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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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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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/ml; 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).

DISCUSSION

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

Abbreviations: BMI, body mass index; CHF, congestive heart failure; IGF, insulin-like growth factor; IGFB, 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. However, in advanced stages of CHF, a reduced myocardial IGF1 expression could be shown. 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. 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.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cut-off value (ng/ml)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC (95% CI)</th>
<th>n (death %)</th>
<th>n (death %)</th>
<th>HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF1</td>
<td>&lt;116</td>
<td>48.1</td>
<td>81.0</td>
<td>0.57 (0.46 to 0.68)</td>
<td>25 (52)</td>
<td>65 (21.5)</td>
<td>2.6 (1.2 to 5.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IGF12</td>
<td>&lt;501</td>
<td>55.6</td>
<td>73.0</td>
<td>0.65 (0.54 to 0.75)</td>
<td>32 (46.9)</td>
<td>58 (20.7)</td>
<td>2.5 (1.2 to 5.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>IGFBP1</td>
<td>&gt;22.6</td>
<td>81.5</td>
<td>47.6</td>
<td>0.66 (0.53 to 0.76)</td>
<td>35 (14.3)</td>
<td>53 (40)</td>
<td>3.2 (1.4 to 6.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IGFBP2</td>
<td>&gt;449</td>
<td>48.1</td>
<td>84.1</td>
<td>0.70 (0.60 to 0.80)</td>
<td>67 (20.9)</td>
<td>23 (58.5)</td>
<td>3.0 (1.4 to 6.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IGFBP3</td>
<td>&lt;1201</td>
<td>44.4</td>
<td>81</td>
<td>0.63 (0.52 to 0.73)</td>
<td>24 (50)</td>
<td>66 (22.7)</td>
<td>2.8 (1.3 to 5.9)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

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

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