Plasma insulin-like growth factor-1 elevated in mild-to-moderate but not severe heart failure

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Background Insulin-like growth factor 1 (IGF-1) promotes favorable cardiac remodeling in heart failure. However, the relation of plasma IGF-1 in patients with various degrees of heart failure is not known.

Methods Venous plasma samples were collected from patients with clinically documented heart failure (n = 24) and from control subjects (n = 21) for measurements of IGF-1 levels. In the heart failure group, functional assessment of the physical capacity was determined by means of the New York Heart Association (NYHA) score. Objective determination of ventricular performance was made by transthoracic echocardiographic measurement of left ventricular fractional shortening (FS).

Results IGF-1 levels were higher in patients with heart failure (mean age, 67 ± 2 years; 17 men) than in control subjects (age, 71 ± 2 years; 9 men) (20.2 ± 2 mU/L, 14.1 ± 2 mU/L, respectively, P < .05). However, the elevated IGF-1 levels were demonstrated only in patients with mild-to-moderate symptoms (NYHA classes I and II) of heart failure (24.7 ± 3.3 mU/L, n = 12, P = .005 vs control subjects) but not in patients with severe symptoms (NYHA classes III and IV) (15.7 ± 2.3 mU/L, n = 12). There was a strong positive correlation between IGF-1 levels and left ventricular FS (%) (r = 0.58, P = .003, n = 24). Adjustments for other potential confounders including age, sex, treatment received, and underlying cause of heart failure did not alter the relation between IGF-1 and left ventricular FS (odds ratio, 2.01; 95% confidence interval, 1.26 to 6.24; P = .01).

Conclusions Plasma levels of IGF-1 show distinct variations with the severity of heart failure and may play a vital role in compensated heart failure. (Am Heart J 2001;142:E10.)
Methods

Subjects

Patients with clinically documented chronic heart failure were recruited for the study with the approval of the local ethics committee at Charing Cross Hospital, London, UK. Full clinical details were recorded for all patients including history of the cardiovascular illness and the treatment received. Limitation of physical capacity by breathlessness was assessed for each individual patient by means of the New York Heart Association (NYHA) score for heart failure. Patients were excluded if the symptoms were of acute onset (<6 weeks) or were preceded by an acute coronary event within 6 weeks of assessment. Patients were also excluded if a concomitant endocrinologic, pulmonary, or renal disorder was present. Cardiomyopathy was diagnosed in the absence of a specific cause for heart failure, including ischemic heart disease, hypertension, valvular heart disease, or myocarditis.

All patients with a diagnosis of heart failure had a transthoracic echocardiography assessment of left ventricular performance; two examiners who were blinded to the results of the study cross-checked this independently. Parasternal long-axis views were recorded at the level of the tip of the mitral valve leaflets. Superimposed electrocardiographic recordings were used to determine left ventricular dimensions in end-systole and end-diastole. Left ventricular fractional shortening was then estimated by the equation LVD – LVS/LVD × 100, where LVD is left ventricular diameter in end-diastole and LVS is left ventricular diameter in end-systole.

Control group

Because of the possibility of both GH and IGF-1 responses to stress, it was important to have a control group subjected to the same hospital environmental factors as the patients with heart failure. Patients with no history of cardiovascular illness, shortness of breath, or renal, hepatic, or endocrine disease were recruited from the hospital outpatient departments. All control patients had a chest radiograph (independently reported by radiologists at the same hospital). Patients with a cardiothoracic ratio of >0.5 were excluded.

Protocol

Venous blood samples were collected for all individuals from an antecubital vein in a sitting or lying position by means of a Vacutainer method into bottles containing lithium-heparin anticoagulant (Becton Dickinson, Meylan Cedex, France). All sampling was performed between 9 AM and 2 PM. Within 1 hour of collection, plasma was separated by 3000 g centrifugation at –4°C. Plasma was then stored at –20°C, pending batch analysis.

