Correlation of serum Ang-2 level with neurohumor indexes and myocardial remodeling indexes in patients with chronic heart failure

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ABSTRACT

Objective: To study the correlation of serum angiogenin 2 (Ang-2) level with neurohumor indexes and myocardial remodeling indexes in patients with chronic heart failure. Methods: The patients with chronic heart failure who were treated in the People's Hospital of Huangmei between March 2015 and October 2017 were selected and divided into NYHA I-II group and NYHA III-IV group according to cardiac function classification; healthy subjects who received physical examination during the same period were selected as the control group. The levels of Ang-2, neurohumor indexes and myocardial remodeling indexes in serum were determined. Results: Serum Ang-2, NT-proBNP, Copeptin, ET-1, AT-II, ALD, FGF23, TGF β 1, Gal-3, PICP and ICTP levels of NYHA I-II group and NYHA III-IV group were significantly higher than those of control group whereas TIMP4 levels were significantly lower than that of control group; serum Ang-2, NT-proBNP, Copeptin, ET-1, AT-II, ALD, FGF23, TGF β 1, Gal-3, PICP and ICTP levels of NYHA III-IV group were significantly higher than those of NYHA I-II group whereas TIMP4 level was significantly lower than that of NYHA I-II group. Serum NT-proBNP, Copeptin, ET-1, AT-II, ALD, FGF23, TGF β 1, Gal-3, PICP and ICTP levels in chronic heart failure patients with high Ang-2 level were significantly higher than those in chronic heart failure patients with low Ang-2 level whereas TIMP4 level was significantly lower than that in chronic heart failure patients with low Ang-2 level. Conclusion: The increase of Ang-2 in patients with chronic heart failure is related to neurohumoral disorder and myocardial remodeling aggravation.

1. Introduction

Chronic heart failure is the clinical complex syndrome when a variety of cardiovascular system diseases develop to end stage, which is characterized by ventricular filling and ejection ability weakening, and will cause the corresponding clinical symptoms and signs of systemic congestion and pulmonary congestion[1,2]. The complicated pathophysiologic changes of multiple organs and systems in the whole body are involved during the development of chronic heart failure, neurohumor disorder and excessive myocardial remodeling are the important pathological features, but the specific regulatory mechanism is still not entirely clear, and the clinical auxiliary examination indexes are also needed to comprehensively evaluate the disease. Endothelial dysfunction is an important pathological change in the occurrence and development of various cardiovascular diseases. When endothelial function is complete, the cardiovascular system has a strong self-compensating and self-repairing function; but when the endothelial function is excessively damaged, the self-compensating and self-repairing function of the cardiovascular system is weakened, which easily causes heart failure[3]. Angiogenin 2 (Ang-2) is the angiopoietin family member that is involved in vascular formation and reconstruction, and has damage effect on the integrity of endothelial cells[4]. It has been reported that the generation of Ang-2 has significantly increased in patients with chronic heart failure[5], but its effects of neurohumor disorders and excessive ventricular remodeling have not been clarified. In the following studies, we specifically analyzed the correlation of serum Ang-2 content with neurohumor indexes and myocardial remodeling indexes in patients with chronic heart failure.
2. Research subjects and methods

2.1 Research subject inclusion and grouping methods

The patients with chronic heart failure who were treated in the People’s Hospital of Huangmei between March 2015 and October 2017 were selected and further divided into NYHA I-II group and NYHA III-IV group according to NYHA cardiac function classification. Healthy subjects who received physical examination during the same period were selected as the control group. There were 39 cases in NYHA I-II group, including 22 males and 17 females who were 53-77 years old; there were 29 cases in NYHA III-IV group, including 16 males and 13 females who were 56-79 years old; there were 40 cases in the control group, including 25 males and 15 females who were 44-70 years old. There was no significant difference in the general data among the three groups (P>0.05).

2.2 Laboratory detection methods

5-6 mL of morning fasting venous blood was collected from the enrolled subjects, placed for 1 to 2 h at room temperature for natural coagulation and then centrifuged at 2 000 r/min for 10 min to get serum, and the Elisa kit instructions were followed for determination of Ang-2, NT-proBNP, Copeptin, ET-1, AT-II, ALD, FGF23, TGF β 1, Gal-3, PICP, ICTP and TIMP4 contents.

