SCIENTIFIC LETTER

Insulin-like growth factor-binding proteins 2 and 3 are independent predictors of a poor prognosis in patients with dilated cardiomyopathy

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Growth hormone and its mediator insulin-like growth factor 1 (IGF1) exert various actions on the growth and proliferation of myocardium and many other cell types. IGF1 is predominantly bound to at least six binding proteins (IGFBP1–6). Growth hormone is the major hormonal factor controlling IGF1 and IGFBP concentrations. Tissue concentrations, bioavailability and effects of IGF1 are regulated by modifications of IGFBP affinities through proteolysis, phosphorylation and binding to cell surfaces.[1]

In a failing myocardium, growth hormone and IGF1 improve cardiac haemodynamics, normalise the calcium homoeostasis and support an efficient myocardial energy metabolism.[2] However, analyses of the IGF1 serum levels in patients with congestive heart failure (CHF) from different causes showed increased as well as unchanged levels. Furthermore, despite improvements of cardiac function in several small open growth hormone-substitution studies, these effects could not be confirmed in two large randomised double-blind studies.[2] Nevertheless, we observed a marked increase of the left ventricular ejection fraction in patients with a pronounced increase of IGF1 serum levels during recombinant human growth hormone treatment.[3] Thus, we assume that the growth hormone/IGF-system is differently altered in patients with CHF due to different causes and might influence the course of the disease.

METHODS

We examined 90 patients with idiopathic dilated cardiomyopathy between 1992 and 1997 after exclusion of secondary forms and diseases, that influence the growth hormone system. The follow-up period ended on 1 October 2000. The end point was death or cardiac transplantation. Additionally, we selected 90 healthy controls matched for sex, age and body mass index (BMI).

Blood samples were taken in the early morning in supine position after 12 h of fasting and rest. The serum levels for IGF1, IGF2, IGFBP2, IGFBP3, growth hormone and growth hormone binding protein were determined by specific radioimmunoassays (Mediagnost, Tuebingen, Germany). IGFBP1 serum levels were measured with an immunoradiometric assay (IRMA, DSL, London, UK).

Data are expressed as median (25th–75th centiles); $p<0.05$ was considered significant. Comparisons between groups were performed with the Mann–Whitney U test and the χ^2 test. We used the Kaplan–Meier technique and the Cox proportional hazards analysis for survival analyses. Patients were stratified according to cut-off values determined by generating receiver operating characteristic curves. We compared the survival curves with the log rank test. All data were analysed with StatView V.4.5 and MedCalc V.7.5 (MedCalc Software, Belgium).

RESULTS

A total of 23 (25.6%; 21 men and 2 women) of the 90 patients died and 4 patients underwent cardiac transplantation (4.4%; 2 men and 2 women). We found no significant differences for age, sex and BMI, but a more severe stage of heart failure in non-surviving patients. Furthermore, we observed significantly lower IGF2 (499 (421–575) vs 556 (498–608) ng/ml; $p = 0.03$) and IGFBP3 (2700 (2311–3026) vs 2877 (2478–3645) ng/ml; $p = 0.05$) as well as higher IGFBP1 (30 (24–50) vs 24 (15–35) ng/ml; $p = 0.02$) and IGFBP2 (372 (235–651) vs 276 (175–397) ng/ml; $p<0.01$) serum levels for non-surviving patients. We found no correlations between the drugs for CHF and the serum levels of growth hormone, IGF or IGFBPs.

Survivors had significantly higher IGF1 values than controls (141 (123–168) vs 123 (96–147) ng/ml; $p<0.001$), whereas non-surviving patients had similar IGF1 levels (126 (107–168) ng/ml; p = NS). For IGFBP2, we observed significantly lower levels in survivors (276 (175–397) vs 423 (229–576) ng/ml; $p<0.001$), but no differences between non-survivors and controls (372 (235–651) ng/m; p = NS). By contrast, the IGFBP3 levels significantly declined from controls to survivors and to non-survivors (3258 (2772–3792) vs 2877 (2478–3645) vs 2700 (2311–3026) ng/ml; $p = 0.02$ and $p = 0.05$).

