Effect of aerobic exercise + relaxation training on the cytokine secretion and endothelial injury in patients with coronary heart disease

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ABSTRACT

Objective: To study the effect of aerobic exercise + relaxation training on the cytokine secretion and endothelial injury in patients with coronary heart disease. Methods: Patients who were diagnosed with stable angina pectoris in West China Hospital, Sichuan University between August 2014 and October 2017 were enrolled in the study and divided into the exercise training group who accepted aerobic exercise + relaxation training and the normal control group who accepted routine intervention. The levels of cytokines and endothelial injury molecules in serum as well as the expression of oxidative stress molecules in peripheral blood were determined before intervention as well as 56 d and 112 d after intervention. Results: Compared with the corresponding indexes of same group before intervention, serum FGF21, MIF, MIP-1α, SDF-1α, sICAM1, vWF, ET-1, sVCAM-1 and ESM1 levels as well as peripheral blood MPO, NOX2, NOX4, LOX-1 and CX3CR1 expression intensity of both groups of patients were significantly lower 56 d and 112 d after intervention, and serum FGF21, MIF, MIP-1α, SDF-1α, sICAM1, vWF, ET-1, sVCAM-1 and ESM1 levels as well as peripheral blood MPO, NOX2, NOX4, LOX-1 and CX3CR1 expression intensity of exercise training group 56 d and 112 d after intervention were lower than those of normal control group. Conclusion: Aerobic exercise + relaxation training can reduce the secretion of inflammatory cytokines and the degree of endothelial oxidative stress injury in patients with coronary heart disease.

1. Introduction

Coronary heart disease is a common cardiovascular disease in China, its incidence is increasing year by year and it poses great harm to people's health[1]. In the progression of coronary heart disease, the increasing of coronary artery atheromatous plaque volume can aggravate the pathological conditions of luminal stenosis and insufficient myocardial perfusion, and the change of plaque nature can cause the platelet activation and aggregation as well as local thrombosis and increase the myocardial ischemia. The mass secretion of inflammatory cytokines and the excessive damage of endothelial function are the important pathological factors for the increase of atherosclerotic plaque volume and the change of its property in the course of coronary heart disease. In clinical practice, antiplatelet agents and statins are the routine drugs for coronary heart disease, and can antagonize platelet activation and aggregation, stabilize atheromatous plaque and prevent coronary thrombosis. In recent years, the value of exercise training for adjuvant treatment of coronary heart disease has received more and more attention, and reasonable exercise and training can not only enhance the cardiac reserve function, but can also adjust homeostasis and hinder or delay several pathological links during atherosclerosis progression[2-3]. It has been confirmed that aerobic exercise and relaxation training have positive application value in patients with coronary heart disease, but it is not yet clear about the changes of cytokine secretion and endothelial damage degree in patients with coronary heart disease after exercise training. In the following studies, we specifically analyzed the effect of aerobic exercise + relaxation training on the cytokine secretion and endothelial injury in patients with coronary heart disease.
2. Research and experimental methods

2.1. Case including and grouping information

Patients who were diagnosed with stable angina pectoris in West China Hospital, Sichuan University between August 2014 and October 2017 were enrolled in the study, all patients were diagnosed with stable angina pectoris by clinical symptoms, signs, electrocardiography and coronary CTA, and the patients combined with cardiac organic diseases such as atrioventricular block and chronic heart failure, and those with history of myocardial infarction or cerebral infarction attack were ruled out. A total of 144 cases were enrolled and divided into two groups by random number table method, each with 72 cases. There were 38 males and 34 females in the exercise training group, and they were 42-67 years old; there were 40 males and 32 females in the control group, and they were 41-65 years old. There was no significant difference in the general data between the two groups (P>0.05).

