

# Comparison and analysis of statins drug use in the treatment of diastolic dysfunction in patients

Guangmei Zou<sup>1\*\*</sup>, Lei Song<sup>2\*\*</sup>, Lili Chang<sup>1</sup> and Haiyan Wang<sup>3\*</sup>

<sup>1</sup>Department of Cardiovascular Surgery, The Affiliated Yantai Yuhuangding Hospital of Qingdao University Medical College, Yantai, China

<sup>2</sup>Department of Geratology, The Affiliated Yantai Yuhuangding Hospital of Qingdao University Medical College, Yantai, China

<sup>3</sup>Department of Cardiology, Yantai Hospital of Traditional Chinese Medicine, Yantai, China

**Abstract:** Statins have multiple anti lipid effects, such as anti-inflammatory, anti-oxidation and anti arteriosclerosis, which are beneficial to improve cardiac function. Statins can effectively improve left ventricular remodeling and protect ventricular diastolic function. In this study, the effects of statin therapy on diastolic function and BNP level and exercise tolerance after exercise were observed by statins in patients with diastolic dysfunction. The results showed that after atorvastatin treatment, the exercise BNP decreased in the treatment group, which was significantly different from that before treatment and in the control group ( $P < 0.05$ ). This study demonstrated that atorvastatin was used to treat patients with diastolic dysfunction and exercise hypertension by lowering blood pressure and reducing exercise SBP, anti-inflammatory and improving vascular endothelial function.

**Keywords:** Statins drugs, cardiac diastolic, atorvastatin, blood lipid, adverse reaction.

## INTRODUCTION

Most of the patients with mild diastolic dysfunction were cardiac Doppler echocardiography, diastolic dysfunction, no heart failure symptoms at rest, and normal brain natriuretic peptide (BNP) in heart failure, however, it often showed impaired exercise tolerance (Bulut *et al.*, 2015). Exercise increased blood pressure, especially abnormal elevated systolic blood pressure (SBP), which often aggravated diastolic heart failure. In patients with hypertension complicated with cardiac diastolic dysfunction, BNP immediately increased after exercise (Chian *et al.*, 2016; Fuu *et al.*, 2017). Statins have multiple anti lipid effects, such as anti-inflammatory, anti-oxidation and anti arteriosclerosis, which are beneficial to improve cardiac function (Hidekatsu *et al.*, 2008). In this study, we observed the effects of statin therapy on diastolic function and BNP level and exercise tolerance after exercise by using statins in patients with diastolic dysfunction. Statins have a significant effect on the treatment of diastolic heart failure (Ching *et al.*, 2016). By taking statins for patients, the left ventricular remodeling can be effectively covered and ventricular diastolic function is protected (Cahill *et al.*, 2015). There is a strong correlation between heart function improvement and statin inhibiting inflammation, lowering blood pressure, arteriosclerosis, improving vascular endothelial function and arterial stiffness (Dimitris *et al.*, 2007; Dobson *et al.*, 2015). Atorvastatin can effectively reduce the concentration of endothelin and plasma hypersensitivity C reaction protein, reduce the IMT of the carotid artery, antagonize the effects of arteriosclerosis and vasodilatation, and can reduce the SBP effectively

and have the effect of lowering blood pressure (Francesco *et al.*, 2017).

Statins inhibit endogenous cholesterol synthesis by inhibiting endogenous enzyme HMG-CoA reductase, blocking the intracellular metholvalic acid metabolism pathway and reducing the intracellular cholesterol synthesis (Cahill *et al.*, 2015). Feedback stimulates low density lipoprotein receptors on the surface of the cell membrane, which increases the number and activity of the cell, increases the clearance of serum cholesterol, and then reduces the serum LDL (Hsuan *et al.*, 2016). Statins can affect left ventricular diastolic function. Simvastatin can reduce myocardial fibrosis and angiogenesis, and improve the diastolic dysfunction induced by hypercholesterolemia (Luo, 2015). Rosuvastatin can relieve left ventricular stiffness in hypertensive rats with left ventricular hypertrophy. MMP plays an important role in various causes of ventricular remodeling (Laura *et al.*, 2017). Statins inhibit the activity of MMP from endothelial cells and macrophages by inhibiting GTP enzyme. Atorvastatin inhibits TGF -  $\beta 1$  or angiotensin II, reduces collagen synthesis and inhibits the expression of  $\alpha 1$  sol-sol and fibrotic connective tissue growth factor 4 gene, and its anti fibrosis effect may help inhibit ventricular remodeling (Fuu *et al.*, 2017).

