European Review for Medical and Pharmacological Sciences 2013; 17: 1590-1593

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

L. WANG, J. SHI[1], Y. ZHANG[1]

Department of Emergency Medicine, People's Hospital of Zhengzhou, Zhengzhou, China
[1]The First Affiliated Hospital of Xinxiang Medical University, Weihui, China

**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, Dihydrochlorothiazide, 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 sensitivity, which easily causes excessive diagnosis and missed diagnosis[1-3]. 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[4,5]. 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 intracorporal blood plasma[6,7]. 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[8-10]. 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[11,12]. Endothelin (ET) is a strong and long-lasting vasoconstrictor peptide that produced by endothelial cells, which can induce myocardial ischemia and reconstruction through promoting the activating and proliferation of vascular smooth muscle cells[13]. Endothelial cell injury mainly shows that



*Corresponding Author:* Ling Wang, MD; e-mail: lingwang001@126.com

secreting of active substance imbalance and apoptosis increase, especially the releasing of ET-1 increase, ET-I can stimulate superoxide formation and damage the endothelial dependent vascular diastolic function[14].

Statins drugs are common antihyperlipidemics in cardiovascular department in clinic. They blocks syntheses 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 plasma[15,16]. In recent years, studies suggest that the main mechanism of statins resisting Aslies in its immunoloregulation 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.

## Patients and Methods

### Patients

80 cases of patients with CHD complicated with CHF were selected. They were all hospitalized patients, and heart function was of NY grade II to IV. CHF disease course was 5 to 12 years, and the average duration was 7.8 ± 5.2 years. There were 52 male cases and 28 cases, their ages were between 40 and 72 years old, and the average age was 63.5 ± 5.3 years old. All cases complied with WHO diagnostic code. Also, cases with acute myocardial infarction (AMI) found within 1 year were excluded in this study. According to the order of hospitalization, they were randomly divided into the conventional treatment control group and the conventional treatment and Simvastatin combination group, and there were 40 cases in each group. For age, gender and disease course, there was no significant difference between the two groups. In the normal group, the subjects were healthy persons examined in our hospital. There were 48 males and 32 females. Their ages were between 39 and 76 years old, and the average age was 60.5 ± 5.9 years old.

### Methods

For all patients, 7 ml fasting venous blood was drawn in the next morning after hospitalization. For normal persons, 7 ml fasting venous blood was drawn in the current morning. Subsequently, 2 ml (detect NO), 3 ml (detect CGRP) and 2 ml (detect ET) venous blood were respectively placed into three tubes with 30 μl EDTA-2Na of 10% and 40 ml trasylol and stored at 4°C for detection of the same batch. Greiss method was used for NO detection. In the acidic condition, Greiss diazo reaction occurred. Therefore, it was feasible to indirectly determine intracorporal NO level by detecting concentrations of NO metabolites nitrate and nitrite. For the detections of CGRT and ET, immunoradiometry method was used (East Asia Immunology Institute of PLA General Hospital, Beijing, China). In the conventional treatment group, 0.125 to 0.25 mg of Digoxin tablet (qd), 10 mg of Isosorbide dinitrate tablet (tid) and 12.5-25 mg of Dihydrochlorothiazide (qd) were administered. For the combination group, besides drugs for the conventional treatment group, 20 mg of simvastatin was administered additionally, 1 time/day. After 4 weeks, venous blood was drawn again for re-examining the above indicators.

### 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,

**Table I.** Comparison of NO, CCRP, ET among different group (± s, μg/ml).

| Group | Case (n) | No | CCRT | ET |
|---|---|---|---|---|
| Normal control | 40 | 119.7 ± 56.5 | 83.7 ± 15.4 | 45.5 ± 9.2 |
| Conventional treatment | | | | |
| Before treatment | 40 | 33.2 ± 20.1[a] | 23.5 ± 7.9[a] | 95.8 ± 12.1[a] |
| After treatment | 40 | 55.5 ± 21.8[b] | 35.6 ± 11.2[b] | 62.3 ± 12.1[b] |
| Combined treatment | | | | |
| Before treatment | 40 | 36.7 ± 18.9[c] | 23.6 ± 10.2[c] | 121.1 ± 18.6[c] |
| After treatment | 40 | 82.5 ± 28.7[d] | 56.1 ± 12.1[d] | 54.8 ± 8.6d |

*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.

CGRP level was lower. It was speculated that decrease of vasocontraction force caused by low CGR level was one of heart failure occurrence mechanisms[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[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 vasocontraction 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 vasocontractive effect. Also, it can inhibit heart function to quicken CHF development. CGRP and ET can generate a opposite and antagonistic effect to heart and hemodynamics *in vivo*[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[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[24]. It will cause great reduction of incidence rate of ndividual 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[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 occurence rate of vascular stenosis. At the same time, it can induce apoptosis of smooth muscle cells.

