher in noncachectic than in cachectic patients with CHF (631 [+240; -174] vs. 48 [+21; -15], p < 0.0001). Compared with noncachectic patients, the cachectic patients showed a trend toward lower IGF-I (-17%, p = 0.06), reduced IGF-BP3 (-15%, p = 0.01) and reduced GH-BP (-36%, p = 0.005). Consequently, the IGF-I/GH ratio was markedly reduced in cachectic patients with CHF (Fig. 1A).

SUBGROUP ANALYSES. As there was considerable overlap of the IGF-I/GH ratio in cachectic and noncachectic patients, we have also analyzed the clinical characteristics of patients in the lowest tertile of the IGF/GH ratios (n = 24) compared with the remaining 48 patients with CHF (Table 3). Patients with a low IGF/GH ratio were more frequently cachectic and they had a lower peak oxygen consumption (both p = 0.006) and abnormal measures of the GH-IGF-I axis (all p ≤ 0.003), but LVEF, NYHA class and CHF etiology were similar. In addition, we assessed the characteristics of the 12 noncachectic patients with CHF with a low IGF/GH ratio (from the group of patients in the overall lowest tertile in the first comparison), and we compared these patients with the 39 noncachectic patients with normal to high IGF/GH ratios (log IGF-I/GH: 1.56 ± 0.07 vs. 3.18 ± 0.12). The noncachectic patients with a low IGF/GH ratio had higher total GH levels (4.09 ± 0.66 vs. 0.32 ± 0.08 ng/ml, p < 0.0001), but otherwise the variables of the GH-IGF-I axis were not altered (all p > 0.09). Nevertheless, these noncachectic patients had a lower BMI (24.6 ± 0.5 vs. 27.3 ± 0.6 kg/m²), and they showed signs of sympathetic activation (noradrenaline: 3.78 ± 0.63 vs.

2.43 ± 0.21 nmol/l, p = 0.026; adrenaline: 1.64 ± 0.52 vs. 0.50 ± 0.10 nmol/l, p = 0.0011), although LVEF, NYHA class and CHF etiology were similar (all p > 0.2).

CORRELATION ANALYSES. The clinical and biochemical correlates of the log IGF-I/GH ratio are detailed in Table 4. The strongest predictor of the log IGF-I/GH ratio was the GH-BP plasma concentration (Fig. 1B). In all patients with CHF, on multivariate regression analysis with seven variables—age, BMI, LVEF, NYHA class, adrenaline, noradrenaline and GH-BP—only GH-BP (standardized coefficient [SC] 0.45, p = 0.0013) and noradrenaline (SC -0.40, p = 0.011) were significantly related to the log IGF-I/GH ratio (age: p = 0.11; all other variables: p > 0.8). In a two-parameter model, GH-BP (SC 0.57) and noradrenaline (SC -0.38, both p < 0.0001) were independently related to the log IGF-I/GH ratio and jointly predicted 61% of the variation of this variable.

On multivariate analysis for the predictors of GH-BP, in all patients with CHF, percent ideal weight was predictive (SC 0.56, p < 0.0001), but noradrenaline (p = 0.13), NYHA class, age and LVEF were not (all p > 0.3). In cachectic patients, total weight loss (in percent of previous weight) also correlated with GH-BP levels (r = -0.60, p = 0.004). In cachectic patients with CHF, IGF-BP3 was closely related to GH-BP (r = 0.70, p = 0.0005; vs. noncachectic patients: r = 0.28, p = 0.10; vs. control subjects: r = 0.16, p = 0.44).

BODY COMPOSITION ANALYSES. Compared with noncachectic patients (n = 40), cachectic patients (n = 18) showed grossly reduced lean tissue content (268 ± 6 vs. 327 ± 5 g/cm height, p < 0.0001) and fat tissue content (75 ± 5 vs. 124 ± 7 g/cm, p < 0.0001). Body composition results in noncachectic patients were similar to those in control subjects (data not shown). Fat and lean tissue

