Relationship of renin–angiotensin–aldosterone system activity with systemic inflammatory response and target organ function in patients with severe acute pancreatitis

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ABSTRACT

Objective: To study the relationship of renin-angiotensin-aldosterone system (RAAS) activity with systemic inflammatory response and target organ function in patients with severe acute pancreatitis. Methods: The patients with acute pancreatitis admitted in Zigong Third People’s Hospital between June 2014 and December 2016 were selected and divided into MAP group and SAP group, and the healthy volunteers who received physical examination during the same period and were with matched general data were selected as control group. Serum was collected to determine the levels of RAAS molecules, inflammation molecules as well as liver and intestinal mucosal barrier injury molecules. Results: Serum PRA, AngII, ALD, TNF-α, sTREM-1, PCT, CRP, LPS, DAO and HBD2 contents of SAP group and MAP group were significantly higher than those of control group; serum PRA, AngII, ALD, TNF-α, sTREM-1, PCT, CRP, LPS, DAO and HBD2 contents of SAP group were significantly higher than those of MAP group; serum PRA, AngII and ALD contents of SAP group were positively correlated with TNF-α, sTREM-1, PCT, CRP, LPS, DAO and HBD2 contents. Conclusion: The activation of RAAS system in patients with severe acute pancreatitis is closely related to the amplification of systemic inflammatory response and the damage of target organs.

1. Introduction

Acute pancreatitis is an inflammatory disease characterized by local hemorrhage and inflammation of pancreas, and the pancreatic tissue edema and hemorrhage as well as acinar cell degeneration and necrosis are the pathological characteristics of local tissue. The condition of severe acute pancreatitis is severe and progresses rapidly, it is easy to develop systemic inflammatory response syndrome and multi-organ dysfunction, and the prognosis is poor. In clinical practice, the accurate assessment of the condition of severe acute pancreatitis is the precondition to establish therapy[1,2]. Renin-angiotensin-aldosterone system (RAAS) is an important endocrine system that regulates the humoral homeostasis and vasomotion. It has been discovered in recent years that there is also RAAS system in the pancreas tissue, and the activation of the system in local tissue is not only associated with capillary contraction as well as acinar cell degeneration and necrosis, but also associated with the cascade activation of the inflammatory response[3]. It has been confirmed that the inhibitor of renin can reduce the disease severity in pancreatitis rat model[4]. At present, the activity of the RAAS system in severe acute pancreatitis and its relationship with systemic inflammatory response and target organ damage are not clear. In the following study, the relationship of RAAS activity with systemic inflammatory response and target organ function in patients with severe acute pancreatitis was analyzed.

2. Case information and research methods

2.1 Case information

A total of 93 cases of patients with acute pancreatitis admitted in Zigong Third People’s Hospital between June 2014 and December 2016 were selected, all cases matched the diagnosis of acute pancreatitis, the history data were complete and serum samples were collected before treatment. The history data of 93 patients with acute pancreatitis were reviewed, and according to the disease severity,
the patients with severe acute pancreatitis and mild acute pancreatitis were enrolled in SAP group and MAP group respectively. The SAP group (n=32) included 19 male cases and 13 female cases that were 35-48 years old; the MAP group (n=61) included 35 male cases and 26 female cases that were 33-47 years old. 60 healthy volunteers who received physical examination during the same period were selected as control group, including 34 male cases and 26 female cases that were 33-48 years old. There was no significant difference in the general data among the three groups of subjects.

2.2 Research methods

2.2.1 Clinical sample collection methods
5 mL peripheral venous blood was collected from SAP group and MAP group of patients with acute pancreatitis at admission, 5 mL peripheral venous blood was collected from control group of healthy volunteers during physical examination, and the blood was centrifuged at 3 000 r/min for 10 min to separate serum.

2.2.2 Clinical index detection methods
Enzyme-linked immunosorbent assay kits were used to determine PRA, AngII, ALD, TNF-α, sTREM-1, PCT, CRP, LPS, DAO and HBD2 contents, and automatic biochemical analyzer was used to determine the content of ALT, AST, TBIL and γ-GT.

2.3 Statistical methods
SPSS 21.0 software was used for data input and t test and correlation analysis between two data was by Pearson test. P<0.05 was the standard of statistical significance in differences.

3. Results

3.1 Serum RAAS molecule contents
Analysis of serum RAAS molecules PRA (ng/mL), AngII (pg/mL) and ALD (pg/mL) contents among three groups of subjects was shown in Table 1: serum PRA, AngII and ALD contents of SAP group and MAP group were significantly higher than those of control group (P<0.05); serum PRA, AngII and ALD contents of SAP group were significantly higher than those of MAP group (P<0.05).

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>PRA (ng/mL)</th>
<th>AngII (pg/mL)</th>
<th>ALD (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAP group</td>
<td>32</td>
<td>2.09±0.42</td>
<td>85.49±10.32</td>
<td>224.28±33.41</td>
</tr>
<tr>
<td>MAP group</td>
<td>61</td>
<td>1.38±0.21</td>
<td>59.62±7.82</td>
<td>145.29±19.25</td>
</tr>
<tr>
<td>Control</td>
<td>60</td>
<td>0.77±0.09</td>
<td>23.49±4.41</td>
<td>84.49±10.25</td>
</tr>
</tbody>
</table>

*: compared with control group, P<0.05; **: compared with MAP group, P<0.05.

