Protective effect of levothyroxine on myocardial and cerebral ischemia reperfusion injury during surgery under cardiopulmonary bypass

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Abstract
Objective: To study the protective effect of levothyroxine on myocardial and cerebral ischemia reperfusion injury during surgery under cardiopulmonary bypass.

Methods: Patients who underwent valve replacement under cardiopulmonary bypass in Mianyang Central Hospital between March 2015 and December 2017 were selected and randomly divided into the Euthyrox group who received preoperative levothyroxine therapy and the control group who received routine preoperative intervention. The myocardial and cerebral injury indexes, pro-inflammatory and adhesion molecules as well as antioxidant indexes were measured before operation and 12 h after operation.

Results: Twelve hours after operation, serum cTnI, LDH, CK-MB, H-FABP, NSE, S100B, CD11b/CD18, sP-selectin, IL-1 and IL-10 contents as well as SjvO2 levels of both groups were higher than those before operation whereas Cu-Zn SOD, CAT and GSH-Px contents were lower than those before operation, and serum cTnI, LDH, CK-MB, H-FABP, NSE, S100B, CD11b/CD18, sP-selectin, IL-1 and IL-10 contents as well as SjvO2 level of Euthyrox group were lower than those of control group whereas Cu-Zn SOD, CAT and GSH-Px contents were higher than those of control group.

Conclusions: Levothyroxine has protective effect on the myocardial and cerebral ischemia reperfusion injury induced by inflammation and oxidative stress during surgery under cardiopulmonary bypass.

1. Introduction
Cardiopulmonary bypass is a necessary condition for open heart surgery in cardiac surgery department, which can provide a favorable local environment for surgical operation. However, the blood perfusion provided by the cardiopulmonary bypass is non-physiological perfusion, and can activate the systemic inflammatory and oxidative stress response to different degrees; the reperfusion process after cardiopulmonary bypass will further amplify the inflammation and oxidative stress through ischemia-reperfusion injury, and the resulting inflammatory mediators, oxygen free radicals and other products can cause myocardial and cerebral injury[1,2]. Studies about cardiopulmonary bypass in recent years have shown that the risk of low T3 syndrome is large after the cardiopulmonary bypass operation, and the decrease of free triiodothyronine levels will affect the body’s ability to tolerate traumatic stress, and increase the incidence of myocardial and cerebral injury[3,4]. Oral levothyroxine is an effective method for clinical thyroid hormone replacement, and supplementing levothyroxine before cardiopulmonary bypass can increase the thyroid hormone reserves in the body and reduce the risk of postoperative low T3 syndrome. In the following studies, we specifically analyzed the protective effect of levothyroxine on myocardial and cerebral ischemia reperfusion injury during surgery under cardiopulmonary bypass.

2. Materials and methods
2.1. Research design and case information
Prospective randomized control study was designed, patients who underwent valve replacement under cardiopulmonary bypass in
Mianyang Central Hospital between March 2015 and December 2017 were selected and randomly divided into the Euthyrox group and the control group, all patients were in line with the diagnosis of valvular disease and the indications of valve replacement, and a total of 62 cases were enrolled. Euthyrox group (n=31) included 17 males and 14 females, they were 22-65 years old, 10 cases underwent aortic valve operation, 13 cases underwent mitral valve operation, and 8 cases underwent mitral valve combined with aortic valve operation; control group (n=31) included 19 males and 12 females, they were 21-67 years old, 11 cases underwent aortic valve operation, 11 cases underwent mitral valve operation, and 9 cases underwent mitral valve combined with aortic valve operation. There was no significant difference in the general data between the two groups (P>0.05).

2.2. Preoperative intervention and intraoperative operation

Euthyrox group began to take levothyroxine tablets 50 mg/time orally, 1 time/d 1 week before operation for 1 week in a row, and then underwent surgery, and control group received no special intervention before operation. In the operation, the same plan was used for anesthesia induction and anesthesia maintenance, cardiopulmonary bypass apparatus was TERUMO Sarns 8000 extracorporeal circulation machine, routine mid-ternal incision was done for aortic as well as superior and inferior vena cava intubation, extracorporeal circulation was established, invasive arterial and venous detection were conducted, and SjvO2 was read.

2.3. Serum index determination

Before surgery and 12 h after surgery, cubital venous blood was collected, let stand for coagulation and then centrifuged to separate serum, the steps in ELISA kit instructions were followed to detect cTnI, LDH, CK-MB, H-FABP, NSE, S100B, CD11b/CD18, sP-selectin, IL-1 and IL-10 levels, and radioimmunoprecipitation kit instructions were referred to determine the levels of Cu-Zn SOD, CAT and GSH-Px.