## MATERIALS AND METHODS

### Case selection

The design is based on a randomized, double-blind, placebo-controlled prospective study. 150 patients were selected in our hospital for year 2016. The study was

\*Corresponding author: e-mail: haiyann1976@sohu.com

\*\*Guangmei Zou and Lei Song contributed equally to this article

approved by Ethics Committee of The affiliated Yantai Yuhuangding hospital of Qingdao university medical college, approval number as AY16QUMD and all patients signed on the informed consent. Selection criteria: (1) there was a certain degree of air closure after a certain degree of activity, according to the standard cardiac function of the New York heart disease association in the United States. The normal blood pressure or the control of blood pressure was normal, and the resting blood pressure was SBP < 150 mmHg; (2) The left ventricular laxity was damaged by echocardiography. (3)The systolic function of the heart was normal. The left ventricular ejection fraction (LVEF) was measured by Simpson method > 50%. (4) The maximum SBP > 200 mmHg during exercise.

Exclusion criteria: (1) patients with coronary heart disease; (2)hypertrophic cardiomyopathy; (3) heart valve disease; (4) diabetes mellitus; (5) combined with respiratory diseases; (6)Severe arrhythmia, impaired liver and kidney function, sequelae of stroke, anemia, thyroid dysfunction and neuromuscular joint disease. (7) The increased inflammatory index; (8) patients have been on statins; (9) patients with hyperlipidemia.

#### **Drugs and instruments**

Atorvastatin calcium, specifications: Each tablet 20mg, batch number: J18566; the same placebo is produced and supplied by a Pharma, color ultrasound and color Doppler ultrasound diagnostic system, Toshiba Medical System Co., Ltd., sports cardiopulmonary function detector.

#### **Grouping and treatment scheme**

Patients were randomly divided into atorvastatin treatment group and control group according to single and double numbers, 75 in each group. The 2 groups of patients were unchanged in the original treatment plan. The treatment group received atorvastatin calcium 20 mg, 1 times/ night, the control group added the same shape placebo for 1 year.

#### **Measurement index**

Blood routine, blood sugar, blood lipid, blood electrolyte, liver and kidney function, myocardial enzyme and cardiac troponin were measured, and some indexes were repeated for 1~3 months. The patients were followed up to determine the resting blood pressure and heart rate. Before and after the treatment, the designated special person did the echocardiography, the exercise cardiopulmonary function test, the exercise blood pressure measurement, and the determination of the plasma BNP concentration after resting and exercise.

*Echocardiography:* left ventricular mass (LVM) was measured by color ultrasonic diagnostic apparatus. The left ventricular systolic and end diastolic volume was measured by Simpson, and LVEF was measured. The E peak velocity, A peak speed, E /A ratio, EDT, and ISO

relaxation time (IVRT) were measured by pulsed Doppler. 3 times were measured continuously, and the average value was taken.

*Carotid ultrasonography:* color Doppler ultrasonography was used to measure carotid artery intima-media thickness (IMT) and carotid plaque area. With IMT > 0.9 mm as carotid artery intima thickening standard, IMT > 1.3 mm was seen as atheromatous plaque formation.

*Exercise cardiopulmonary function test:* exercise program started at 25 W exercise load and lasted for 2 min, and increased by 10~25 W according to subjects' condition. The maximum oxygen intake ( $VO_{2max}$ ), anaerobic threshold (AT), exercise time and metabolic equivalent (METs) were measured continuously during the exercise. All the subjects encouraged the maximum exercise load.

*Exercise blood pressure measurement:* During exercise examination, blood pressure was measured and recorded 1 times every 2 min and the maximal exercise blood pressure was measured. The maximal systolic blood pressure exceeds 200 mmHg during exercise, which is defined as exercise hypertension.

*Determination of plasma BNP concentration:* before exercise, first resting 20 min, extracting venous blood 2 mL, and setting ethylene diamine tetra acetic acid (EDTA) tube anticoagulant, to prepare for resting plasma BNP concentration. After 1 min of exercise, venous blood was drawn again for EDTA tube and the plasma BNP concentration after exercise was examined. The concentration of BNP in plasma was measured by TRIAGE and immunofluorescence. BNP concentration was measured within 1 h after blood sample extraction.

