Influences of simvastatin on vascular endothelial function of patients with coronary heart disease complicated with congestive heart failure

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Abstract. – OBJECTIVES: The aim of this study was to investigate the influences of Simvastatin (Zocor) on nitric oxide (NO), calcitonin gene related peptide (CGRP) and endothelin (ET) in blood plasma of patients with coronary heart disease (CHD) complicated with congestive heart failure (CHF).

PATIENTS AND METHODS: 80 cases of patients with CHD complicated with CHF were randomly divided into two groups: the conventional treatment (control) group (Digoxin, Dihydropyridone, Isosorbide dinitrate) containing 40 cases and the conventional treatment and Simvastatin (combination) combination group containing 40 cases. In addition, there were 40 healthy persons in the normal group. Greiss method was used for NO detection, and immunoradiometry method was used to detect CGRP and ET levels in blood before and after treatment.

RESULTS: NO and CGRP levels in blood of patients with CHD complicated with CHF was apparently lower than those of the normal group, and there were significant differences (p < 0.01). Also, ET was significantly higher than that of the normal group (p < 0.01). After treatment, all indicators were significantly improved (p < 0.01). Also, the improvement of the conventional treatment plus Simvastatin group was more significant. Compared with the conventional treatment group after treatment, there was a significant difference (p < 0.05).

CONCLUSIONS: The combination of conventional treatment and Simvastatin could significantly improve metabolic disturbances of NO, CGRP and ET of patients with CHD complicated with CHF.

Key Words: Simvastatin, Coronary heart disease, Congestive heart failure, Nitric oxide, Calcitonin gene related peptide, Endothelin.

Introduction

Coronary heart disease (CHD) complicated with congestive heart failure is a common critical illness. For a long time, diagnosis and evaluation criteria usually are lack of specificity and sensitivtiy, which easily causes excessive diagnosis and missed diagnosis. Congestive heart failure (CHF) is one of severe stages and the final destination of various heart diseases. It has become one of main problems of influencing human health due to high mortality rate. Vascular endothelial cell (VEC) injury is the initiation stage of coronary heart disease, and a series of pathophysiological changes occurring after VEC injury. Especially the imbalance of vasoconstriction and vasodilation substances, are the main factors of CHD progress. As vascular endothelial dysfunction, patients with congestive heart failure suffer from vasodilation function damage, which causes increase of basic angiotasis. This is related to the increase of endothelin (ET) in intracorporeal blood plasma. As a peptide substance, CGRP is an important neurotransmitter of regulating cardiovascular activity. At present, CGRP is the strongest found vasodilatory substance, and it maintains the stability of systemic circulation by regulating local angiotasis and has an antagonism to ET. The two play an important role in maintaining normal angiotasis. ET with vasoconstriction function and calcitonin gene related peptide (CGRP) with vasodilation function have an important effect for maintaining normal angiotasis. Nitric oxide (NO) is an enzymatic biological active substance synthesized by vascular endothelial cell, and its precursor is L-arginine with a strong vasodilative effect. Also, the precursor can inhibit platelet adhesion and aggregation, and it is the important informational molecule and effector molecule in body. Endothelin (ET) is a strong and long-lasting vasoconstrictor peptide that produced by endothelial cells, which can induce myocardial ischemia and re-construction through promoting the activating and proliferation of vascular smooth muscle cells. Endothelial cell injury mainly shows that

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secretion of active substance imbalance and apoptosis increase, especially the releasing of ET-1 increase, ET-1 can stimulate superoxide formation and damage the endothelial dependent vascular diastolic function14.

Statins drugs are common antihyperlipidemics in cardiovascular department in clinic. They blocks synthesis of the intermediate products and the final product cholesterol of mevalonate metabolism by competitively inhibiting 3-hydroxy-3-methylglutaric acid Coenzyme A (HMG-CoA) reductase and reduces total cholesterol and LDL cholesterol in blood plasma15,16. In recent years, studies suggest that the main mechanism of statins resisting Aslies in its immunomodulation effect, rather than blood lipid regulation. For influences of statins on vascular function of patients with coronary heart disease complicated with congestive heart failure, it is still unclear. Therefore, this study is to observe the influences of Simvastatin (Zocor) on VEC function of patients with CHD complicated with CHF.

Statistical Analysis

All data were expressed as ± SD. t test was used for comparison between two groups, and variance analysis was used for comparisons among multiple groups.

Results

Results were shown in Table I. NO and CGRP levels in blood plasma of CHD complicated with CHF were significantly lower than those of the normal group (p < 0.01), and ET was significantly higher than that of the normal group (p < 0.01); Compared with before treatment, NO, CGRP and ET of the two groups after treatment were significantly improved (p < 0.05), and the improvement of the combination group was more significant (p < 0.01). After treatment, there was a significant difference between the combination group and the conventional treatment group (p < 0.05).