2.4. Statistical methods

Software SPSS 19.0 was used to input data, the comparison between two groups was by t test and P<0.05 showed statistical significance in differences.

3. Results

3.1. Myocardial injury marker molecules

Serum cTnI, LDH, CK-MB and H-FABP contents were not significantly different between the two groups before surgery (P>0.05) whereas serum cTnI, LDH, CK-MB and H-FABP contents were significantly different after surgery (P<0.05), and serum cTnI, LDH, CK-MB and H-FABP contents of Euthyrox group after surgery were lower than those of control group; serum cTnI, LDH, CK-MB and H-FABP contents of both groups were significantly different between before and after surgery (P<0.05), and serum cTnI, LDH, CK-MB and H-FABP contents of both groups after surgery were higher than those before surgery (Table 1).

3.2. Cerebral injury indexes

NSE and S100B contents as well as SjvO2 levels were not significantly different between the two groups before surgery (P>0.05) whereas NSE and S100B contents as well as SjvO2 levels were significantly different after surgery (P<0.05), and NSE and S100B contents as well as SjvO2 level of Euthyrox group after surgery were lower than those of control group; NSE and S100B contents as well as SjvO2 levels of both groups were significantly different between before and after surgery (P<0.05), and NSE and S100B contents as well as SjvO2 levels of both groups after surgery were higher than those before surgery.

Table 1
Comparison of serum cTnI, LDH, CK-MB and H-FABP before and after surgery.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>cTnI (ng/mL)</th>
<th>LDH (U/L)</th>
<th>CK-MB (U/L)</th>
<th>H-FABP (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euthyrox group</td>
<td>31</td>
<td>Before surgery</td>
<td>0.36±0.05</td>
<td>189.42±22.62</td>
<td>13.32±2.25</td>
<td>4.85±0.62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After surgery</td>
<td>0.89±0.12</td>
<td>274.41±34.52</td>
<td>29.46±4.76</td>
<td>11.35±1.39</td>
</tr>
<tr>
<td>Control group</td>
<td>31</td>
<td>Before surgery</td>
<td>0.38±0.06</td>
<td>190.31±19.35</td>
<td>13.81±1.93</td>
<td>4.98±0.59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After surgery</td>
<td>1.33±0.17</td>
<td>384.52±47.94</td>
<td>46.52±6.37</td>
<td>23.13±3.49</td>
</tr>
</tbody>
</table>

*: comparison between Euthyrox group and control group after surgery, P<0.05; #: comparison between before and after surgery within the two groups, P<0.05.

Table 2
Comparison of NSE, S100B and SjvO2 before and after surgery.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>NSE (ng/mL)</th>
<th>S100B (ng/mL)</th>
<th>SjvO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euthyrox group</td>
<td>31</td>
<td>Before surgery</td>
<td>5.39±0.78</td>
<td>0.32±0.05</td>
<td>64.09±8.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After surgery</td>
<td>11.32±1.45</td>
<td>1.33±0.17</td>
<td>76.21±9.33</td>
</tr>
<tr>
<td>Control group</td>
<td>31</td>
<td>Before surgery</td>
<td>5.44±0.83</td>
<td>0.35±0.04</td>
<td>63.85±8.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After surgery</td>
<td>19.45±2.46</td>
<td>3.12±0.46</td>
<td>86.62±10.85</td>
</tr>
</tbody>
</table>

*: comparison between Euthyrox group and control group after surgery, P<0.05; #: comparison between before and after surgery within the two groups, P<0.05.
Comparison of serum CD11b/CD18, sP-selectin, IL-1 and IL-10 before and after surgery.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>CD11b/CD18 (ng/mL)</th>
<th>sP-selectin (ng/mL)</th>
<th>IL-1 (ng/mL)</th>
<th>IL-10 (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euthyrox group</td>
<td>31</td>
<td>Before surgery</td>
<td>2.32±0.35</td>
<td>32.39±4.38</td>
<td>7.72±0.89</td>
<td>45.61±7.62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After surgery</td>
<td>3.89±0.56</td>
<td>47.12±6.34</td>
<td>10.36±1.46</td>
<td>60.32±8.79</td>
</tr>
<tr>
<td>Control group</td>
<td>31</td>
<td>Before surgery</td>
<td>2.44±0.31</td>
<td>31.89±4.24</td>
<td>7.58±0.81</td>
<td>45.48±6.59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After surgery</td>
<td>5.72±0.78</td>
<td>65.59±8.23</td>
<td>15.42±1.88</td>
<td>82.31±10.39</td>
</tr>
</tbody>
</table>

*: comparison between Euthyrox group and control group after surgery; **: comparison between before and after surgery within the two groups, P < 0.05.

