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Deficient Insulin-Like Growth Factor I in Chronic Heart Failure Predicts Altered Body Composition, Anabolic Deficiency, Cytokine and Neurohormonal Activation

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Background. **Recent studies of growth hormone supplementation in chronic heart failure have been associated with variable results. Acquired abnormalities of biochemical parameters of the growth hormone insulin-like growth factor I axis have been associated with severe chronic heart failure. There are suggestions of an acquired growth hormone resistance with deficient insulin-like growth factor I in some patients.**

Objectives. **Therefore, we set out to investigate the clinical and functional status and the degree of cytokine and neurohormonal alteration of chronic heart failure patients with deficient insulin-like growth factor I responses.**

Methods. **Patients with chronic heart failure were divided into two groups according to their insulin-like growth factor I levels (classified according to the manufacturer's assay range in normal controls): low insulin-like growth factor I <104 (n = 20; 89 ± 9.6 ng/ml), and normal/high >104 ng/ml (n = 32; 169 ± 52 ng/ml). Between groups there was no difference in age (low versus high: 65.3 ± 12.1 versus 61.6 ± 9.1 years, p = 0.21), body mass index, aerobic capacity (peak oxygen consumption: low versus high: 15.5 ± 5.2 versus 17.3 ± 6.3 mL/kg/min, p = 0.23), left ventricular ejection fraction, New York Heart Association classification.**

Results. **During quadriceps strength testing, patients with low insulin-like growth factor I had reduced absolute strength (−24%), and strength per unit area muscle (−14%) than patients with normal/high insulin-like growth factor I. Leg muscle cross-sectional area was lower in the low insulin-like growth factor I group (−12% and −13% for right and left legs, respectively). These alterations were accompanied by increased levels of growth hormone (+145%), tumor necrosis factor-alpha (+46%), cortisol/dehydroepiandrosterone ratio (+60%), noradrenaline (+49%) and adrenaline (+136%) (all at least p < 0.05).**

Conclusions. **Patients with low insulin-like growth factor I levels show signs of altered body composition, cytokine and neuroendocrine activation, to a greater extent than patients with normal/high levels.**

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The syndrome of chronic heart failure (CHF) has as its cardinal symptom exercise limitation. The genesis of fatigue and breathlessness is associated with abnormalities of skeletal muscle (1,2), but the origin of the skeletal myopathy is not clear. There is imbalance between catabolic and anabolic steroid metabolism (3,4) and cytokine activation (5–7), both of which appear to be related to the loss of muscle bulk and the development of cachexia in chronic heart failure. There is some evidence for the existence of a catabolic state within skeletal muscle in this syndrome (8). Abnormalities of the growth hormone insulin-like growth factor I (IGF-I) axis have been described in CHF. These include increased levels of growth hormone coexistent with inappropriately normal levels of IGF-I being associated with the presence of cachexia (4). This may suggest the development of a growth hormone-resistant state. Furthermore, growth hormone can be strikingly increased in patients with untreated heart failure (9). This may represent the early response to heart failure, with a secondary decrease in IGF-I representing a failure of the compensatory mechanism, which eventually leads to muscle wasting.

We were interested to explore further the possible relation between growth hormone, IGF-I and the development of skeletal myopathy in patients with CHF.

Methods

The research protocol was approved by the ethics committee of the Royal Brompton Hospital. Fifty-two patients were recruited for study. All had a diagnosis of CHF on the basis of symptomatic exercise limitation in the presence of objective

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Abbreviations and Acronyms

CHF	=	chronic heart failure
CSA	=	cross-sectional area
DHEA	=	dehydroepiandrosterone
GH	=	human growth hormone
IGF-I	=	insulin-like growth factor I
TNF-alpha	=	tumor necrosis factor-alpha

evidence of left ventricular dysfunction. All subjects underwent maximal exercise testing with metabolic gas exchange measurements to derive peak oxygen consumption and the slope of the ventilation, carbon dioxide production relation as an index of the ventilatory response to exercise (10,11).

Muscle measurements. Quadriceps muscle strength and fatiguability was measured by previously described methods (12,13). The subject was seated in a rigid frame, with the legs hanging freely. An inelastic strap was attached from the ankle to a pressure transducer. The recording (Multitrace 2, Lectromed, Jersey, Channel Islands) from the pressure transducer was used to assess strength and provide visual feedback to the subject. The loss of a superimposed 1-Hz muscle twitch during the plateau of maximum force production indicated that the contraction was maximal. The best of three voluntary contractions on each leg, with a rest period of at least 1 min in between, was taken to represent the maximal voluntary quadriceps muscle strength of the right and left leg, respectively.