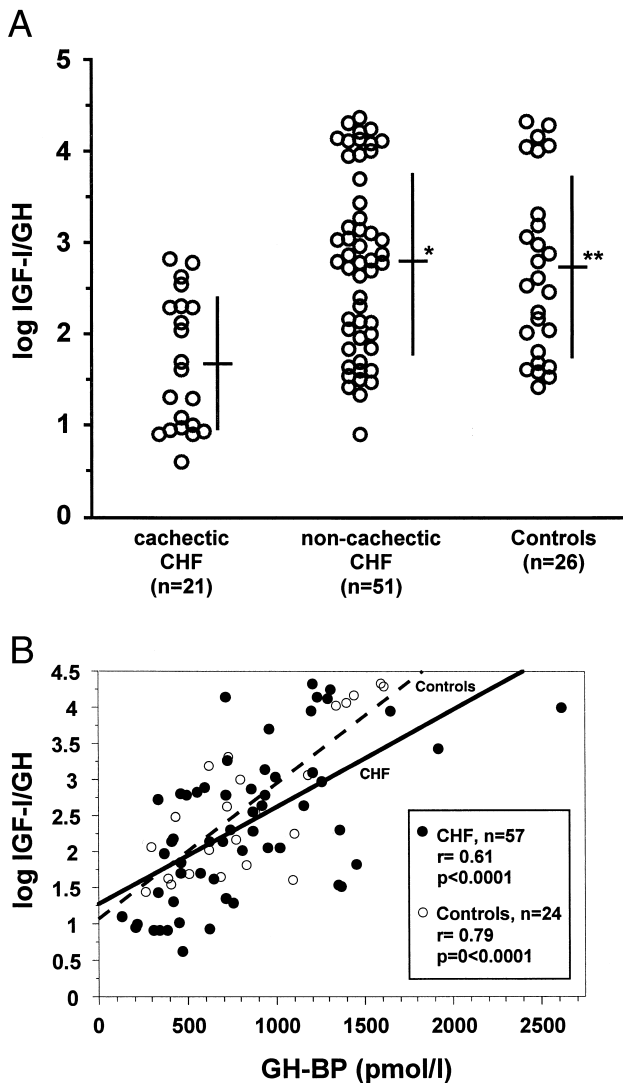


Figure 1. (A) Relationship between circulating growth hormone (GH) and insulin-like growth factor-I (IGF-I) levels (log IGF-I/GH ratio) in patients with chronic heart failure (CHF) and healthy control subjects. (B) Relationship between functionally intact GH-binding protein (BP) and the log IGF-I/GH ratio. Data are from study 1 and are presented as the mean value \pm SD. * $p < 0.0001$; ** $p = 0.0001$ vs. cachectic patients with CHF.

content correlated with the log IGF-I/GH ratio in these 58 patients with CHF (both $r = 0.45$, $p = 0.0004$). In 46 patients, body composition could be related to GH-BP levels (GH-BP vs. lean tissue content: $r = 0.44$, $p < 0.003$; GH-BP vs. fat tissue content: $r = 0.56$, $p < 0.0001$). On multivariate analysis of these 46 patients with CHF, GH-BP was related to the log IGF-I/GH ratio (SC 0.52, $p = 0.0001$) independently of the fat tissue content (SC 0.31, $p = 0.014$; adjusted joint $r^2 = 0.49$, $p < 0.0001$).

Study 2. OVERNIGHT PROFILES. In 10 patients with CHF and 9 control subjects, early morning GH (2.00 ± 0.73 vs. 1.07 ± 0.16 ng/ml, $p = 0.25$) and IGF-I levels (175 ± 17 vs. 165 ± 16 ng/ml, $p = 0.68$), as well as the log IGF-I/GH ratio (2.19 ± 0.20 vs. 2.23 ± 0.08 , $p = 0.83$), were found to be not significantly different. In overnight blood samples of these subjects, mean GH (12.45 ± 2.65 vs. $2.91 \pm$

1.20 ng/ml, $p < 0.006$), peak GH (24.42 ± 4.97 vs. 8.43 ± 1.42 ng/ml, $p = 0.009$) and the ratio of mean to peak GH ($55.1 \pm 6.2\%$ vs. $29.5 \pm 6.4\%$, $p = 0.01$) were increased in patients with CHF, whereas the nighttime mean log IGF-I/GH ratio (1.09 ± 0.16 vs. 1.94 ± 0.10 , $p = 0.0004$) was reduced in patients with CHF compared with control subjects. Only in patients with CHF were close correlations found between the morning log IGF-I/GH ratios and overnight mean and peak GH levels (Fig. 2A and B) and nighttime mean log IGF-I/GH ratio ($r = 0.78$, $p = 0.007$; vs. control subjects: $r = 0.14$, $p = 0.72$).