Discussion

CHD is one kind of complex disease induced by a variety of causes. CGRP can protect ischemic cardiac muscle cells and endothelial cells and can inhibit the proliferation of vascular smooth muscle cells. Some researchers found that in case of CHD or CHF, CGRP in blood plasma reduced. Worse heart function was,
CGRP level was lower. It was speculated that decrease of vasocostriction force caused by low CGR level was one of heart failure occurrence mechanisms\textsuperscript{16}. At present, it is thought that the receptor affecting vascular endothelial cell enhances intracellular calcium ion concentration by cyclic adenosine monophosphate pathway and up-regulates the activity of nitric oxide synthetase (NOS) to generate nitric oxide and achieve the vasodilatory effect\textsuperscript{[17,18]}. As angiotasis is the result of interaction of vascular contraction factor and relaxing factor, it is the method of improving heart function of patients with heart failure to correct the imbalance of basic vasoconstriction force and vasodilatation force by reducing increased basic angiotasis. The results of this study also showed that in case of CHD complicated with CHF, CGRP level in blood plasma significantly reduced. ET is a 21-peptide vasoactive substance secreted by endothelial cell. It has a strong vasoconstrictive effect. Also, it can inhibit heart function to quicken CHF development. CGRP and ET can generate a opposite and antagonisticeffect to heart and hemodynamics in vivo\textsuperscript{19,20}.

Non-lipid-lowering effect of Statins refers to the direct anti-atherosclerotic effect other than lipid-lowering effect, and it specifically includes enhancing plaque stability, anti-inflammatory, antimicrobial and antithrombotic effects and inhibiting migration and proliferation of vascular smooth muscle cells\textsuperscript{21-23}. Statins possibly stabilize plaque by reducing macrophage and cholesterol lipid contents in atherosclerotic plaque and increasing local collagen and smooth muscle cell contents; Statins can maintain the good balance of prothrombin and fibrinolytic system to reduce the thrombosis opportunity after plaque rupture by inhibiting local platelet aggregation of plaque\textsuperscript{24}. It will cause great reduction of incidence rate of individual cardiovascular event to use Simvastatin to control ET secretion and increase the effect of NO and CGRP resisting ET and can significantly improve the prognosis of CHD complicated with CHF\textsuperscript{25,26}.

For patients with CHD, due to endothelial cell injury caused by atherosclerosis, NO and CGRP secretions reduce and ET secretion increases, which further causes the unbalance of vascular endothelial function and promotes and aggravates coronary atherosclerosis formation. In cases of CHD complicated with CHF, vascular endothelial function unbalance is aggravated. According to this study, it was found that both the conventional treatment and the combination of conventional treatment and Simvastatin could improve the metabolic disturbances of NO, CGRP and ET of patients with CHD complicated with CHF, and the improvement of combination of conventional treatment and Simvastatin was more significant. After treatment, Simvastatin significantly increased NO and CGRP in serum (\( p < 0.05 \)) and reduced serum ET (\( p < 0.05 \)), indicating that one of mechanisms of Simvastatin relieving coronary heart disease complicated with congestive heart failure was to increase NO and CGRP contents and reduce ET.

### Conclusions

Besides the traditional blood lipid regulation, statins can regulate inflammation, inhibit thrombosis, regulate cell adhesion, inhibit migration and proliferation of smooth muscle cells and regulate endothelial cell function. Also, statins can more easily induce apoptosis of vascular smooth muscle cells in hyperplasia intima after vascular injury and thus possibly reduce the occurrence rate of vascular stenosis. At the same time, it can induce apoptosis of smooth muscle cells.

### Table I. Comparison of NO, CGRP, ET among different group (\( \pm s, \mu g/ml \)).

<table>
<thead>
<tr>
<th>Group</th>
<th>Case ( n )</th>
<th>NO</th>
<th>CCRT</th>
<th>ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control</td>
<td>40</td>
<td>119.7 ± 56.5</td>
<td>83.7 ± 15.4</td>
<td>45.5 ± 9.2</td>
</tr>
<tr>
<td>Conventional treatment</td>
<td></td>
<td>33.2 ± 20.1(^a)</td>
<td>23.5 ± 7.9(^a)</td>
<td>95.8 ± 12.1(^a)</td>
</tr>
<tr>
<td>After treatment</td>
<td>40</td>
<td>55.5 ± 21.8(^b)</td>
<td>35.6 ± 11.2(^b)</td>
<td>62.3 ± 12.1(^b)</td>
</tr>
<tr>
<td>Combined treatment</td>
<td>40</td>
<td>36.7 ± 18.9(^c)</td>
<td>23.6 ± 10.2(^c)</td>
<td>121.1 ± 18.6(^c)</td>
</tr>
<tr>
<td>After treatment</td>
<td>40</td>
<td>82.5 ± 28.7(^d)</td>
<td>56.1 ± 12.1(^d)</td>
<td>54.8 ± 8.6(^d)</td>
</tr>
</tbody>
</table>

Note: \(^a\) \( p < 0.01 \), versus normal control group; \(^b\) \( p < 0.05 \), versus before treatment; \(^c\) \( p < 0.05 \), versus before treatment; \(^d\) \( p < 0.05 \), versus before treatment of conventional treatment group.
References


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