2.2. Exercise training intervention

After exercise training group were enrolled, 6 min walk test (6MWT) results were referred to establish aerobic exercise and relaxation training plan, and the method was as follows: patients with 6MWT<300 meters mainly walked, 20-30 min every time, 2-3 times per week; patients with 6MWT > 300 meters conducted 15 min of walking, 10 min of cycling and 10 min of cranking each time, 3-4 times a week; when no aerobic exercise was done, relaxation exercises were conducted every week: patients took a comfortable lying or sitting posture, breathed through nose and kept physical relaxation and inner peace, which lasted for 20-30 min.

2.3. Laboratory index detection

Before intervention as well as 56 d and 112 d after intervention, two parts of cubital venous blood specimens were collected, one was about 6-8 mL and centrifuged to separate serum, and Elisa kit instructions were followed to determine FGF21, MIF, MIP-1α, SDF-1α, sICAM1, vWF, ET-1, sVCAM-1 and ESM1 contents; the other part was about 1-2 mL and anti-coagulated with EDTA to incubate the fluorescence antibody of MPO, NOX2, NOX4, LOX-1 and CX3CR1, and then their expression intensity was determined on the flow cytometer.

2.4. Statistical methods

Software SPSS 23.0 was used for statistical processing, the measurement data between two groups were analyzed by t test and P <0.05 indicated statistical significance in differences.

3. Results

3.1. Changes of serum cytokine levels before and after intervention

Before intervention as well as 56 d and 112 d after intervention, analysis of serum cytokines FGF21 (pg/mL), MIF (pg/mL), MIP-1α (pg/mL), SDF-1α (μg/mL) and sICAM1 (ng/mL) levels in the two groups of patients was as follows: compared with the cytokines of same group before intervention, serum FGF21, MIF, MIP-1α, SDF-1α and sICAM1 levels of both groups of patients were significantly lower 56 d and 112 d after intervention (P<0.05); serum FGF21, MIF, MIP-1α, SDF-1α and sICAM1 levels were not significantly different between the two groups before intervention (P>0.05) while they were significantly different 56 d and 112 d after intervention (P<0.05), and serum FGF21, MIF, MIP-1α, SDF-1α and sICAM1 levels of exercise training group were lower than those of normal control group.

3.2. Changes of serum endothelial injury molecule levels before and after intervention

Before intervention as well as 56 d and 112 d after intervention, analysis of serum endothelial injury molecules vWF (U/mL), ET-1, sVCAM-1 (ng/mL) and ESM1 (ng/mL) levels in the two groups of patients was as follows: compared with the endothelial injury molecules of same group before intervention, serum vWF, ET-1, sVCAM-1 and ESM1 levels of both groups of patients were significantly lower 56 d and 112 d after intervention (P<0.05); serum vWF, ET-1, sVCAM-1 and ESM1 levels were not significantly different between the two groups before intervention (P>0.05) while they were significantly different 56 d and 112 d after intervention (P<0.05), and serum vWF, ET-1, sVCAM-1 and ESM1 levels of exercise training group were lower than those of normal control group.

Table 1.

Differences of serum cytokine levels in the two groups of patients before and after intervention.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time</th>
<th>FGF21</th>
<th>MIF</th>
<th>MIP-1α</th>
<th>SDF-1α</th>
<th>sICAM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise training</td>
<td>328.6±42.6</td>
<td>73.6±9.3</td>
<td>28.5±3.6</td>
<td>2.4±0.32</td>
<td>584.8±72.3</td>
<td></td>
</tr>
<tr>
<td>group 72</td>
<td>56 d after</td>
<td>193.5±22.5</td>
<td>48.7±6.6</td>
<td>16.5±2.2</td>
<td>1.35±0.17</td>
<td>304.6±38.7</td>
</tr>
<tr>
<td></td>
<td>112 d after</td>
<td>159.4±18.3</td>
<td>36.7±5.1</td>
<td>12.7±1.8</td>
<td>1.02±0.15</td>
<td>256.4±29.3</td>
</tr>
<tr>
<td>Control group</td>
<td>331.2±46.2</td>
<td>74.5±9.7</td>
<td>29.1±3.2</td>
<td>2.36±0.38</td>
<td>591.2±72.5</td>
<td></td>
</tr>
<tr>
<td>group 72</td>
<td>56 d after</td>
<td>245.6±29.5</td>
<td>60.2±8.8</td>
<td>22.4±2.9</td>
<td>1.88±0.24</td>
<td>413.6±55.8</td>
</tr>
<tr>
<td></td>
<td>112 d after</td>
<td>221.3±26.4</td>
<td>54.6±7.1</td>
<td>18.6±2.5</td>
<td>1.61±0.20</td>
<td>356.2±42.3</td>
</tr>
</tbody>
</table>

