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The relation between endothelin-1 levels and myocardial injury in chronic ischemic heart failure

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Abstract We evaluated whether there was any relation between myocardial injury and endothelin-1 (ET-1) levels, which has been suggested as a contributor to the progression of ischemic heart failure. One hundred and twenty-one patients with chronic ischemic heart failure and 37 healthy individuals were included in the study. Cardiac troponin-I (cTn-I) and ET-1 levels of all subjects were measured on admission. Echocardiographic evaluations were also performed. The positivity of cTn-I increased significantly as the severity changed from New York Heart Association (NYHA) Class I to IV (P < 0.01). This was also true for quantitative cTn-I levels (P < 0.05). The ET-1 levels of patients were higher than controls on admission (P < 0.001). The ET-1 levels increased significantly upon the progression from NYHA Class I to IV (P < 0.001). Moreover, patients with cTn-I positivity had higher ET-1 levels (P < 0.05) and a lower ejection fraction (P < 0.001). A negative correlation was found between ejection fraction and the ET-1 levels (r = -0.312, P = 0.019). In patients with cTn-I positivity, the ET-1 levels showed a positive correlation with the ET-1 levels (r = 0.328, P = 0.014) and a negative correlation with ejection fraction (r = -0.671, P < 0.001). In chronic ischemic heart failure, an increase in ET-1 may exert an influence on the progression of cardiac failure by leading to myocardial injury which may be demonstrated by higher cTn-I levels.

Key words Chronic ischemic heart failure · Endothelin-1 · Myocardial injury

Introduction

The initial mainstay of chronic ischemic heart failure is myocardial injury and a decrease in functional myocardial mass. In later stages, an increase in neuroendocrinological activity in response to the progression of the disease leads to higher metabolic requirements and lower coronary blood supply, and these changes contribute to impaired myocardial perfusion. As a consequence, myocardial injury, which may be demonstrated by cardiac troponins, occurs and further impairment in the clinical situation will be observed.

In patients with chronic ischemic heart failure, long-lasting activation of the endothelin (ET) system plays a crucial role in the progression of heart failure and dysfunction of the left ventricle. In heart failure, plasma ET-1 levels have been demonstrated to increase in parallel with functional capacity and the severity of the disease. However, in these patients the relation between myocardial injury and ET-1 levels has not been investigated adequately. In this study, we investigated the relation between myocardial injury and plasma ET-1 levels in patients with chronic ischemic heart failure.

Materials and methods

Patient eligibility

A total of 121 patients (75 males and 46 females, mean age: 60 ± 10 years) with angiographically demonstrated coronary artery disease and chronic ischemic heart failure were included in the study in 2002 and 2003. All patients had myocardial infarction (MI) older than 6 months and had an ejection fraction below 45%. For comparison, 37 healthy individuals (18 males and 12 females, mean age: 58 ± 11 years) without any known cardiovascular disease were selected as controls.

All of the patients in New York Heart Association (NYHA) Class IV (n = 28) and 13 of 38 patients in NYHA Class III were hospitalized because of recent decompen-
at added to the serum samples and they were kept centrifuged at 4000 rpm for 15 min at 20°C. Polypropylene was ethylenediamine tetraacetic acid (EDTA) and were centrifuged after a 5-min rest, were collected in tubes containing the Helsinki Declaration were applied.

Patients with a new ischemic attack, organic valvular disease, diabetes, hypertension, and severe renal or hepatic failure were excluded. Oral informed consent of all patients was received before each procedure and the principles of the Helsinki Declaration were applied.