RESPONSE OF IGF-I TO 24-H TREATMENT WITH GH. In nine patients with CHF, intravenous infusion of 0.1 IU/kg GH over 24 h increased plasma IGF-I levels by 97 ± 18 ng/ml, from 157 ± 25 to 254 ± 28 ng/ml. Baseline GH-BP levels (mean 678 ± 38 pmol/l [range 331 to 1,367]) strongly predicted the IGF-I response ($r^2 = 0.693$, $p = 0.005$) (Fig. 2C).

Study 3. RESPONSE OF IGF-I TO THREE-MONTH TREATMENT WITH GH. In 25 patients with CHF, the baseline biochemical characteristics were GH 1.96 ± 0.26 ng/ml, IGF-I 140 ± 11 ng/ml, log IGF-I/GH ratio 2.38 ± 0.06 and absolute GH-BP 1.78 ± 0.06 pg/ml (corresponds to a mean level of functionally intact GH-BP of $1,940 \pm 206$ pmol/l). After 44 days of GH treatment, the IGF-I plasma levels were found to be increased by a mean of 123 ± 15 pg/ml ($p = 0.0001$ vs. baseline; $n = 25$), and after 96 days, the IGF-I increase, compared with baseline, amounted to 72 ± 9 pg/ml ($p = 0.0001$ vs. baseline, $p = 0.001$ vs. 44 days; $n = 24$). Baseline GH-BP levels correlated with the IGF-I increases at 44 days ($r = 0.52$, $p = 0.007$) and at 96 days ($r = 0.54$, $p = 0.006$) (Fig. 3). The baseline log IGF-I/GH ratio did not significantly correlate with the change in IGF-I levels. No other baseline clinical marker (age, NYHA class, LVEF or exercise time) correlated with the change in IGF-I levels during GH treatment (8). On multivariate analysis with these biochemical and clinical variables, only baseline GH-BP (SC -0.52 , $p < 0.01$) predicted the change in IGF-I levels during GH treatment (all other variables: $p > 0.10$).

SUBGROUP ANALYSES. From Figure 3, it appears that there were two groups of responders to GH treatment—patients with GH-BP levels < 1.6 ng/ml ($n = 8$) and patients with GH-BP levels > 1.6 ng/ml ($n = 16$). To describe these two patient groups in more detail, Table 5 is provided. Patients in the lowest tertile of GH-BP levels at baseline were similar in terms of age, NYHA class and LVEF (all $p > 0.20$) to those patients with higher GH-BP levels, but they had lower BMIs ($p = 0.024$), higher noradrenaline levels ($p = 0.02$) and lesser increases of IGF-I levels during treatment ($p < 0.004$). Although a low IGF-I response to GH treatment is related to less increase in left ventricular mass (8), GH-BP levels at baseline were not directly related to the change in left ventricular mass.

Table 3. Clinical and Biochemical Characteristics of Patients With CHF in the Lowest Tertile of the Log Ratio of IGF-I to GH, Compared With Patients in the Two Upper Tertiles in Study 1

	Patients With CHF in the Lowest Tertile of Log IGF-I/GH (n = 24)	Patients With CHF in the Second and Third Tertile of Log IGF-I/GH (n = 48)	p Value
Age (yr)	66 ± 2	59 ± 2	0.010
Weight (kg)	69 ± 2	78.8 ± 2	0.0005
Height (cm)	172 ± 1	173 ± 1	0.36
Body mass index (kg/m ²)	22.6 ± 0.5	26.2 ± 0.6	0.0003
Etiology			
CAD	14 (58%)	30 (62%)	0.73
DCM	10 (42%)	18 (38%)	
Presence of cachexia			
Yes	12 (50%)	9 (19%)	0.006
No	12 (50%)	39 (81%)	
NYHA functional class	2.8 ± 0.2	2.6 ± 0.1	0.48
LVEF	25 ± 3	28 ± 2	0.36
Peak oxygen consumption (ml/kg/min)	13.6 ± 1.2	17.9 ± 0.9	0.006
Total GH (ng/ml)	6.4 ± 1.0	0.4 ± 0.07	<0.0001
Intact GH (ng/ml)	2.47 ± 0.39	0.21 ± 0.03	<0.0001
IGF-I (ng/ml)	116 ± 8	156 ± 8	0.003
Log (IGF-I/GH)	1.34 ± 0.07	3.04 ± 0.11	—
IGF-BP3 (μg/ml)	2.87 ± 0.15	3.83 ± 0.13	<0.0001
GH-BP (pmol/l)	581 ± 86	954 ± 75	0.003

Data are presented as the mean value ± SEM or number (%) of patients.