<sup>*</sup> Comparison between before and after intervention within the two groups, P<0.05; <sup>#</sup> comparison between the two groups after intervention, P>0.05.
than those of normal control group. CX3CR1 expression intensity of exercise training group were lower than those of normal control group. Smoking and hypertension are all its risk factors. In the progression of coronary heart disease, the increase of coronary artery atheromatous plaque and lumen stenosis, and diabetes, hypertension, hyperlipidemia can accelerate the formation of atherosclerotic plaque. Studies have shown that the cardiac function of patients with coronary heart disease has been significantly improved after aerobic exercise and relaxation training intervenes, but there is no report about the influence of aerobic exercise and relaxation training on atheromatous plaque-related pathophysiological links in the course of coronary heart disease.

Inflammatory response is an important pathological change throughout the course of coronary heart disease. Artery atheromatous plaque formation depends on the foam cells formed after mononuclear macrophages devour lipids, the change of plaque nature volume can cause narrowed coronary vascular lumen and reduced myocardial blood supply, and when exercise, fatigue, stress and other factors increase cardiac work and oxygen consumption, insufficient myocardial blood supply will occur, and cause the clinical manifestations of angina pectoris attack; when the nature of coronary artery atheromatous plaque changes and its stability reduces, the platelets will accumulate in local plaque and form thrombus, and severe cases can cause lumen occlusion and lead to the occurrence of acute myocardial infarction. In clinical practice, antiplatelet agents and statins can antagonize platelet activation and aggregation, stabilize atheromatous plaque and prevent coronary thrombosis, so they are widely used in the routine treatment of coronary heart disease. In addition to medication, exercise training is a common intervention method for patients with coronary heart disease, especially those with stable angina pectoris, and reasonable exercise intervention method for patients with coronary heart disease, and can also regulate homeostasis and delay the development of atherosclerosis. Studies have shown that the cardiac function of patients with coronary heart disease has been significantly improved after aerobic exercise and relaxation training intervenes, but there is no report about the influence of aerobic exercise and relaxation training on atheromatous plaque-related pathophysiological links in the course of coronary heart disease.

### Table 2.
Differences of serum endothelial injury molecule levels in the two groups of patients before and after intervention.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>vWF</th>
<th>ET-1</th>
<th>sVCAM-1</th>
<th>ESM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise training group</td>
<td></td>
<td>Before intervention</td>
<td>1.74±0.2236</td>
<td>131.2±16.8</td>
<td>237.2±33.6</td>
<td>1.62±0.22</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>56 d after intervention</td>
<td>1.23±0.1426</td>
<td>89.3±11.5</td>
<td>125.7±15.6</td>
<td>1.03±0.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>112 d after intervention</td>
<td>0.89±0.1126</td>
<td>70.3±8.9</td>
<td>101.2±13.6</td>
<td>0.89±0.12</td>
</tr>
<tr>
<td>Control group</td>
<td>72</td>
<td>Before intervention</td>
<td>1.75±0.2026</td>
<td>132.1±15.4</td>
<td>239.1±25.2</td>
<td>1.66±0.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>56 d after intervention</td>
<td>1.89±0.1642</td>
<td>113.6±13.2</td>
<td>177.5±20.3</td>
<td>1.35±0.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>112 d after intervention</td>
<td>1.13±0.1437</td>
<td>103.5±12.8</td>
<td>136.3±16.4</td>
<td>1.15±0.14</td>
</tr>
</tbody>
</table>

*: Comparison between before and after intervention within the two groups, P<0.05; #: comparison between the two groups after intervention, P<0.05.