## References


1) Nappi JM, Sieg A. Aldosterone and aldosterone receptor antagonists in patients with chronic heart failure. Vasc Health Risk Manag 2011; 7: 353-363.
2) Palazzuoli A, Caputo M, Calabrò A, Nuti R. Clinical impact of BNP and other emerging biomarkers in heart failure evaluation and management. Minerva Cardioangiol 2012; 60: 183-194.
3) Saczynski JS, Andrade SE, Harrold LR, Tjia J, Cutrona SL, Dodd KS, Goldberg RJ, Gurwitz JH. A systematic review of validated methods for identifying heart failure using administrative data. Pharmacoepidemiol Drug Saf 2012; 21(Suppl 1): 129-140.
4) Lampka M, Gr bczewska Z, Jendryczka-Ma kiewicz E, Hoły ska-Iwan I, Sukiennik A, Kubica J, Halota W, Tyrakowski T. Circulating endothelial cells in coronary artery disease. Kardiol Pol 2010; 68: 1100-1105.
5) Martínez-Sales V, Sánchez-Lázaro I, Vila V, Almenar L, Contreras T, Reganon E. Circulating endothelial cells in patients with heart failure and left ventricular dysfunction. Dis Markers 2011; 31: 75-82.
6) Jarolim P. Serum biomarkers for heart failure. Cardiovasc Pathol 2006; 15: 144-149.
7) Moraes DL, Colucci WS, Givertz MM. Secondary pulmonary hypertension in chronic heart failure: the role of the endothelium in pathophysiology and management. Circulation 2000; 102: 1718-1723.
8) Dong YL, Vegiraju S, Chauhan M, Gangula PR, Hankins GD, Goodrum L, Yallampalli C. Involvement of calcitonin gene-related peptide in control of human fetoplacental vascular tone. Am J Physiol Heart Circ Physiol 2004; 286: H230-239.
9) Félétou M, Huang Y, Vanhoutte PM. Endothelium-mediated control of vascular tone: COX-1 and COX-2 products. Br J Pharmacol 2011; 164: 894-912.
10) Supowit SC, Ethridge RT, Zhao H, Katki KA, Dipette DJ. Calcitonin gene-related peptide and substance P contribute to reduced blood pressure in sympathectomized rats. Am J Physiol Heart Circ Physiol 2005; 289: 1169-1175.
11) Cattaneo MG, Cappellini E, Benfante R, Ragni M, Omodeo-Salè F, Nisoli E, Borgese N, Vicentini LM. Chronic deficiency of nitric oxide affects hypoxia inducible factor-1$\alpha$ (HIF-1$\alpha$) stability and migration in human endothelial cells. PLoS One 2011; 6: e29680.
12) Tousoulis D, Kampoli AM, Tentolouris C, Papageorgiou N, Stefanadis C. The role of nitric oxide on endothelial function. Curr Vasc Pharmacol 2012; 10: 4-18.
13) Burg MM, Martens EJ, Collins D, Soufer R. Depression predicts elevated endothelin-1 in patients with coronary artery disease. Psychosom Med 2011; 73: 2-6.
14) Amiri F, Virdis A, Neves MF, Iglarz M, Seidah NG, Touyz RM, Reudelhuber TL, Schiffrin EL. Endothelium-Restricted overexpression of human endothelin-1 causes vascular remodeling and endothelial dysfunction. Circulation 2004; 110: 2233-2240.
15) Ballantyne C, Gleim G, Liu N, Sisk CM, Johnson-Levonas AO, Mitchel Y. Effects of coadministered extended-release niacin/laropiprant and simvastatin on lipoprotein subclasses in patients with dyslipidemia. J Clin Lipidol 2012; 6: 235-243.
16) Gopa B, Bhatt J, Hemavathi KG. A comparative clinical study of hypolipidemic efficacy of Amla (Emblica officinalis) with 3-hydroxy-3-methylglutaryl-coenzyme-A reductase inhibitor simvastatin. Indian J Pharmacol 2012; 44: 238-242.
17) Hsu JH, Yeh JL, Dai ZK, Chen IJ, Wu JR. Increased circulating calcitonin gene-related peptide in congestive heart failure caused by congenital heart disease. Int Heart J 2005; 46: 867-875.
18) Wang LH, Zhou SX, Li RC, Zheng LR, Zhu JH, Hu SJ, Sun YL. Serum levels of calcitonin gene-related peptide and substance P are decreased in patients with diabetes mellitus and coronary artery disease. J Int Med Res 2012; 40: 134-140.
19) Ou XP, Deng HZ. Study of plasma endothelin and calcitonin gene related peptide in patients with heart failure. Hunan Yi Ke Da Xue Xue Bao 2000; 25: 309-311.
20) Wang T, Luo F, Shan R, Zhen Y, Zhao J, Zhang S. Changes of endothelin and calcitonin gene-related peptide during desflurane anesthesia in patients undergoing intracranial aneurysm clipping. J Neurosurg Anesthesiol 2004; 16: 236-239.
21) Hwang DS, Shin ES, Kim SJ, Lee JH, Kim JM, Lee SG. Early differential changes in coronary plaque composition according to plaque stability following statin initiation in acute coronary syndrome: classification and analysis by intravascular ultrasound-virtual histology. Yonsei Med J 2013; 54: 336-344.
22) Maneechotesuwan K, Kasetsinsombat K, Wamanuttajinda V, Wongkajornsilp A, Barnes PJ. Statins enhance the effects of corticosteroids on the balance between regulatory T cells and Th17 cells. Clin Exp Allergy 2013; 43: 212-222.
23) Chan KC, Wu CH, Huang CN, Lan KP, Chang WC, Wang CJ. Simvastatin inhibits glucose-stimulated vascular smooth muscle cell migration involving increased expression of RhoB and a block of Ras/Akt signal. Cardiovasc Ther 2012; 30: 75-84.
24) Dangas G, Badimon JJ, Smith DA, Unger AH, Levine D, Shao JH, Meraj P, Fier C, Fallon JT, Ambrose JA. Pravastatin therapy in hyperlipidemia: effects on thrombus formation and the systemic hemostatic profile. J Am Coll Cardiol 1999; 33: 1294-304.
25) Arnold SV, Spertus JA, Tang F, Krumholz HM, Borden WB, Farmer SA, Ting HH, Chan PS. Statin use in outpatients with obstructive coronary artery disease. Circulation 2011; 124: 2405-2410.
26) Kulik A, Ruel M. Lipid-lowering therapy and coronary artery bypass graft surgery: what are the benefits? Curr Opin Cardiol 2011; 26: 508-517.