The quadriceps fatigue protocol (13) was performed on the stronger leg after the strength test. The patients were asked to undertake repeated voluntary contractions at 30% to 40% of the maximum, using visual feedback as a guide. Contractions of 1 s were followed by 1-s relaxations for 40 s, followed by 20 s of complete rest. These series were repeated for 20 min. In the rest period after 5, 10, 15 and 20 min a maximum voluntary contraction was repeated. All values for muscle strength are presented in newtons. The fatiguability at each time point was expressed as percentage of baseline maximal quadriceps muscle strength.

Ultrafast computerized tomography (Imatron) was used in 48 patients to measure the cross-sectional area of the total thigh, the four major muscles of the thigh (quadriceps, hamstrings, gracilis and sartorius) and the femur in both legs (13). The scans were performed in the supine position after at least 5 min of rest. A single 6-mm slice was scanned transaxial at midfemur level, marked as 12.5% of patient height above the knee joint (14). The cross-sectional area (CSA) was calculated in square centimeters by semiautomatic generation of an outline of the area of interest using the console software of the computer tomography scanner. To get an estimate of the cross-sectional area of the fat tissue of the thigh, we calculated the difference between the total thigh CSA and the CSAs of the four thigh muscles and the femur combined.

Hormonal measurements. Blood samples were collected in the morning, between 9 and 10 AM, after a fasting period of 12 h. An antecubital polyethylene catheter was inserted and after supine rest of at least 20 min, 25 ml of venous blood was drawn. After immediate centrifugation aliquots were stored at −70°C until analysis. The IGF-I (Medgenix, Fleurus, Belgium, sensitivity 0.25 ng/ml), and human growth hormone (GH) (Nichols Institute Diagnostics, sensitivity 0.02 ng/ml) were measured. The IGF-I radioimmunoassay within-assay coefficients of variation at concentrations of 54, 194 and 491 ng/ml were 6.1%, 4.1% and 4.7%; between-assay coefficients of variation were 9.9%, 9.6%, and 9.3% at concentrations of 121, 251 and 494 ng/ml. The GH immunoradiometric assay within-assay coefficients of variation at concentrations of 1.4, 6.0 and 12.2 μg/liter were 4.2%, 2.9% and 2.8%; between-assay coefficients of variation were 7.2%, 3.5% and 4.6%, respectively. Adrenaline and noradrenaline were measured using high power liquid chromatography (sensitivity 0.1 ng/ml for both). Tumor necrosis factor-alpha (TNF-alpha) was measured using an ELISA assay with a lower limit of detectability of 3.0 pg/ml (Medgenix, Fleurus, Belgium). Cortisol was measured using an enzyme-linked immunosorbent assay (Boeringer Mannheim, Germany) and dehydroepiandrosterone (DHEA) was measured by radioimmunoassay with a lower limit of detectability of 0.04 ng/ml (DPC).

Statistical analysis. Patients were dichotomized on the basis of their IGF-I levels into a group with low IGF-I (n = 20) and a group with high or normal IGF-I (n = 32) according to the manufacturer's normal range, which was in keeping with the lowest level measured in a normal subject in our laboratory of 104 ng/ml. Data are presented as mean ± standard deviation. Between group comparisons were made using Student's unpaired *t* test. Some of the data were log transformed before analysis to form a normal distribution. Normality was assessed by the Kolmogorow–Smirnoff test. We also performed univariate correlation analyses to establish the relationship between variables.

Results

There was no significant difference between the two groups of patients in age, body mass index, degree of left ventricular dysfunction as assessed by ejection fraction or exercise capacity (Table 1). The average daily dose of diuretic was 100.5 mg of frusemide (where 1 mg of bumetanide was assumed equivalent to 40 mg of frusemide) in the low IGF-I group and 119 in the normal IGF-I group. Respectively, in the low and normal IGF-I group, 15 and 25 patients were receiving angiotensin-converting enzyme inhibitors. A total of 21 patients were receiving digoxin, 16 amiodarone and 15 nitrates or other vasodilators. There were no significant differences in drug use between the two groups. Average creatinine was 133 ± 56 μmol/L and this did not differ between the two groups. There was no difference between the two groups in the presence of cachexia as previously defined (4) (9 of 20 in the low IGF group; 9 of 32 in the normal IGF-I group).