3.2 Serum inflammation molecule contents
Analysis of serum inflammation molecules TNF-α (ng/mL), sTREM-1 (ng/mL), PCT, CRP, LPS, DAO and HBD2 contents of SAP group and MAP group were significantly higher than those of control group; serum TNF-α, sTREM-1, PCT and CRP contents of SAP group and MAP group were significantly higher than those of control group; serum TNF-α, sTREM-1, PCT and CRP contents of SAP group and MAP group were significantly higher than those of MAP group. Differences in pair-wise comparison of serum TNF-α, sTREM-1, PCT and CRP contents of SAP group and MAP group were statistically significant among three groups of subjects (P<0.05). Pearson test showed that serum TNF-α, sTREM-1, PCT and CRP contents of SAP group and MAP group were positively correlated with PRA, AngII and ALD contents.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>TNF-α (ng/mL)</th>
<th>sTREM-1 (ng/mL)</th>
<th>PCT (ng/mL)</th>
<th>CRP (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAP group</td>
<td>32</td>
<td>163.41±20.32</td>
<td>50.31±7.25</td>
<td>72.39±9.35</td>
<td>28.41±4.41</td>
</tr>
<tr>
<td>MAP group</td>
<td>61</td>
<td>98.41±11.25</td>
<td>9.22±1.02</td>
<td>28.41±4.41</td>
<td>6.39±0.91</td>
</tr>
<tr>
<td>Control</td>
<td>60</td>
<td>15.68±2.26</td>
<td>0.20±0.04</td>
<td>6.53±0.78</td>
<td>0.35±0.06</td>
</tr>
</tbody>
</table>

*: compared with control group, P<0.05; **: compared with MAP group, P<0.05.

3.3 Serum target organ injury index contents
Analysis of serum liver injury indexes ALT, AST, γ-GT and TBIL contents among three groups of subjects was shown in Table 3: serum ALT, AST, γ-GT and TBIL contents of SAP group and MAP group were significantly higher than those of control group.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>ALT (U/L)</th>
<th>AST (U/L)</th>
<th>γ-GT (U/L)</th>
<th>TBIL (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAP group</td>
<td>32</td>
<td>92.14±12.16</td>
<td>79.41±9.27</td>
<td>125.12±15.86</td>
<td>63.58±8.29</td>
</tr>
<tr>
<td>MAP group</td>
<td>61</td>
<td>48.75±6.41</td>
<td>50.31±7.25</td>
<td>72.39±9.45</td>
<td>41.29±6.48</td>
</tr>
<tr>
<td>Control</td>
<td>60</td>
<td>20.32±3.58</td>
<td>18.39±2.96</td>
<td>29.52±5.28</td>
<td>17.48±2.95</td>
</tr>
</tbody>
</table>

*: compared with control group, P<0.05; **: compared with MAP group, P<0.05.

4. Discussion

4.1 Serum RAAS molecule contents
The results showed that serum PRA, AngII and ALD contents of SAP group and MAP group were significantly higher than those of control group, which indicated that the RAAS system was activated in acute pancreatitis and was closely related to the severity of disease.

4.2 Serum inflammation molecule contents
The results showed that serum TNF-α, sTREM-1, PCT and CRP contents of SAP group and MAP group were significantly higher than those of control group, which indicated that the inflammation response was activated in acute pancreatitis and was closely related to the severity of disease.

4.3 Serum target organ injury index contents
The results showed that serum ALT, AST, γ-GT and TBIL contents of SAP group and MAP group were significantly higher than those of control group, which indicated that the target organ injury was activated in acute pancreatitis and was closely related to the severity of disease.

5. Conclusion

The results showed that the RAAS system, inflammation response and target organ injury were activated in acute pancreatitis, which was closely related to the severity of disease. Further research is needed to explore the mechanism of these changes and to develop effective therapeutic strategies.
MAP group were significantly higher than those of control group; serum ALT, AST, γ-GT and TBIL contents of SAP group were significantly higher than those of MAP group. Differences in pair-wise comparison of serum ALT, AST, γ-GT and TBIL contents were statistically significant among three groups of subjects (P<0.05). Pearson test showed that serum ALT, AST, γ-GT and TBIL contents of SAP group were positively correlated with PRA, AngII and ALD contents.

Analysis of serum intestinal mucosal barrier indexes LPS (EU/mL), DAO (μg/mL) and HBD2 (ng/mL) contents among three groups of subjects was shown in Table 4: serum LPS, DAO and HBD2 contents of SAP group and MAP group were significantly higher than those of control group; serum LPS, DAO and HBD2 contents of SAP group were significantly higher than those of MAP group. Differences in pair-wise comparison of serum LPS, DAO and HBD2 contents were statistically significant among three groups of subjects (P<0.05). Pearson test showed that serum LPS, DAO and HBD2 contents of SAP group were positively correlated with PRA, AngII and ALD contents.