2.3 Statistical processing methods

Software SPSS 22.0 was adopted to input data, the data among two groups were analyzed by variance analysis, the data between each group were analyzed by variance analysis, the data among three groups were analyzed by variance analysis, the data between chronic heart failure patients with different Ang-2 levels was as follows: serum NT-proBNP, Copeptin, ET-1, AT-II and ALD levels of NYHA I-II group and NYHA III-IV group were significantly higher than those of control group, and serum NT-proBNP, Copeptin, ET-1, AT-II and ALD levels of NYHA III-IV group were significantly higher than those of NYHA I-II group. Pair-wise comparison of Ang-2 was significantly different among the three groups (P<0.05).

Comparison of serum neurohumor indexes between chronic heart failure patients with different Ang-2 levels.

Table 1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>NT-proBNP (pg/mL)</th>
<th>Copeptin (pg/mL)</th>
<th>ET-1 (pg/mL)</th>
<th>AT-II (pg/mL)</th>
<th>ALD (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>40</td>
<td>0.20±0.03</td>
<td>1.18±0.16</td>
<td>75.78±9.93</td>
<td>14.85±1.85</td>
<td>126.81±15.85</td>
</tr>
<tr>
<td>NYHA I-II group</td>
<td>39</td>
<td>1.03±0.16</td>
<td>1.87±0.24</td>
<td>99.41±11.38</td>
<td>23.12±3.29</td>
<td>185.52±22.47</td>
</tr>
<tr>
<td>NYHA III-IV group</td>
<td>29</td>
<td>4.28±0.62(1)</td>
<td>3.04±0.47(1)</td>
<td>120.36±14.85</td>
<td>38.69±5.23(1)</td>
<td>233.12±32.94</td>
</tr>
</tbody>
</table>

*: compared with control group, P<0.05; (1): compared with NYHA I-II group, P<0.05.

Table 2.

Comparison of serum neurohumor indexes between chronic heart failure patients with different Ang-2 levels.

<table>
<thead>
<tr>
<th>Ang-2</th>
<th>n</th>
<th>NT-proBNP (pg/mL)</th>
<th>Copeptin (pg/mL)</th>
<th>ET-1 (pg/mL)</th>
<th>AT-II (pg/mL)</th>
<th>ALD (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>34</td>
<td>3.77±0.58</td>
<td>3.13±0.52</td>
<td>124.41±16.84</td>
<td>40.27±5.83</td>
<td>241.23±36.84</td>
</tr>
<tr>
<td>Low</td>
<td>34</td>
<td>1.52±0.22</td>
<td>1.66±0.20</td>
<td>91.28±10.89</td>
<td>21.38±2.89</td>
<td>174.28±20.18</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>17.938</td>
<td>12.337</td>
<td>9.283</td>
<td>13.485</td>
<td>11.039</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

3. Results

3.1 Serum Ang-2 levels

Serum Ang-2 level of NYHA I-II group was (282.41±37.85) pg/mL, serum Ang-2 level of NYHA III-IV group was (174.51±22.35) pg/mL and serum Ang-2 level of control group was (125.23±15.54) pg/mL. After variance analysis, serum Ang-2 levels of NYHA I-II group and NYHA III-IV group were significantly higher than that of control group, and serum Ang-2 level of NYHA III-IV group was significantly higher than that of NYHA I-II group. Pair-wise comparison of Ang-2 was significantly different among the three groups (P<0.05).

3.2 Serum neurohumor index levels

Comparison of serum neurohumor indexes NT-proBNP (ng/mL), Copeptin (pg/mL), ET-1 (pg/mL), AT-II (pg/mL) and ALD (pg/mL) among the three groups of subjects was as follows: serum NT-proBNP, Copeptin, ET-1, AT-II and ALD levels of NYHA I-II group and NYHA III-IV group were significantly higher than those of control group, and serum NT-proBNP, Copeptin, ET-1, AT-II and ALD levels of NYHA III-IV group were significantly higher than those of NYHA I-II group. Pair-wise comparison of NT-proBNP, Copeptin, ET-1, AT-II and ALD was significantly different among the three groups (P<0.05).