BP = binding protein; CAD = coronary artery disease; CHF = chronic heart failure; DCM = dilated cardiomyopathy; GH = growth hormone; IGF-I = insulin-like growth factor-I; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

DISCUSSION

This study shows that the presence of cachexia in patients with CHF is linked to the biochemical pattern of acquired GH resistance. This finding is supported by the demonstration that reduced fat and lean tissue content in patients with CHF correlate with the abnormalities of the GH-IGF-I axis. Also, in the absence of cachexia, a proportion of patients with CHF appears to be hormonally resistant to GH treatment. The principal predictor of the biochemical features of GH resistance and poor biochemical response to short-term and longer term GH treatment appears to be the GH-BP plasma level. This strongly suggests that a reduction of tissue GH receptors is causal for the presence of GH resistance.

The principal concept of GH resistance in patients with CHF has been developed from data derived from a detailed cross-sectional study (study 1), and methodologically, it is supported by the analysis of GH overnight profiles (study 2). Growth hormone is secreted in a pulsatile fashion, and this may make analyses using single morning blood samples questionable. However, the results of study 2 suggest that in patients with CHF, single morning blood samples assessing the IGF-I/GH ratio may be useful to characterize the GH-IGF-I axis in patients with CHF. To prove the concept of GH resistance determining the response to GH treatment, we have presented data on 25 patients treated with GH in a controlled trial for three months (study 3 [8]). To date, this is the largest group of patients with CHF

Table 4. The Relationship of the Biochemical Marker of GH Resistance (IGF-I/GH log ratio) to Clinical and Biochemical Variables in Healthy Control Subjects and Patients With CHF*

Variable	All Subjects	Control Subjects	All Patients With CHF	Noncachectic Patients With CHF	Cachectic Patients With CHF
Age	-0.41*	-0.26	-0.45*	-0.35†	-0.26
Body mass index	0.48*	0.23	0.54*	0.37‡	0.22
Percent ideal weight	0.48*	0.23	0.54*	0.37‡	0.20
LVEF	—	—	0.04	-0.06	0.36
NYHA functional class	—	—	-0.20	-0.11	-0.49†
Peak oxygen consumption	0.21†	-0.07	0.35‡	0.28†	0.48†
IGF-BP3	0.36‡	0.06	0.43§	0.24	0.52†
GH-BP	0.65*	0.79*	0.61*	0.50‡	0.68§

*Data are from study 1. Regression coefficients of simple linear regression: *p < 0.0001, †p < 0.05, ‡p < 0.01, §p < 0.001. Abbreviations as in Table 3.