### Table 3.
Differences of peripheral blood oxidative stress molecule expression in the two groups of patients before and after intervention.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>MPO</th>
<th>NOX2</th>
<th>NOX4</th>
<th>LOX-1</th>
<th>CX3CR1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise training group</td>
<td>72</td>
<td>Before intervention</td>
<td>0.66±0.07</td>
<td>1.02±0.13</td>
<td>0.98±0.15</td>
<td>0.72±0.08</td>
<td>0.38±0.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>56 d after intervention</td>
<td>0.42±0.07</td>
<td>0.58±0.07</td>
<td>0.67±0.08</td>
<td>0.51±0.07</td>
<td>0.47±0.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td>112 d after intervention</td>
<td>0.42±0.07</td>
<td>0.58±0.07</td>
<td>0.67±0.08</td>
<td>0.51±0.07</td>
<td>0.47±0.07</td>
</tr>
<tr>
<td>Control group</td>
<td>72</td>
<td>Before intervention</td>
<td>1.03±0.14</td>
<td>0.98±0.13</td>
<td>1.02±0.13</td>
<td>1.02±0.14</td>
<td>0.99±0.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>56 d after intervention</td>
<td>0.79±0.08</td>
<td>0.72±0.08</td>
<td>0.84±0.11</td>
<td>0.65±0.08</td>
<td>0.62±0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>112 d after intervention</td>
<td>0.66±0.07</td>
<td>0.56±0.06</td>
<td>0.62±0.08</td>
<td>0.51±0.07</td>
<td>0.41±0.06</td>
</tr>
</tbody>
</table>

*: Comparison between before and after intervention within the two groups, P<0.05; #: comparison between the two groups after intervention, P<0.05.

3.3. Changes of peripheral blood oxidative stress molecule expression before and after intervention.

Before intervention as well as 56 d and 112 d after intervention, analysis of peripheral blood oxidative stress molecules MPO, NOX2, NOX4, LOX-1 and CX3CR1 expression in the two groups of patients was as follows: compared with the oxidative stress molecules of same group before intervention, peripheral blood MPO, NOX2, NOX4, LOX-1 and CX3CR1 expression intensity of both groups of patients were significantly lower 56 d and 112 d after intervention (P<0.05), and serum vWF, ET-1, sVCAM-1 and ESM1 levels of exercise training group were lower than those of normal control group.

4. Discussion

Coronary heart disease is a basic cardiovascular disease with the pathological basis of coronary atherosclerotic plaque formation and lumen stenosis, and diabetes, hypertension, hyperlipidemia and smoking are all its risk factors. In the progression of coronary heart disease, the increase of coronary artery athromatous plaque...
plaques by promoting the proliferation of fibroblast[8]; MIP-1 α is a kind of cytokine with extensive chemotaxis effect, which has chemotactic effect on mononuclear macrophages, lymphocytes, neutrophils and various other inflammatory cells, and can make inflammatory cells infiltrate in vascular endothelium and damage endothelial function[9]; SDF-1 α is a cytokine that has chemotactic effect on smooth muscle cells and inflammatory cells, which can not only activate the inflammation inside the atheromatous plaque, but can also cause smooth muscle cell proliferation, lead to arterial intima-media thickening and aggravate luminalstenosis[10]; sICAM1 is a cytokine with adhesion effect, which promotes the adhesion of inflammatory cells and platelets to atherosclerotic plaques[11]. Analysis of the changes in above serum cytokine levels before and after exercise training intervention showed that compared with the cytokines of same group before intervention, serum FGF21, MIF, MIP-1 α, SDF-1 α and sICAM1 levels of both groups of patients were decreasing after intervention, and serum FGF21, MIF, MIP-1 α, SDF-1 α and sICAM1 levels of exercise training group after intervention were lower than those of normal control group. This indicates that aerobic exercise + relaxation training can reduce the secretion of inflammatory cytokines in patients with stable angina pectoris and inhibit the inflammatory response in the course of coronary heart disease.