Comparison of serum neurohumor indexes NT-proBNP (ng/mL), Copeptin (pg/mL), ET-1 (pg/mL) and ALD (pg/mL) between chronic heart failure patients with different Ang-2 levels was as follows: serum NT-proBNP, Copeptin, ET-1, AT-II and ALD levels in chronic heart failure patients with high Ang-2 level were significantly higher than those in chronic heart failure patients with low Ang-2 level. Serum NT-proBNP, Copeptin, ET-1, AT-II and ALD levels were significantly different between chronic heart failure patients with different Ang-2 levels (P<0.05).

3.3 Serum myocardial remodeling index levels

Comparison of serum myocardial remodeling indexes FGF23, TGF β 1, Gal-3, PICP, ICTP and TIMP4 among the three groups of subjects was as follows: serum FGF23, TGF β 1, Gal-3, PICP and ICTP levels of NYHA I-II group and NYHA III-IV group were significantly higher than those of control group whereas TIMP4 levels were significantly lower than that of control group, and serum FGF23, TGF β 1, Gal-3, PICP and ICTP levels of NYHA III-IV group were significantly higher than those of NYHA I-II group whereas TIMP4 level was significantly lower than that of NYHA I-II group. Pair-wise comparison of FGF23, TGF β 1, Gal-3, PICP, ICTP and TIMP4 was significantly different among the three groups (P<0.05).

Comparison of serum myocardial remodeling indexes FGF23,
I-II group. This indicates that the increased generation of Ang-2 is closely related to the occurrence of chronic heart failure.

Further analysis of the changes of serum Ang-2 levels in patients with chronic heart failure showed that serum Ang-2 levels of NYHA III-IV group were significantly higher than those of control group. This indicates that the increased generation of Ang-2 is closely related to the aggravation of chronic heart failure.

In the development of chronic heart failure, the decrease of cardiac function and the increase of systemic preload and afterload can cause significant changes in the neurohumoral system. BNP is the active peptide secreted by ventricular muscle cells, AVP is the neurohormone stored and released by the neurohypophysis, and they can adjust water sodium reabsorption and increase circulating blood volume and exert self-compensatory effects on heart failure condition[9,10]. NT-proBNP and Copeptin are the by-products in the process of BNP and AVP synthesis and secretion, which have more stable chemical structure and longer half-life, and can more accurately reflect the secretion of BNP and AVP[11,12]. ET-1 is a vasoactive peptide with strong vasoconstriction, which is massively produced and released during endothelial injury. AT-II and ALD are the endocrine hormones produced during the activation of RAAS endocrine system, and the decrease of ejection volume in the course of heart failure will stimulate the RAAS system and increase the secretion of corresponding hormones[13,14]. The analysis of the change of above neurohumor indicators in patients with chronic heart failure showed that serum NT-proBNP, Copeptin, ET-1, AT-II and ALD levels of NYHA I-II group and NYHA III-IV group were significantly higher than those of control group, and the worse the cardiac function, the more obvious the increase of corresponding neurohumor index levels in serum. This indicates that the neurohumoral disorder is gradually aggravating in the occurrence of chronic heart failure and the deterioration of cardiac function. Further analysis of the effect of Ang-2 on neurohumor in patients with chronic heart failure showed that serum NT-proBNP, Copeptin, ET-1, AT-II and ALD levels significantly increased in chronic heart failure patients with high Ang-2 level. This indicates that the abnormal secretion of Ang-2 in the course of chronic heart failure can aggravate the degree of neurohumoral disorder.