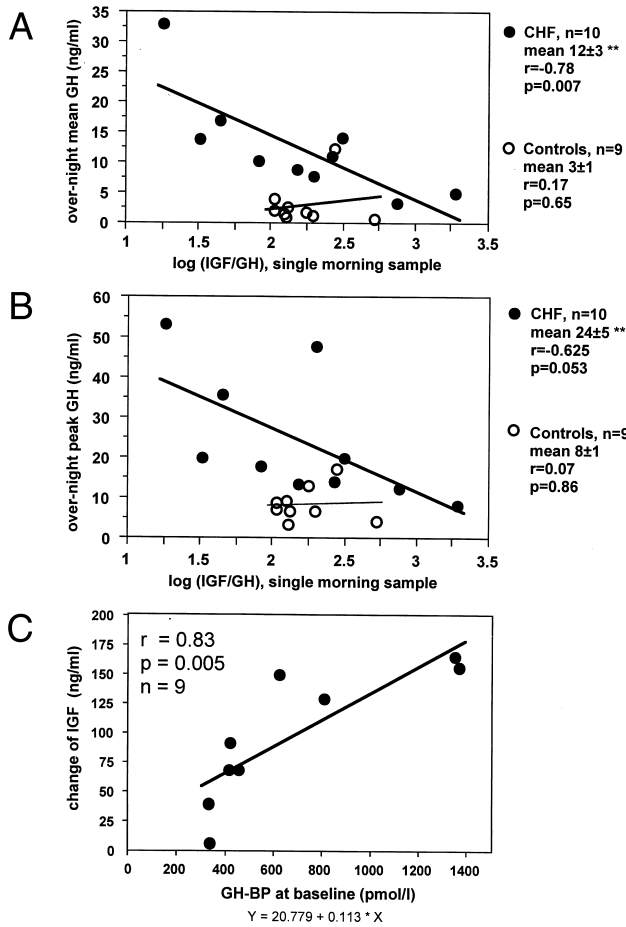


Figure 2. Relationship between the log insulin-like growth factor-I/growth hormone (IGF-I/GH) ratio (from a single sample in the morning) and mean (A) and peak (B) GH levels in 8-h overnight blood samples (study 2). ** $p < 0.01$ vs. control subjects. (C) Relationship between baseline GH-binding protein (BP) levels and the IGF-I response to GH (2 IU/day for 24 h) in nine patients with chronic heart failure (CHF) (study 2) (polynomial correlation: $r = 0.90$, $p = 0.006$).

available for such analyses. The main finding of study 3 (i.e., the direct relationship between baseline GH-BP levels and the IGF-I response to GH treatment, $p = 0.006$) was confirmed with data from study 2 (18). In this study, as well, baseline GH-BP levels strongly correlated with the changes in IGF-I levels after GH treatment (duration 24 h, $p = 0.005$).

Like resistance to the action of insulin (22), GH resistance may be a potentially important hormonal resistance syndrome in CHF. In particular, in noncachectic patients with a low IGF/GH ratio (study 1), it was interesting to note that these patients showed signs of sympathetic activation and lowered BMI, although they had not (yet) developed weight loss as a consequence. Also, the patients with low GH-BP levels and an impaired IGF-I response in study 3 had a lower BMI and higher noradrenaline levels. These noncachectic patients may be metabolically similar to cachectic patients. Potentially, the noncachectic patients with a low IGF/GH ratio are those who are at a higher risk of developing cachexia and may be (already) GH resistant.

Cardiac cachexia is independently related to impaired survival in patients with CHF (23). Interestingly, in patients with liver cirrhosis also, low IGF-I responses to GH were related to impaired survival (24).

On multivariate analyses, the main predictor of a lower IGF-I/GH ratio (as the main indicator of GH resistance) was a lower level of GH-BP. As GH-BP levels reflect the cellular GH receptor status (10,11), the development of GH resistance may be due to changes at the cellular level. These changes occur independently of age, peak VO_2 , LVEF and NYHA class, and GH resistance cannot be predicted from these conventional markers of disease severity. It could be argued that the reduced fat tissue content, by itself, in cachectic patients may contribute to a reduction of GH-BP (25), leading to a reduced IGF-I/GH ratio. However, in study 1, the relationship between GH-BP levels and the IGF-I/GH ratio was much stronger and independent of the fat tissue content in these patients. The decreased ratio of immunofunctionally intact GH to total GH in the cachectic subgroup (35% vs. 56% in noncachectic patients and control subjects) can be interpreted as further indirect evidence of a decreased GH-GH-receptor interaction in these patients, consequently leading to an increased proteolytic degradation of GH in the circulation.

Growth hormone treatment in patients with CHF. In several reviews and commentaries, the importance of GH as an active cardiovascular drug and its possible impact on treatment of patients with CHF have recently been discussed (26,27), although no clear picture emerges. In 1996, a pilot study of seven patients with CHF showed that cardiac function and exercise tolerance improved after three months of treatment with GH (14 IU/week) (5). Frustaci et al. (7) were not able to document any significant benefit of three months of treatment with GH ($n = 5$, dose 28 IU/week). Recent randomized, controlled studies investigating the effects of GH in a total group of 72 patients with CHF (2 IU/day) (8,9) have shown that GH treatment is safe, but it did not improve NYHA class, LVEF, 6-min walking time or neurohormonal status. In the larger study ($n = 50$, [8]) the only significant nonhormonal effect of GH treatment was an increase of left ventricular mass, as assessed by magnetic resonance imaging. Isgaard et al. (9) were not able to confirm this using echocardiography. Previously, hemodynamic benefit of 24-h intravenous GH infusion has been reported (18), but in randomized studies (8), this could not be confirmed. Recently, Genth-Zotz et al. (6) reported that GH treatment for three months (2 IU/day) over a period of three months significantly improved hemodynamic data, clinical status and exercise capacity in patients with ischemic cardiomyopathy. A recent study confirmed these results in patients with moderately severe CHF secondary to coronary artery disease (dose 0.02 IU/kg/day, duration 6 months [28]). If the differences between the studies are not entirely due to the placebo effect of GH treatment, the reasons for the differing results must rest with the patient groups studied, as the treatment