Muscle function. The low IGF-I group had a lower quadriceps muscle strength in the stronger leg (−24%). Cross-sectional muscle area at midfemur was lower in the low IGF-I

Table 1. Characteristics of the Two Patient Groups

	Low IGF-I (n = 20)	High/Normal IGF-I (n = 32)
IGF-I (ng/ml)	89.2 (9.6)	169.2 (52.0)
Age (yr)	65.3 (12.1)	61.6 (9.1)
BMI (kg/m^2)	24.6 (4.9)	25.1 (2.7)
Peak Vo_2 (ml/kg/min)	15.5 (5.2)	17.3 (6.3)
V_E/Vco_2 slope	38.9 (14.7)	37.2 (14.3)
LVEF (%)	29.5 (17.4)	26.6 (15.2)
NYHA	2.6 (0.6)	2.8 (0.9)

BMI = body mass index; peak Vo_2 = peak oxygen consumption; V_E/Vco_2 = slope of the relation between ventilation and carbon dioxide production; LVEF = left ventricular ejection fraction by radionucleide ventriculography; NYHA = New York Heart Association classification of symptoms in chronic heart failure. None of the differences is significant; $p > 0.2$.

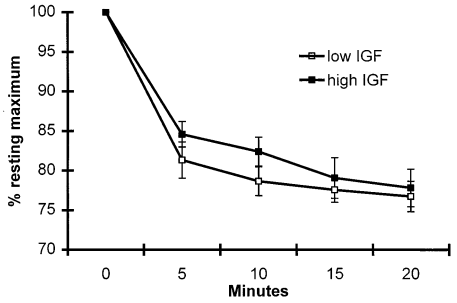


Figure 1. Fatigue testing. Muscle strength is expressed as proportion of the initial maximal contraction (i.e., 100% at rest). Measurements were repeated at 5, 10, 15 and 20 min of the fatigue protocol (see text for details). There was no significant difference between the two groups. Error bars are shown as the SEM for clarity.

group (right leg, 12%; left leg, 13%) (Table 2). Muscle strength corrected for bulk (using CSA) was thus still lower in the low IGF-I group (−14%). Fat formed a higher proportion of the total leg CSA in the low IGF-I group. Muscle strength during fatigue testing decreased by the same proportion and at the same rate in both groups (Fig. 1), although strength was at a lower absolute level in the low IGF-I group throughout.

Neurohormonal activation. There were higher levels of catecholamines (noradrenaline +49%; adrenaline +136%), TNF (+46%) and GH (+145%) in the low IGF group (Tables 3 and 4). There were no significant differences in the absolute levels of cortisol and DHEA, but the ratio (used as an index of catabolic:anabolic steroid ratio) was higher in the low IGF group (+60%). The IGF-I-to-GH ratio was lower in the low IGF-I group (−78%), suggesting that there is some degree of GH resistance in the low IGF-I group. There was no difference in liver function between the two groups as represented by aspartate transaminase (28.9 [13.1] IU/l in the low IGF-I group versus 25.8 [6.9]).

Correlations with IGF-I. There were no significant correlations between IGF-I and exercise variables, or with muscle variables other than a weak negative relationship between IGF-I and the fat-to-muscle ratio on computed tomographic scanning ($r = -0.35$; $p < 0.01$), that is, the lower the level of IGF-I, the higher the ratio of fat to muscle in the leg. There was a relationship between the IGF-I-to-GH ratio and body mass index ($r = -0.58$; $p < 0.001$; Fig. 2). Levels of IGF-I did not correlate with GH levels or with TNF.

Growth hormone levels correlated with noradrenaline and adrenaline ($r = 0.65$, $p < 0.001$ and $r = 0.56$, $p < 0.001$, respectively; Fig. 3) and with the levels of cortisol ($r = 0.51$; $p < 0.001$). There was a negative relation between the IGF-I-to-GH ratio and the cortisol-to-DHEA ratio ($r = -0.5$; $p < 0.001$) (Fig. 4).

There was a negative relation between TNF levels and muscle bulk as measured by CSA ($r = -0.44$; $p < 0.001$) and strength ($r = -0.37$; $p = 0.007$).