The neurohumoral disorders in patients with chronic heart failure can further cause abnormal collagen degradation and deposition in myocardial matrix, which will gradually lead to myocardial reconstruction and promote the deterioration of cardiac function[15]. FGF23 and TGFβ1 are the cytokines that play an important role in myocardial remodeling. FGF23 can promote fibroblast proliferation, and may increase the number of fibroblasts in myocardial matrix to increase myocardial remodeling[15-17], and the latter can identify the receptors on the cell membrane to conduct signal transduction through Smad2/3, then increase the expression of various proteases and promote the degradation of collagen[18]. Gal-3 is the galectin

4. Discussion

Neurohumoral disorders and excessive myocardial remodeling are the important pathophysiological features in the development of chronic heart failure, but the mechanism regulating neurohumoral changes and myocardial remodeling is not clear. Endothelial cell damage is a pathological change that plays an important role in several pathological links of cardiovascular diseases. When endothelial function is normal, the growth of endothelial cells is in a relatively inhibited state, and the inhibitory effect on growth is stronger than the promoting effect on growth; but when the endothelial function is damaged, the secretion of a variety of molecules with endothelial growth effect will increase, and endothelial dependent vasomotor dysfunction will occur and participate in the occurrence of a variety of cardiovascular diseases. During the occurrence of chronic heart failure, the endothelial function damage can directly affect vascular function, increase blood flow resistance and gradually cause pumping failure[6,7]. Ang-2 is the molecule involved in vascular formation and reconstruction, which on the one hand, promotes the growth of endothelial cells, and on the other hand, can reduce for the stability of the blood vessels and increase the permeability of blood vessel walls, and also reflect the degree of endothelial dysfunction[8]. In the above studies, analysis of the changes in serum Ang-2 levels in patients with chronic heart failure showed that serum Ang-2 levels of NYHA I-II group and NYHA III-IV group were significantly higher than that of control group. This indicates that the increased generation of Ang-2 is closely related to the occurrence of chronic heart failure. Further analysis of the changes of serum Ang-2 levels in patients with different severity of heart failure showed that serum Ang-2 level of NYHA III-IV group was significantly higher than that of NYHA I-II group. This indicates that the increased generation of Ang-2 is closely related to the aggravation of chronic heart failure.

In the above studies, analysis of the changes in serum Ang-2 levels in patients with chronic heart failure showed that serum Ang-2 levels of NYHA I-II group and NYHA III-IV group were significantly higher than that of control group. This indicates that the increased generation of Ang-2 is closely related to the occurrence of chronic heart failure. Further analysis of the changes of serum Ang-2 levels in patients with different severity of heart failure showed that serum Ang-2 level of NYHA III-IV group was significantly higher than that of NYHA I-II group. This indicates that the increased generation of Ang-2 is closely related to the aggravation of chronic heart failure.
family member that is located in the intercellular substance and can promote the abnormal deposition of collagen in the interstitial[19,20]. PICP and ICTP are the synthesis and degradation products of type I collagen in myocardial matrix, and the excessive degradation and accumulation of collagen can result in changes in corresponding metabolism indicators[21,22]. TIMP4 is an inhibitor of protease activity and inhibits the excessive hydrolysis of collagen during myocardial remodeling by blocking protease hydrolysis of collagen[23]. The analysis of the change trend of above myocardial remodeling indexes in patients with chronic heart failure showed that serum FGF23, TGF β 1, Gal-3, PICP and ICTP levels of NYHA I-II group and NYHA III-IV group were significantly higher than those of control group whereas TIMP4 levels were significantly lower than that of control group, and the worse the cardiac function, the more obvious the change of corresponding myocardial remodeling index levels in serum. It indicates that the myocardial remodeling is gradually aggravating in the occurrence of chronic heart failure and the deterioration of cardiac function. Further analysis of the effect of Ang-2 on myocardial remodeling in patients with chronic heart failure showed that serum FGF23, TGF β 1, Gal-3, PICP and ICTP levels significantly increased whereas TIMP4 level significantly decreased in chronic heart failure patients with high Ang-2 level. This indicates that the abnormal secretion of Ang-2 in the course of chronic heart failure can aggravate the degree of myocardial remodeling.

To sum up, it can be concluded that serum Ang-2 level abnormally increased in patients with chronic heart failure; the increased Ang-2 can aggravate neurohumoral disorders and myocardial remodeling.

References