Endothelial injury is the initiating link in the formation of coronary artery atheromatous plaque, both inflammatory cells and lipids can deposit and infiltrate in local damaged area after the vascular endothelial structure and function are damaged, and then the formation process of atheromatous plaque is started through the lipid phagocytosis by inflammatory cells. vWF and ET-1 are marker molecules to reflect endothelial injury, the former is a kind of adhesion protein and participates in the platelet and endothelial cell adhesion, the latter is a kind of vasoactive peptide and participates in the platelet aggregation. vWF and ET-1 increase the release of vWF and ET-1[12-14]. sVCAM-1 is the soluble form of endothelial cell-specific adhesion molecule VCAM-1, VCAM-1 can mediate endothelial cell adhesion process and ensure the integrity of endothelial structure and function, and VCAM-1 falls off in great quantities and becomes sVCAM-1 when endothelial injury occurs[15]. ESM1 is the newly discovered endothelial cell-specific molecule in recent years, which is widely expressed in the macrovascular and microvascular endothelial matrix, has significantly promoting effect on the vascular smooth muscle cell proliferation and is closely related to the thickening of intima-media in the process of atherosclerosis. Analysis of the changes in above serum endothelial injury molecule levels exercise training before and after intervention showed that compared with the endothelial injury molecules of same group before intervention, serum vWF, ET-1, sVCAM-1 and ESM1 levels of both groups of patients were decreasing, and serum vWF, ET-1, sVCAM-1 and ESM1 levels of exercise training group after intervention were lower than those of normal control group. This indicates that aerobic exercise + relaxation training can reduce the release of endothelial injury molecules in patients with stable angina pectoris and reduce the degree of endothelial injury in the course of coronary heart disease.

The occurrence of endothelial function injury in patients with coronary heart disease is closely related to the excessive activation of oxidative stress and the mass production of oxygen free radicals. MPO is a kind of metabolic enzyme massively expressed after neutrophil activation, which can use hydrogen peroxide to catalyze and generate the strongly oxidizing hypochlorous acid, then modify LDL into ox-LDL through the oxidation activity of hypochlorous acid, participate in the formation of atheromatous plaque, cause the oxidation of lipids and proteins in the endothelial cell structure and damage the endothelial integrity[16,17]. NOX2 and NOX4 are the NOX family members mainly expressed in cardiovascular system, which can catalyze the mass generation of hydrogen peroxide, superoxide anion and other reactive oxygen species in the local area, and then cause endothelial oxidative damage through the oxidation activity of reactive oxygen species[18,19]. LOX-1 and CX3CR1 are receptors located in the cell membrane, the former identifies ox-LDL, the latter identifies CX3CL1, and they can mediate the mass formation and infiltration of foam cells, and then accelerate the formation of atheromatous plaque[20]. Analysis of the changes in above peripheral blood oxidative stress molecule expression before and after exercise training intervention showed that compared with the oxidative stress molecules of same group before intervention, peripheral blood MPO, NOX2, NOX4, LOX-1 and CX3CR1 expression intensity of both groups of patients were decreasing after intervention, and peripheral blood MPO, NOX2, NOX4, LOX-1 and CX3CR1 expression intensity of exercise training group after intervention were lower than those of normal control group. This indicates that aerobic exercise + relaxation training can reduce the expression of oxidative stress molecules in peripheral blood of patients with stable angina pectoris and reduce the activation degree of oxidative stress response in the course of coronary heart disease. Aerobic exercise + relaxation training can reduce the release of inflammatory cytokines and endothelial injury molecules as well as the expression of oxidative stress molecules in patients with coronary heart disease, and it has positive clinical value for reducing both inflammation and endothelial oxidative stress injury.

References