## **STATISTICAL ANALYSIS**

SPSS16. 0 software package was used for statistical analysis. The measurement data were expressed in  $X \pm s$ . The paired data t test was used before and after the treatment. The group designed t test was compared between the groups. The count data were tested by  $\chi^2$  test, and the correlation analysis adopted the single factor linear regression method. Due to the non normal distribution of BNP data, the BNP data were compared with the man Whitney U test after rest and movement, and the multivariate linear regression model was used for the analysis of the related factors of sports BNP.

## **RESULTS**

### **General situation of patients**

Among 150 patients, 42 patients with essential hypertension, 82 males and 68 females, aged 53~78 years. The average age, sex composition, the proportion of smokers and the average body mass index of the 2 groups

**Table 1:** General information

Variable	Treatment group	Control group
Age	59.3±7.28	61.2±7.59
Gender ( M/F)	45/30	37/38
Smoker	8	10
Body Mass Index	23.8±3.15	25.2±4.72
Hypertension	12	15
Basic- medicine		
A-converting enzyme-I	11	13
A receptor blocker	18	17
Beta-blocker	25	26
Calcium channel blocker	9	8
Diuretic	5	6
Aspirin	16	14

**Table 2:** Ultrasound data before and after treatment

Factor	Treatment group		Control group	
	Before treatment	After treatment	Before treatment	After treatment
LAD ( mm)	37.51±6.41	35.25±6.13	36.12±7.28	36.3±7.05
LVMI (g·m <sup>-2</sup> )	108.22±11.41	102.36±10.58	112.93±12.3	113.62±10.85
LVEF (%)	55.27±12.54	62.34±10.46	58.94±8.14	58.71±7.46
E (cm·s <sup>-1</sup> )	58.13±13.76	68.15±15.17	62.48±10.14	65.12±12.41
A (cm·s <sup>-1</sup> )	79.43±9.41	74.12±8.23	80.96±10.25	81.65±11.57
E/A ( ratio)	1.24±0.58	1.35±0.74	1.28±0.62	1.25±0.82
EDT ( ms)	204.13±21.34	201.54±30.57	212.45±28.46	203.47±32.14
IVRT (ms)	78.64±26.34	74.12±21.13	79.41±21.34	76.14±20.17
IMT (mm)	0.88±0.35	0.84±0.21	0.91±0.22	0.85±0.13

were equal. The proportion of the 2 groups of hypertensive patients, the drug treatment and the blood pressure, blood lipid and blood sugar before the medication were also similar. The difference between the 2 groups was not statistically significant (table 1).

#### **Contrast of ultrasonic data**

Before treatment, there was no significant difference between 2 groups of indicators, including left ventricular mass index (LVMI) and cardiac diastolic function index (E /A, EDT, IVRT). After treatment, the E/A ratio in the treatment group was larger than that in the control group, while LVMI was smaller than that in the control group, the difference was statistically significant (P<0.05). The improvement of LVMI and E/A in treatment group was statistically significant compared with that before treatment (P<0.05). There was no significant difference in the indexes between the control group before and after treatment, see table 2. Before treatment, there was no significant difference in IMT between the 2 groups. After treatment, the IMT of the treatment group was alleviated, which was significantly different from that before treatment and in the control group (P<0.05) (table 2).

#### **Motion parameters**

Before treatment, there was no significant difference between the 2 groups (P>0.05). Linear regression analysis showed that there was a negative correlation between

VO<sub>2max</sub> and LVMI in 2 groups (P=0.002), indicating that left ventricular remodeling was associated with decreased activity tolerance. After treatment, the rest maximum systolic pressure (SBP) and pulse pressure difference (PP) decreased, exercise SBP decreased, exercise tolerance was improved, exercise time prolonged, METS, VO<sub>2max</sub>, AT value increased, and the differences were statistically significant (P<0.05) before treatment (all P<0.05). Compared with the control group, after treatment, PP and transport were resting. There was a statistically significant difference in maximal SBP and exercise time (P<0.05), but no significant difference was found in the other indexes (P>0.05). There was no significant difference in the indexes between the control group before and after treatment (all P>0.05) (table 3).