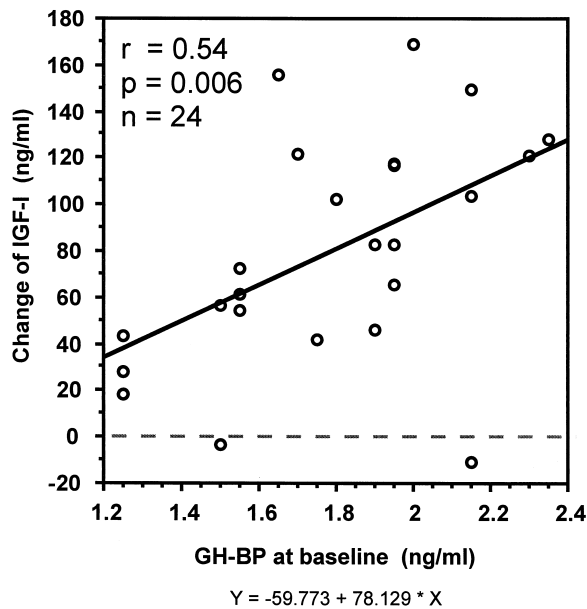


Figure 3. Relationship between growth hormone-binding protein (GH-BP) levels at baseline and biochemical (insulin-like growth factor-I [IGF-I]) response to GH (2 IU/day for 14 weeks) in 24 patients with chronic heart failure. Data are from study 3.

scheme was similar in all studies. Conventional markers of disease severity were also similar in the different trials. Therefore, the observed differences may be due to metabolic differences that may exist, but were not assessed, between patients.

Therapeutic implications. We have demonstrated that, in particular, cachectic patients, but also some noncachectic patients with CHF show the characteristics of acquired GH resistance, and this may prevent a beneficial response to GH

therapy. From our studies, it may be estimated that ~60% to 70% of cachectic patients with CHF and 20% to 30% of noncachectic patients with CHF are GH resistant. In the future, it may be considered beneficial to recruit patients for GH treatment on the basis of baseline GH-BP plasma levels, or on the basis of the first-dose IGF-I response to a test dose of GH (29). Future studies would need to prospectively determine useful cut-off values. Theoretically, there are several possibilities to overcome GH resistance in patients with CHF. First, the therapeutic dose of GH could be increased, although this is generally thought to be risky because of the many possible side effects (e.g., promotion of a diabetogenic condition, sympathetic activation or sodium/water retention and carpal tunnel syndrome) (30). Recently, the results of GH treatment using 5.3 mg (16 IU) or 8.0 (24 IU) mg/day, compared with placebo, in critically ill adults who had been in an intensive care unit for five to seven days due to cardiac surgery, abdominal surgery, multiple trauma or acute respiratory failure were reported (31). In these studies, mortality in the GH treatment group was about twofold higher than that in the placebo group. The majority of the deaths was attributable to multiple organ failure and septic shock or uncontrolled infection, and >50% of the deaths occurred in the first 10 days of treatment. It has been suggested that the outcome of these patients after GH treatment was poor, because these patients very likely did not have systemic inflammation and neurohormonal activation as a component of their disease (32). Among patients with CHF, those with cachexia clearly show the highest plasma levels of catecholamines and inflammatory cytokines (1,17).

The intensive care trials (31) did not aim to achieve

Table 5. Clinical and Biochemical Characteristics of Patients With CHF in the Lowest Tertile* of GH-Binding Protein Levels at Baseline, Compared With Patients in the Two Other Tertiles in Study 3

	Patients in Lowest Tertile of GH-BP Levels at Baseline (n = 8)	Patients in Second or Third Tertile of GH-BP Levels at Baseline (n = 16)	p Value
Age (years)	57 ± 4	53 ± 3	0.34
Weight (kg)	75.6 ± 5.6	86.6 ± 3.8	0.11
Height (cm)	175 ± 3	173 ± 2	0.61
Body mass index (kg/m ²)	24.5 ± 1.4	28.8 ± 1.1	0.024
NYHA functional class	2.6 ± 0.2	2.2 ± 0.2	0.23
LVEF	25 ± 5	27 ± 2	0.68
Noradrenaline (pg/ml)	489 ± 133	229 ± 30	0.02
Total GH (ng/ml)	1.59 ± 0.21	1.70 ± 0.16	0.69
IGF-I (ng/ml)	105 ± 21	148 ± 10	0.049
IGF-I (ng/ml), change from baseline	+41 ± 9	+100 ± 12	0.0036
Log (IGF-I/GH)	1.78 ± 0.15	1.95 ± 0.04	0.20
GH-BP (ng/ml)	1.42 ± 0.05	1.97 ± 0.05	—
Left ventricular mass	262 ± 7	228 ± 18	0.24
Increase in left ventricular mass, change from baseline	+22 ± 12	+32 ± 8	0.47