Table 2. Results of Muscle Testing

	Low IGF-I (n = 20)	High/Normal IGF-I (n = 32)
Strength (N)	311 (91)	410 (124)*
Leg CSA (cm^2)	163.6 (48.8)	165.3 (28.8)
Muscle CSA (cm^2): right	100.1 (23.9)	114.0 (20.6)†
Muscle CSA (cm^2): left	95.6 (24.4)	109.9 (21.4)†
Fat CSA (cm^2)	56.9 (30.6)	46.0 (12.0)
Strength/CSA (N/cm^2)	5.99 (0.98)	6.94 (1.02)‡
Fat/muscle	0.56 (0.24)	0.41 (0.10)*

CSA = cross sectional area. The difference between the two groups in fat CSA did not reach statistical significance ($p = 0.07$). Fat/muscle is the relative proportion of fat and muscle on computerized tomography scanning at midfemur. Tomography was available for 48 patients (4 missing from the normal/high IGF-I group). Unless otherwise stated, data for the stronger leg are shown. †$p < 0.05$; *$p < 0.01$; ‡$p < 0.005$.

Table 3. Results of Neuroendocrine Assays

	Low IGF-I (n = 20)	High/Normal IGF-I (n = 32)
Arrhytmetic Mean ± Standard Deviation		
GH (ng/ml)	4.2 (6.1)	1.3 (2.6)*
TNFα (pg/ml)	13.7 (12.3)	8.4 (5.7)*
Noradrenaline (nmol/liter)	4.9 (3.0)	3.3 (2.1)*
Adrenaline (nmol/liter)	2.3 (2.1)	0.9 (1.2)†
Cortisol (nmol/liter)	406.8 (81.6)	422.0 (108.5)
DHEA (nmol/liter)	7.7 (7.3)	10.5 (5.9)
IGF-I:GH	1,738.4 (3,517.0)	3,414.5 (6,251.3)*
Cortisol:DHEA	104.7 (88.0)	55.7 (39.1)†
Geometric Mean ± Asymetric Standard Deviation		
GH (ng/ml)	0.71 (0.05–9.46)	0.29 (0.04–2.23)
TNFα (pg/ml)	9.94 (4.14–23.67)	6.83 (3.37–13.86)
Noradrenaline (nmol/liter)	4.00 (2.06–7.75)	2.69 (1.45–4.98)
Adrenaline (nmol/liter)	1.37 (0.43–4.42)	0.58 (0.26–1.27)
DHEA (nmol/liter)	5.52 (2.44–12.46)	9.09 (5.15–16.05)
IGF-I:GH	124.8 (9.17–1699.95)	557.51 (71.97–4318.98)
Cortisol:DHEA	72.12 (27.80–187.11)	44.94 (23.65–85.39)

The geometric mean together with asymetric standard deviations for those variables log-normally distributed. GH = human growth hormone; TNFα = tumour necrosis factor-alpha; DHEA = dehydroepiandrosterone. *$p < 0.05$; †$p < 0.01$.

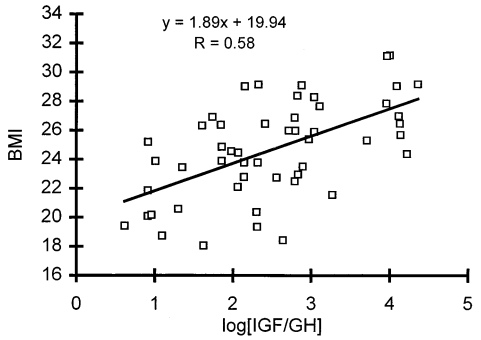


Figure 2. The relation between IGF-I and GH and body mass index (BMI).

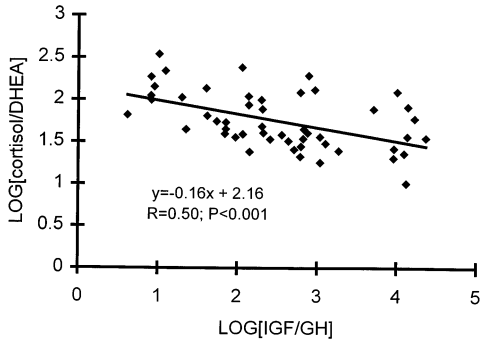


Figure 4. The relation between corisol-to-DHEA ratio and IGF-to-GH ratio.