Blood sampling and measurements

Five milliliters of blood samples, obtained from a superficial vein after a 5-min rest, were collected in tubes containing ethylenediamine tetraacetic acid (EDTA) and were centrifuged at 4000 rpm for 15 min at 20°C. Polypropylene was added to the separated serum samples and they were kept at −70°C until the processing day. The concentrations of human ET-1 in the plasma samples were determined using the Parameter enzyme-linked immunosorbent assay (ELISA) system (R&D Systems, Minneapolis, MN, USA) according to the manufacturer’s protocol. Absorbance was measured at 450 nm, using a microplate reader with a wavelength correction set at 650 nm. Serum troponin-I levels were measured quantitatively via an Immulite Analyzer (ELISA) system (R&D Systems, Minneapolis, MN, USA) according to the manufacturer’s protocol. Absorbance was measured at 450 nm and levels below this were accepted as negative. Cardiac troponin-I (cTn-I) levels of above 0.20 ng/ml were accepted as positive and measured quantitatively.

Table 1. Clinical characteristics of patients and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 37)</th>
<th>NYHA I (n = 26)</th>
<th>NYHA II (n = 29)</th>
<th>NYHA III (n = 38)</th>
<th>NYHA IV (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58 ± 11</td>
<td>61 ± 12</td>
<td>57 ± 11</td>
<td>62 ± 9</td>
<td>64 ± 12</td>
</tr>
<tr>
<td>Male/female</td>
<td>25/12</td>
<td>17/9</td>
<td>18/11</td>
<td>22/16</td>
<td>18/10</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.5 ± 3.2</td>
<td>24.3 ± 3.6</td>
<td>25.7 ± 4.1</td>
<td>23.5 ± 2.1</td>
<td>22.5 ± 3.4</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>47 ± 3</td>
<td>59 ± 9*</td>
<td>60 ± 12*</td>
<td>63 ± 11*</td>
<td>71 ± 6*</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>32 ± 7</td>
<td>46 ± 10*</td>
<td>49 ± 11*</td>
<td>52 ± 9*</td>
<td>64 ± 8*</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>65.5 ± 4.3</td>
<td>41.5 ± 2.1</td>
<td>38.9 ± 2.3</td>
<td>35.6 ± 3.5</td>
<td>26.5 ± 5.6</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction

* P = 0.05 vs controls

+ P < 0.05 vs NYHA I, II, III and P < 0.01 vs controls

$ P < 0.01$ vs controls

$ P < 0.05$ vs NYHA I, II, and IV

$ P < 0.001$ vs controls and $ P < 0.01$ vs NYHA I, II

Echocardiographic evaluation

All subjects in the patient and control groups underwent echocardiographic evaluation on admission. For this purpose, a “Vingmed system five” device was used. Ejection fraction (EF) and end-systolic and end-diastolic diameters of the left ventricle were measured using the Teicholz method.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and noncontinuous variables were given as rates. Comparison of noncontinuous variables between groups was performed by the χ² test and the Fisher exact test. Inter- and intragroup comparisons of continuous variables were performed using analysis of variance (ANOVA). Relationships between continuous variables were evaluated by Spearman correlation analysis and P values below 0.05 were accepted as statistically significant.

Results

Clinical and echocardiographic characteristics of the patients and controls are summarized in Table 1. On admission, patients were using diuretics (79%), digitalis (88%), angiotensin-converting enzyme inhibitors or angiotensin II receptor agonists (92%), spironolactone (85%), nitrates (31%), and β-blockers (21%). Of these, all patients with NYHA Class I and II and 25 patients with Class III were being followed as outpatients by their own physicians. The others were hospitalized and intravenous nitroglycerin (88%), positive inotropic agents (34%), and diuretics (100%) were added.

No statistically significant difference in end-systolic (LVESD) and end-diastolic (LVEDD) diameters of the left ventricle was found between the patients who were in NYHA Classes I, II, or III ($ P > 0.05$), but in NYHA Class IV patients, both diameters were significantly higher than in patients in the lower classes ($ P < 0.05$) and controls ($ P < 0.01$) (Table 1).

The left ventricle ejection fraction (EF) of all patients with heart failure was lower than in controls ($ P < 0.01$). In NYHA Class I and II patients, EF was lower than in controls ($ P < 0.01$), but higher than in the NYHA Class III and IV patients ($ P < 0.05$ and $ P < 0.01$, respectively). The lowest EF values were in NYHA Class IV patients.