*Cut-off value for lowest tertile was 1.6 ng/ml (absolute GH-BP), corresponding to a level of 1324 pmol/l for functionally intact GH-BP (see Methods). Data are presented as the mean value ± SEM.

Abbreviations as in Table 3.

anabolic effects on lean tissue; however, this would be the aim of treating cachectic patients with CHF. The metabolic status of cachectic patients with CHF is somewhat comparable to that of patients with AIDS-associated wasting, and these patients also show the biochemical characteristics of GH resistance. In the U.S., higher dose GH therapy has been approved by the Food and Drug Administration for use in treating AIDS-associated wasting (subcutaneous injections of 4 to 6 mg/day [12 to 18 IU/day]) (33). Most common side effects include increases of tissue turgor complex and musculoskeletal discomfort (34). The experience with anabolic doses of GH in patients with CHF is very limited. Two case reports (35,36) with three cachectic patients with CHF demonstrated that short periods (1 week to 3 months) of high-dose GH therapy (70 to 98 IU/week) resulted in profound increases of muscle mass, strength and exercise capacity, with no reported side effects. Alternatively, IGF-I itself might be given; IGF-I can reverse weight loss induced by starvation (37) and can induce hypoglycemia (the immediate effectiveness of IGF compared with insulin in healthy adults is ~6% [38]) and also peripheral edema (30). This treatment approach might be considered problematic, because high IGF-I levels correlate with an increased risk of breast cancer development in premenopausal women <50 years old (but not in postmenopausal women) (39) and with the risk of prostate cancer in men (40). Nevertheless, these studies have not assessed the relationship between IGF-I and survival, which is important, because high IGF-I levels are also linked to better nutritional status (41) and improved survival in patients with severe liver disease (42). Interestingly, a study in dogs with heart failure has shown that high IGF-I levels relate to better survival (43). The combination of GH and IGF-I will have a powerful anabolic action, may overcome GH resistance and may minimize side effects (3,44). On the basis of the results of the present study, we aim to perform treatment studies in patients with cardiac cachexia similar to those done in cachectic patients with AIDS. However, the GH doses we plan to use would be ~50% below the doses used in the intensive care unit trials (31).

Study limitations. This report is a cooperative statement of the participating investigators on the relevance and significance of GH therapy and GH resistance in patients with CHF. We are aware that there are limitations to our approach of combining data from three distinct studies, but we believe this also has distinct advantages. Our studies provide circumstantial evidence. Nevertheless, we believe that the concept of GH resistance is logical, and definitive proof could only be obtained if future studies take this issue into account. Until then, we may continue to see a number of studies grossly differing in outcome. The issue of interchangeability of data from the study groups is particularly important. We have tried to establish that CHF and disease etiology were defined similarly in each study. The issues of definition and assessment of CHF were discussed, but only marginal differences were found, mainly due to availability

of resources. Blood samples were always taken in the fasting state. Some differences in analytic procedures remain. The two methods for assessing GH-BP are different; however, the results correlate well, and with both test kits, a correlation between GH-BP and the subsequent increase of IGF-I levels was found (in studies 2 and 3). In addition, the overall sample size is relatively small (particularly for study 3, although it is the world's largest available). Our results did not depend on an arbitrary definition of cachexia. Using other definitions of significant weight loss (e.g., ideal weight <90% or <85%), similar differences in the GH-IGF-I axis were found (data not shown).

Conclusions. Cachectic patients with CHF show features of acquired GH resistance. This resistance may be mediated by a reduction of GH receptors and may contribute causally to the syndrome of cardiac cachexia. Also, some noncachectic patients show GH resistance. The presence or development of GH resistance may influence the response to GH therapy. Assessment of the GH-IGF-I axis before GH administration may increase the effectiveness of this treatment approach.

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**Acquired growth hormone resistance in patients with chronic heart failure:
implications for therapy with growth hormone**

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