Discussion

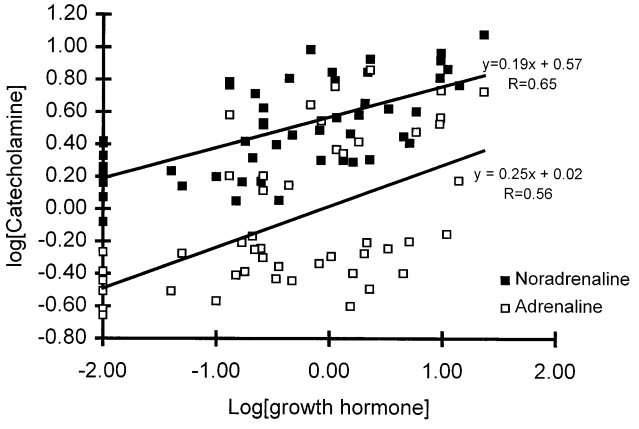
Loss of muscle bulk happens early in the course of CHF (15) and the development of cachexia is an adverse prognostic feature (16). The origin of the weight loss is not clear, but recent studies have drawn attention to the potential importance of neurohormonal and immune activation. Tumor necrosis factor is elevated in CHF (5,6); there is an increase in the ratio between circulating levels of catabolic and anabolic steroids (3), and an insulin-resistant state develops (17,18). The resting metabolic rate of patients with heart failure is increased (19) and resting leg oxygen consumption has been shown to be increased (8).

Growth hormone is secreted by the anterior pituitary, and mediates its major metabolic effects through activation of somatomedins, predominantly IGF-I (20,21). Levels of GH can be greatly elevated in untreated heart failure (9) and we have found elevated levels in patients with cardiac cachexia (4). Paradoxically, perhaps, there is some evidence for a beneficial effect in patients with heart failure from the exogenous treatment with GH (22), although other investigators have found the converse (23). This suggests that there may be a group of patients who are not "sensitive" to GH, who are GH resistant.

This group of patients might be expected to have low levels of circulating IGF-I and elevated levels of GH. Therefore, we studied a group of patients intending to characterize those patients with low IGF-I levels. The lower level of IGF-I is not related to abnormal liver function, as transaminase levels were the same in the two groups.

We have found these patients to have a higher level of circulating GH, giving some support for the GH resistance hypothesis, and higher levels of neuroendocrine activation. In addition, these patients had a higher catabolic-to-anabolic steroid ratio. Previously, we have reported an alteration in the cortisol-to-DHEA ratio with relative catabolic steroid excess in heart failure (3) and the present report suggests a relationship between this and the apparently independent GH and IGF-I systems. The relationship may be underestimated in the present report; GH levels peak at night and thus we may have underestimated the abnormalities in IGF-I-to-GH ratio. The pathophysiologic link between the two systems is not known, but warrants further investigation.

Figure 3. The relation between levels of catecholamines and growth hormone.



The low IGF-I group of patients had a reduced muscle strength, even after correction for muscle bulk, and there was a direct relationship between the degree of GH sensitivity, as represented by the IGF-I-to-GH ratio, and body mass index. Furthermore, although leg CSA was unchanged in the low IGF-I group, there was a reduction in muscle CSA and an increase in the ratio of fat to muscle in the leg. These findings suggest a possible role for GH resistance in the development of muscle loss in CHF. Additional mechanisms for muscle catabolism include insulin resistance (17,18). Growth hormone can enhance sympathetic activation (24). It may be that as IGF-I levels decline, GH increases and sympathetic activation is augmented.

Insulin-like growth factor and apoptosis. The decline in IGF-I levels may itself be deleterious. The IGF-I promotes tumor growth (25,26), an effect mediated through the IGF-I receptor (27). A decrease in the number of IGF-I receptors is associated with massive apoptosis in some tumor models, and overexpression of IGF-I protects cells from apoptosis (28,29). Antibodies against the IGF-I receptor (30,31) or the induction of IGF-I receptor mutant (32) also inhibit tumor growth. The frequency with which apoptosis is seen in tissue samples is increased in CHF (33,34). It may be that in heart failure as IGF-I levels decline, a protective factor is removed allowing apoptosis of skeletal muscle cells and muscle.

Insulin-like growth factor and cytokines. The TNF levels were significantly higher in patients with low IGF-I levels than in those with normal to high levels, and were also inversely correlated with muscle bulk. The TNF-induced cell killing is prevented by IGF-I alone (35). Furthermore, embryonic fibroblasts derived from mice with targeted disruption of the IGF-I receptor showed a marked sensitivity to TNF, which was not observed in fibroblasts derived from wild-type littermates. There may be a link between loss of muscle bulk and low IGF-I levels in patients with CHF.

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