4. Discussion

Severe acute pancreatitis is an acute abdominal pain with critical condition and high mortality, the pancreatic tissue hemorrhage and necrosis caused by inflammatory reaction activation are the important pathologic characteristics. In the development and change of severe acute pancreatitis, pancreatic tissue shows degeneration and edema at first, and then develops hemorrhage and necrosis during the inflammation cascade amplification activation. The cascade activation of systemic inflammatory response is the key link in progression of severe acute pancreatitis, but there are numerous cytokines involving inflammation cascade activation, and it difficult to accurately assess the disease through the single index. It has been discovered in recent years that the RAAS plays an important regulating role in the pancreas, and the activation of the system will cause massive analysis of PRA, AngII and ALD, which can not only cause vasoconstriction and pancreatic perfusion reduction and lead to acinar cell edema, degeneration and necrosis[5,6], but can also act on multiple links the inflammatory response and cause the cascade activation and amplification of the inflammatory response[7]. It has been reported that the inhibitor of renin can reduce the disease severity in rat model with pancreatitis. In order to define the role that RAAS activation played in the development and change of severe acute pancreatitis, serum levels of RAAS molecules were analyzed in the study, and the results showed that serum PRA, AngII and ALD contents of patients with SAP and MAP were significantly higher than those of healthy volunteers, and serum PRA, AngII and ALD contents of patients with SAP were significantly higher than those of patients with MAP. This shows that the activation of RAAS is related to the occurrence and development of severe acute pancreatitis.

The activation of SIRS is the core link of the development of severe acute pancreatitis, and the abnormal secretion of various inflammatory mediators is closely related to the injury of the pancreatic tissue. TNF-α is secreted by activated mononuclear macrophages, and the over-secreted TNF-α can directly mediate the tissue and visceral damage[8,9]; sTREM-1 is a soluble form of the cell membrane receptor TREM-1, which activates and promotes the release of inflammatory mediators[10]; PCT is the calcitonin precursor synthesized by a variety of parenchymal cells, and a variety of pro-inflammatory mediators can promote PCT secretion into the blood circulation and reflect the degree of inflammation[11,12]; CRP is synthesized by hepatocytes, which is a type of non-specific acute phase protein, and is closely related to the activation of the acute inflammatory response[13]. In the study, analysis of serum contents of these inflammatory mediators in patients with SAP and MAP showed that serum TNF-α, sTREM-1, PCT and CRP contents of patients with SAP and MAP were significantly higher than those of healthy volunteers, and serum TNF-α, sTREM-1, PCT and CRP contents of patients with SAP were significantly higher than those of patients with MAP. This shows that the progression of severe acute pancreatitis involves the cascade activation of inflammatory response. Further analysis of the relationship between the RAAS activity and the inflammatory response showed that serum TNF-α, sTREM-1, PCT and CRP contents of SAP group were positively correlated with PRA, AngII and ALD contents. This confirms that the RAAS activity in patients with SAP is correlated with cascade amplification of inflammatory response, and endocrine hormones such as AngII and ALD have a cascading effect on inflammation.

The poor prognosis of patients with severe acute pancreatitis is not only related to the pancreatic tissue hemorrhage and necrosis, but also associated with the target organ injury caused by the SIRS. The liver is the place for inflammatory marker processing and metabolism, and the massively synthesized inflammatory factors in patients with severe acute pancreatitis will accumulate in local liver and cause liver damage. In the study, the analysis of the contents of liver damage indexes showed that serum ALT, AST, γ-GT and TBIL contents of patients with SAP and MAP were significantly higher than those of healthy volunteers, and serum ALT, AST, γ-GT and TBIL contents of patients with SAP were significantly higher than those of patient with MAP and positively correlated with the contents of PRA, AngII and ALD. This indicates that the activation of RAAS in severe acute pancreatitis is closely related to the damage of liver function. The intestinal tract is where the inflammatory cells and bacterial flora gather in the body, and normal intestinal mucosal barrier function can keep the balance of intestinal flora and avoid
flora ectopia into the bloodstream under physiological conditions[14]; when the inflammatory response is activated and causes the intestinal mucosal barrier damage, the intestinal flora will enter the blood circulation and synthesize a large number of LPS[15]. At the same time, the intestinal mucosal epithelial cell damage can also result in increased compensatory synthesis of the DAO and HBD-2 in the cells and release them into the blood circulation. In the study, analysis of the contents of liver injury indexes showed that serum LPS, DAO and HBD2 contents of patients with SAP and MAP were significantly higher than those healthy volunteers, and serum LPS, DAO and HBD2 contents of patients with SAP were significantly higher than those of patients with MAP and positively correlated with the contents of PRA, AngII and ALD. This shows that the activation of RAAS in severe acute pancreatitis is closely related to the damage of the intestinal mucosal barrier.

The RAAS is significantly activated in patients with severe acute pancreatitis; the activation of RAAS can cause the systemic inflammation cascade amplification as well as liver and intestinal mucosa barrier injury in the patients with severe acute pancreatitis.

References