Biochemical assays

GH levels were determined with the use of an automated ELISA method (Boehringer Mannheim ES700); IGF-1 concentrations were measured with an extraction and radioimmunoassay procedure.

Statistical analysis

Results are summarized throughout the text and figures as mean ± standard error of the mean. Group comparisons were made by nonparametric methods; Mann-Whitney test for 2 groups, and analysis of variance (Kruskal–Wallis H) for more than 2 groups. Nonparametric correlations between variables were performed with the Spearman-rank method and correlation coefficients (r). The association of IGF-1 levels with other potential confounders were examined in a multivariate linear regression model with IGF-1 as the dependent variable. All reported probability values are 2-sided. Analyses were performed with the use of SPSS for Windows (SPSS Inc).

Results

The basic characteristics of the heart failure group are shown in Table I.

Table II illustrates the absence of significant differences in either IGF-1 or GH levels in patients with heart failure, based on the underlying cause or treatment.
received. However, left ventricular fractional shortening was lower in patients with cardiomyopathy than in patients with ischemic heart disease (IHD) \( (P < .05) \). In addition, patients who were receiving ACEI treatment tended to have a more severe impairment of left ventricular function.

The control patients \( (n = 21; 9 \text{ men}; \text{mean age, 71} \pm \text{2 years}) \) were age- and sex-matched to the patients with heart failure. The cause for hospital presentation of the control group was as follows: 5 patients had chest infection, 13 had musculoskeletal pain, 2 had urinary tract infection, and 1 patient had deep-vein thrombosis.

IGF-1 levels were significantly higher in patients with heart failure than in the control group \( (20.2 \pm 2 \text{ mU/L}, 14.1 \pm 2 \text{ mU/L}, \text{respectively}; P < .05; \text{Figure 1}) \). GH levels were not different between the two groups \( (3.1 \pm 0.8 \text{ mU/L} \text{ and } 3.5 \pm 0.8 \text{ mU/L}, \text{respectively}) \).

Categorizing the patients with heart failure by the NYHA classification revealed patients with milder symptoms (NYHA classes I and II) having a prominent elevation of IGF-1 \( (24.7 \pm 3.3 \text{ mU/L}, n = 12) \) over the control group \( (14.1 \pm 2 \text{ mU/L}, n = 21; P < .005) \). In contrast, patients with more severe symptoms (NYHA classes III and IV) had IGF-1 levels \( (15.7 \pm 2.3 \text{ mU/L}, n = 12) \) that were not different from the control group (Figure 1).

Further analysis of the relations between IGF-1 and the degree of myocardial impairment was sought by correlation analysis. Figure 2 illustrates a strong positive correlation between IGF-1 levels and left ventricular fractional shortening \( (r = 0.58, P = .003, n = 24) \). No correlation was noted between GH levels and fractional shortening \( (r = -0.14, P = .5) \). Adjustments for other potential confounders including age, sex, treatment received, and underlying cause of heart failure did not alter the relation between IGF-1 and left ventricular fractional shortening \( (P = .01; \text{odds ratio, 2.01; 95% confidence interval, 1.26 to 6.24; Table III}) \).

Categorizing the patients with heart failure by the degree of myocardial impairment determined by fractional shortening estimation further confirmed the split of IGF-1 levels in the patients with heart failure. Mild-to-moderate impairment of left ventricular function (fractional shortening >10) was associated with a significantly higher IGF-1 level \( (23.5 \pm 2.2 \text{ mU/L}, n = 19) \) when compared with the control group \( (n = 21, P < .001) \) or with the patients with severe impairment of left ventricular function (fractional shortening <10; 8.3 \pm 2.5 \text{ mU/L}, n = 5, P < .0001; Figure 3). GH levels did not differ between those groups \( (2.9 \pm 0.8 \text{ mU/L}, 3.4 \pm 0.8 \text{ mU/L}, \text{and } 5.4 \pm 2.4, \text{mU/L, respectively}) \).