Table 3

Comparison of serum Cu-Zn SOD, CAT and GSH-Px before and after surgery (U/L).

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>Cu-Zn SOD</th>
<th>CAT</th>
<th>GSH-Px</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euthyrox group</td>
<td>31</td>
<td>Before surgery</td>
<td>89.31±10.35</td>
<td>45.62±6.72</td>
<td>103.41±13.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After surgery</td>
<td>77.64±8.49</td>
<td>38.49±5.62</td>
<td>78.65±9.33</td>
</tr>
<tr>
<td>Control group</td>
<td>31</td>
<td>Before surgery</td>
<td>90.12±10.77</td>
<td>45.91±6.88</td>
<td>102.94±14.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After surgery</td>
<td>63.35±8.95</td>
<td>27.52±3.75</td>
<td>55.69±7.96</td>
</tr>
</tbody>
</table>

*: comparison between Euthyrox group and control group after surgery; **: comparison between before and after surgery within the two groups, P < 0.05.

Table 4

3.3. Pro-inflammatory and adhesion molecules

Serum CD11b/CD18, sP-selectin, IL-1 and IL-10 contents were not significantly different between the two groups before surgery (P>0.05) whereas serum CD11b/CD18, sP-selectin, IL-1 and IL-10 contents were significantly different after surgery (P<0.05), and serum CD11b/CD18, sP-selectin, IL-1 and IL-10 contents of Euthyrox group after surgery were lower than those of control group; serum CD11b/CD18, sP-selectin, IL-1 and IL-10 contents of both groups were significantly different before and after surgery (P<0.05), and serum CD11b/CD18, sP-selectin, IL-1 and IL-10 contents of both groups after surgery were higher than those before surgery.

3.4. Antioxidant indexes

Serum Cu-Zn SOD, CAT and GSH-Px contents were not significantly different between the two groups before surgery (P>0.05) whereas serum Cu-Zn SOD, CAT and GSH-Px contents were significantly different after surgery (P<0.05), and serum Cu-Zn SOD, CAT and GSH-Px contents of Euthyrox group after surgery were higher than those of control group; serum Cu-Zn SOD, CAT and GSH-Px contents of both groups were significantly different between before and after surgery (P<0.05), and serum Cu-Zn SOD, CAT and GSH-Px contents of both groups after surgery were lower than those before surgery.

4. Discussion

The myocardial injury in the process of cardiopulmonary bypass surgery is related to a variety of factors. On the one hand, the myocardial tissue traction by operation can cause different degrees of local tissue damage; on the other hand, the heart experiences ischemia reperfusion process after arrest, which will damage the myocardial cells through the over-activation of local inflammation and oxidative stress[5,6]. In recent years, the studies on the factors related to myocardial injury during cardiopulmonary bypass have shown that the low thyroid hormone level in the body is closely related to the occurrence of myocardial injury[7,8]. cTnl, LDH, CK-MB and H-FABP are important structural and functional molecules in myocardial cells, which are released into the blood circulation during cell injury[9,10]. In the study, preoperative oral levothyroxine was adopted to supplement thyroid hormones and increase thyroid hormone reserves in the body, and analysis of the changes in serum myocardial injury markers before and after cardiopulmonary bypass operation showed that compared with myocardial injury markers of same group before surgery, serum cTnl, LDH, CK-MB and H-FABP contents were significantly higher after surgery. This indicates that there are different degrees of myocardial injury during cardiopulmonary bypass. Further analysis of the differences in serum myocardial injury markers between the two groups after surgery showed that compared with myocardial injury markers of control group after surgery, serum cTnl, LDH, CK-MB and H-FABP contents of Euthyrox group were significantly lower. This indicates that preoperative supplementation of levothyroxine may help reduce myocardial injury during cardiopulmonary bypass.