We defined a multivariate Cox proportional hazards model which included clinical parameters that were significant in univariate analysis, and controlled this model for age, sex and BMI. Owing to colinearities between the factors of the growth hormone-system, we manually included the parameters into the model. IGF2, IGFBP2 or IGFBP3 alone as well as IGFBP2 combined with IGFBP3 were independently associated with a poor prognosis.

We stratified the patients with dialated cardiomyopathy according to optimal cut-off values. Probands with serum levels below the IGF2 and IGFBP3, as well as above the IGFBP1 and IGFBP2 cut-off values had an approximately three times higher risk of death (table1).

Interestingly, we observed high death rates within the lowest IGF1 quartile (1st quartile $\leqslant$112 ng/ml, 47.8%; 2nd quartile $\leqslant$139.0 ng/ml, 20.8%; 3rd quartile $\leqslant$169 ng/ml, 22.7%; 4th quartile >169 ng/ml, 28.6%). Furthermore, we observed a 2.6 times higher risk of death for patients with IGF1 serum levels <116 ng/ml ($p<0.01$).

DISCUSSION

We present the first study to demonstrate that low IGF1 and IGFBP3 levels and high IGFBP2 levels are associated with a

Abbreviations: BMI, body mass index; CHF, congestive heart failure; IGF, insulin-like growth factor; IGFB, insulin-like growth factor-binding protein.

Table 1 Hazard ratios (log rank test) after stratification of patients according to cut-off values determined by receiver operating characteristic-analysis

Variable	Cut-off value (ng/ml)	Sensitivity (%)	Specificity (%)	AUC (95% CI)	n (death %) < cut-off	n (death %) > cut-off	HR (95% CI)	p Value
IGF1	⩽116	48.1	81.0	0.57 (0.46 to 0.68)	25 (52)	65 (21.5)	2.6 (1.2 to 5.6)	<0.01
IGF12	⩽501	55.6	73.0	0.65 (0.54 to 0.75)	32 (46.9)	58 (20.7)	2.5 (1.2 to 5.3)	0.02
IGFBP1	>22.6	81.5	47.6	0.66 (0.55 to 0.76)	35 (14.3)	55 (40)	3.2 (1.2 to 8.5)	0.01
IGFBP2	>449	48.1	84.1	0.70 (0.60 to 0.80)	67 (20.9)	23 (56.5)	3.0 (1.4 to 6.3)	<0.01
IGFBP3	⩽2401l	44.4	81	0.63 (0.52 to 0.73)	24 (50)	66 (22.7)	2.8 (1.3 to 5.9)	0.01

AUC, area under the curve; IGF, insulin-growth factor; IGFBP, insulin-like growth factor-binding protein

worse prognosis in patients with CHF due to idiopathic dilated cardiomyopathy.

Growth hormone and IGF1 positively influence myocardial hypertrophy, calcium homeostasis and energy demand in heart failure.[2] However, in advanced stages of CHF, a reduced myocardial IGF1 expression could be shown.[4] Therefore, we assume an increased need for local myocardial IGF1. In survivors of our study, this might be compensated by an increased systemic IGF1 expression. In non-survivors, the levels were not different from controls. In these cases, the decreasing myocardial IGF1 reservoir might partly be compensated by an increased proteolysis of IGFBP3 and by a shift towards binary complexes composed of IGF1 and IGFBP2. These complexes improve the diffusion of IGF1 from circulation into tissue, and IGF1 is predominantly bound to binary complexes in tissue.[1] If these compensatory mechanisms are not sufficient for myocardial IGF1 supplementation, this will eventually promote the death of further cardiomyocytes. IGFBP2 is the major binding protein for IGF2. We assume that IGF2 is displaced by IGF1 and degraded. This will explain the relationship between low IGF2 levels and a worse prognosis.

The lack of increased IGF1 levels in non-survivors could either be due to an impaired growth hormone secretion or to a peripheral growth hormone-resistance. We are not able to determine the exact cause because we did not analyse the 24 h growth hormone secretion profiles.

Large prospective trials with serial laboratory and clinical analyses, regular 24 h growth hormone secretion profiles and stimulation tests should be performed to further elucidate the changes of the growth hormone system in the course of heart failure of different aetiologies. This might identify patients who could benefit from a treatment that modifies the growth hormone system.

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