**Discussion**

The main finding in this study is the inverse relation observed between IGF-1 levels and the severity of heart failure determined by both clinical assessment and by left ventricular contractile performance. The latter defined more clearly a group with left ventricular fractional shortening of <10% as having significantly lower IGF-1 levels than patients with high fractional shortening. The finding of low IGF-1 levels in severe heart failure was also reported by Anker et al \( ^{12} \) in patients with cachetic heart failure; however, our study is the first
to examine variations of IGF-1 in a range of patients with heart failure with varying severity.

Although disease progression from mild-to-moderate to severe heart failure may be multifactorial and poorly understood, our data suggest that IGF-1 may be implicated in this process. Recent communication by Serneri et al. suggested that participation by IGF-1 in left ventricular hypertrophy is selectively related to both the type of hemodynamic overload and to ventricular function. They reported undetectable levels of IGF-1 in the coronary sinus of patients with end-systolic ventricular wall stress of >90 kdyne/cm². Our data are consistent with their findings; however, it is important to mention that neither our study nor the other mentioned studies establish a cause-and-effect relation between severity of heart failure and IGF-1 levels. Nevertheless, on the basis of the evidence available thus far, it may be possible to speculate that progression of disease from compensated to decompensated heart failure may be partly influenced by myocardial ability to generate IGF-1 for the purpose of promotion of specific myofibril hypertrophy and modulation of surviving myocardial cell growth. Further larger-scale studies will be needed to validate this hypothesis.

IGF-1 is a mediator of GH at the tissue level. It was previously thought that IGF-1 is synthesized in the liver in response to GH stimulation. Although this concept may still hold true, new evidence has shown that IGF-1 is also synthesized in a wide range of tissues including myocardial tissue. The extrahepatic source of IGF-1 appears to be largely independent from GH stimulation. In the heart, hemodynamic overload or ischemic injury is associated with increased local generation of IGF-1. The relative contribution of either hepatic or extrahepatic sources of the measured plasma levels of IGF-1 is not known; therefore, our measurements of plasma IGF-1 may reflect the combined variations of both sources of IGF-1. Heart failure of any cause is associated with changes in the hemodynamic load on the left ventricle; changes in wall stress also influence the remodeling of the left ventricle after myocardial injury. In animal models, both of these influences have been shown to increase local myocardial IGF-1 receptor expression and synthesis. How these changes are reflected in the total plasma IGF-1 concentration is not known. In our study, GH levels showed very little variation between the various degrees of heart failure. This would suggest that the observed elevations in IGF-1 in patients with heart failure are from a source that synthesizes IGF-1 independent from GH influence, for example, local myocardial source.

Angiotensin II is a potent inhibitor of local IGF-1 synthesis; it has therefore been suggested that ACEI exert their beneficial effect at least in part by enhancing local IGF-1 formation, thereby improving myocardial contractile performance. However, our study did not show significant variations in IGF-1 levels between patients.

### Table III. Multiple linear regression analysis of IGF-1 (dependent variable) with other variables

<table>
<thead>
<tr>
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<th>Unstandardized coefficients</th>
<th>Standardized coefficients</th>
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<td></td>
<td>B</td>
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<tr>
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<td>Fraction shortening (%)</td>
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</table>

Treatment refers to patients receiving ACEI.

### Figure 3

Plasma IGF-1 levels in patients with heart failure (n = 24) grouped by left ventricular fractional shortening compared with control group (n = 21). ANOVA, Analysis of variance.
who are receiving ACEI and those who were not receiving the medication. This could partly be explained by the possibility of ACEI to normalize IGF-1 expression in those patients who otherwise would have low IGF-1 expression.

We conclude that plasma IGF-1 levels show distinct variations with severity of heart failure and may play a vital role in compensated heart failure.

References