Brain is the organ most sensitive to ischemia hypoxia and ischemia reperfusion in the body, and both non-physiological blood perfusion during cardiopulmonary bypass and ischemia reperfusion during cardiac arrest can cause brain damage. NSE and S100B are the markers in neurons and glial cells in the brain tissue. The rupture of cells during ischemia reperfusion injury may cause these molecules to be released into the blood circulation. The cerebral damage during cardiopulmonary bypass operation is not only manifested...
in the changes of serum biochemical indexes, but will also be manifested in the increase of cerebral oxygen metabolism, and the increase of SjvO$_2$ level may reflect the increase of cerebral oxygen metabolism.$^{[11,12]}$. In the study, analysis of the changes in serum cerebral injury indexes before and after cardiopulmonary bypass surgery showed that compared with cerebral injury indexes of same group after surgery, NSE and S100B contents as well as SjvO$_2$ levels were significantly higher after surgery. This indicates that there are different degrees of cerebral injury during cardiopulmonary bypass. Further analysis of the differences in cerebral injury indexes between the two groups after surgery showed that compared with cerebral injury markers of control group after surgery, NSE and S100B contents as well as SjvO$_2$ level of Euthyrox group were significantly lower. This shows that the preoperative supplementation of levothyroxine may help to reduce the cerebral damage during cardiopulmonary bypass operation.

Inflammation is an important pathological link causing tissue viscera injury in the process of cardiopulmonary bypass, and a variety of pro-inflammatory and adhesion molecules can promote inflammatory cell infiltration in local tissue and activate inflammation to cause inflammatory tissue damage.$^{[13]}$. CD11b/CD18 and sP-selectin are the cytokines with adhesion effect, the former identifies the ICAM, VCAM and other molecules to promote CD11b/CD18 and sP-selectin, IL-1 and IL-10 have pro-inflammatory and anti-inflammatory effects respectively, the mass secretion of the former mediates the cascade activation of the inflammatory response, and the compensatory secretion of the latter increases during the excessive activation of inflammatory response.$^{[15]}$. Analysis of the changes in serum pro-inflammatory and adhesion molecules before and after cardiopulmonary bypass surgery showed that compared with pro-inflammatory and adhesion molecules of same group before surgery, serum CD11b/CD18, sP-selectin, IL-1 and IL-10 contents were significantly higher after surgery. This indicates that the inflammatory response is activated in different degrees during the cardiopulmonary bypass. Further analysis of the differences in serum pro-inflammatory and adhesion molecules between the two groups after surgery showed that compared with antioxidant indexes of same group before surgery, serum Cu-Zn SOD, CAT and GSH-Px contents of Euthyrox group were significantly higher after surgery. This indicates that there are different degrees of cerebral injury indexes before and after cardiopulmonary bypass surgery showed that compared with antioxidant indexes of same group before surgery, serum Cu-Zn SOD, CAT and GSH-Px contents were significantly lower after surgery. This indicates that the oxidative stress response is activated in different degrees and the antioxidant enzymes are continuously consumed during cardiopulmonary bypass. Further analysis of the differences in serum antioxidant indexes between the two groups after surgery showed that serum Cu-Zn SOD, CAT and GSH-Px contents of Euthyrox group were significantly higher than those of control group. This means that preoperative supplementation of levothyroxine can help relieve the oxidative stress and reduce the consumption of antioxidant enzymes during cardiopulmonary bypass surgery.

Levothyroxine supplementation one week before cardiopulmonary bypass operation can alleviate the myocardial and cerebral injury during the operation, and inhibiting the activation of inflammatory and oxidative stress response in the process of cardiopulmonary bypass is the possible mechanism for preoperative levothyroxine to protect the tissue.

Excessive activation of oxidative stress response is another pathological link closely related to the tissue viscera damage during cardiopulmonary bypass, and the mass generation of oxygen free radicals will directly cause oxidizing damage to the tissue, and can also cause the mass consumption of a variety of antioxidants.$^{[16,17]}$. Cu-Zn SOD, CAT and GSH-Px are catalytic enzymes that play an antioxidant role in myocardial and cerebral tissue, and they can catalyze the reduction reaction of oxygen free radicals and be removed.$^{[18-20]}$. Analysis of the changes in serum antioxidant indexes before and after cardiopulmonary bypass surgery showed that compared with antioxidant indexes of same group before surgery, serum Cu-Zn SOD, CAT and GSH-Px contents were significantly lower after surgery. This indicates that the oxidative stress response is activated in different degrees and the antioxidant enzymes are continuously consumed during cardiopulmonary bypass. Further analysis of the differences in serum antioxidant indexes between the two groups after surgery showed that serum Cu-Zn SOD, CAT and GSH-Px contents of Euthyrox group were significantly higher than those of control group. This means that preoperative supplementation of levothyroxine can help relieve the oxidative stress and reduce the consumption of antioxidant enzymes during cardiopulmonary bypass surgery.

Levothyroxine supplementation one week before cardiopulmonary bypass operation can alleviate the myocardial and cerebral injury during the operation, and inhibiting the activation of inflammatory and oxidative stress response in the process of cardiopulmonary bypass is the possible mechanism for preoperative levothyroxine to protect the tissue.

References