#### **Changes of plasma BNP after exercise**

Before treatment, plasma BNP concentration in 2 groups was similar after rest and exercise, and the difference was not statistically significant (P>0.05). After exercise, the plasma BNP concentration of 2 groups increased significantly compared with rest, and the difference was statistically significant (P<0.05 to 0.01). After treatment, the exercise BNP decreased in the treatment group. There was a significant difference between the treatment group and the control group (P<0.05), while the resting BNP was also decreased compared with that before the treatment, but the difference was not statistically

**Table 3:** Comparison of motion parameters and BNP concentration

Factor	Treatment group		Control group	
	Before treatment	After treatment	Before treatment	After treatment
Heart rate (times·min <sup>-1</sup> )				
Rest	71.0±6.1	70.4±5.8	72.2±7.3	71.5±6.4
Peak exercise	135.2±19.8	136.1±15.4	133.9±18.4	133.5±17.2
Blood pressure at rest ( mmHg)				
SBP	132.4±12.7	129.6±11.5	133.4±13.5	132.7±11.8
DBP	74.5±5.6	73.1±4.8	76.2±7.2	75.8±6.7
PP	58.2±11.5	51.3±10.2	60.1±9.6	59.4±9.2
Peak exercise SBP (mmHg)	214.1±25.1	201.6±23.3	213.2±22.8	208.6±20.6
Exercise time ( min)	7.3±1.5	8.2±2.4	7.6±2.1	7.7±2.5
Metabolic equivalents	4.6±1.3	5.8±1.8	4.7±1.4	4.9±1.3
VO <sub>2max</sub> ( mL·kg <sup>-1</sup> ·min <sup>-1</sup> )	17.5±4.6	21.3±5.8	19.2±3.7	19.8±4.5
AT( mL·kg <sup>-1</sup> ·min <sup>-1</sup> )	12.6±4.8	15.7±3.9	12.5±3.2	13.7±4.1
BNP (pg·mL <sup>-1</sup> )	35.4±3.7	32.1±4.6	35.8±3.4	34.2±3.1

**Table 4:** blood lipid and blood glucose before and after treatment

Factor	Treatment group		Control group	
	Before treatment	After treatment	Before treatment	After treatment
TC (mmol·L <sup>-1</sup> )	4.28±1.56	3.89±1.24	4.31±1.25	4.16±1.12
LDL-C (mmol·L <sup>-1</sup> )	3.13±0.84	2.72±0.72	2.82±0.81	2.79±0.78
TG (mmol·L <sup>-1</sup> )	1.56±0.51	1.47±0.42	1.62±0.61	1.70±0.72
HDL-C (mmol·L <sup>-1</sup> )	1.32±0.45	1.38±0.49	1.21±0.37	1.26±0.51
FPG (mmol·L <sup>-1</sup> )	4.28±0.72	4.31±0.73	4.35±0.68	4.41±0.72
HbA1c (%)	4.52±0.67	4.61±0.72	4.61±0.75	4.70±0.64

significant, as shown in table 3. The analysis of multiple linear regression model showed that before the treatment, the concentration of BNP in the 2 groups was positively correlated with the resting BNP (P<0.001), and was negatively correlated with the maximum heart rate (P<0.002).

**Changes of blood lipid after treatment**

Before treatment, the indexes of blood lipid and blood sugar in the 2 groups were all similar, and the difference was not statistically significant. After treatment, the total cholesterol and low density lipoprotein cholesterol in the treatment group decreased significantly (P<0.001), compared with the control group, the difference was statistically significant (P<0.01). Atorvastatin calcium has little effect on high density lipoprotein cholesterol and three acylglycerol, fasting blood glucose and glycosylated hemoglobin. After treatment, all indexes in the control group were similar to those before treatment (table 4).

**Safety evaluation**

There was no serious adverse reaction in the 2 groups. There were 2 cases of skin pruritus in statin treatment group, but they were tolerable. There were 3 cases of mild gastrointestinal reaction in the control group. The 2 groups had no abnormal changes in liver and kidney function and no serious muscle toxicity. No muscle enzyme increased.

**DISCUSSION**

Statins mainly inhibit the synthesis of HMG-CoA reductase inhibitors, reduce the level of low density lipoprotein receptor, inhibit the cholesterol synthesis of liver cells and have a more prominent clinical effect on the treatment of diastolic blood pressure failure (Liu *et al.*, 2017). Statins better improve left ventricular remodeling, better protect the ventricular diastolic function, inhibit inflammation, improve vascular endothelial function and resist coronary arteriosclerosis (Ozgur *et al.*, 2015; Sung *et al.*, 2017). Lower blood hypersensitivity C reactive protein and carotid IMT, reduce endothelin concentration, anti-inflammatory, vasodilatation, antagonistic arteriosclerosis, effective control of SBP and PP levels, additional hypotension, and so on (Pistevou *et al.*, 2015). To sum up, the use of statins to treat patients with cardiac insufficiency is of great significance. It can better improve the diastolic function of the patients, the level of BNP after exercise and the concentration of brain natriuretic peptide in the serum of the patients under the condition of inconcentric function, which can provide a more sudden clinical value for the treatment of the patients and it is worthy of clinical progress. The step is popularized and adopted.

Statins have strong anti-inflammatory effects. Inflammation and heart failure are widely linked (Sheng

et al., 2015; Wang, 2016). Proinflammatory cytokines can lead to cardiac systolic dysfunction, cardiac hypertrophy, and extra cellular matrix (Santarelli et al., 2016). Atorvastatin inhibits extra cellular signal regulated kinase (ERK), reduce the mRNA level of Toll like receptor. Endothelial dysfunction is associated with the pathogenesis of heart failure, and it can promote left ventricular remodeling and increase the afterload of patients with heart failure. Studies have shown that statins can improve vascular endothelial function in patients with cardiovascular disease (Yung et al., 2015). Statins can up regulate endothelial nitric oxide synthase (eNOS) through a variety of mechanisms, and endothelium derived nitric oxide (no) is an important determinant of endothelial cell function. The integrity of endothelial cell is also dependent on the oxidation state. Inhibition of the activity of coenzyme II oxidase is the classic effect of statins. Statins can affect left ventricular diastolic function. Simvastatin can reduce myocardial fibrosis and angiogenesis and improve the diastolic dysfunction induced by hypercholesterolemia.

The results of this study showed that after 1 years of atorvastatin calcium treatment, the LVMI and E /A in the treatment group improved, the maximum exercise SBP decreased, the exercise tolerance was improved, and the exercise time was prolonged, and METS,  $VO_{2max}$  and AT were improved. It indicates that atorvastatin calcium can improve left ventricular remodeling, reduce exercise induced hypertension, improve cardiac diastolic function and exercise tolerance to some extent. This study shows that exercise tolerance ( $VO_{2max}$ ) is negatively correlated with LVMI ( $P = 0.002$ ), indicating that intervention of left ventricular remodeling can improve the activity tolerance of patients (Wilbert et al., 2018). Statins play a therapeutic role in diastolic heart failure, which can effectively improve left ventricular remodeling and protect ventricular diastolic function (Tural et al., 2015). The improvement of cardiac function is related to the reduction of statin, inhibition of inflammation, improvement of vascular endothelial function, anti arteriosclerosis, and improvement of arterial stiffness (Vekov et al., 2015). In this study, atorvastatin can effectively reduce the concentration of plasma hypersensitivity C reactive protein and endothelin, reduce the IMT of the carotid artery, improve the anti inflammation, improve vascular endothelial function, diastolic blood vessel, antagonize the arteriosclerosis, and can reduce the SBP and PP effectively, and play an additional antihypertensive effect. The results showed that the concentration of plasma BNP in the patients with mild diastolic dysfunction was significantly higher than that at rest ( $P < 0.01$ ). The concentration of exercise BNP was positively correlated with the resting BNP ( $P < 0.001$ ), and was negatively correlated with the maximum heart rate ( $P < 0.002$ ).

## CONCLUSION

In this study, the effects of statin therapy on diastolic function and BNP level and exercise tolerance after exercise were observed by statins in patients with diastolic dysfunction. The results showed that after atorvastatin treatment, the exercise BNP decreased in the treatment group, which was significantly different from that before treatment and in the control group ( $P < 0.05$ ). This study shows that atorvastatin can effectively improve cardiac diastolic function by lowering blood pressure and reducing SBP, anti-inflammatory, improving vascular endothelial function, anti arteriosclerosis, and ventricular remodeling, and reducing the plasma BNP concentration and exercise tolerance.

## ACKNOWLEDGEMENTS

Authors are thankful for the support and laboratory equipment from The Affiliated Yantai Yuhuangding Hospital of Qingdao University Medical College.

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