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Original Article

Effects of atorvastatin plus trimetazidine for patients with coronary heart disease on myocardial protection and renal function

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Abstract: Objective: The aim of this study was to investigate the clinical efficacy of atorvastatin plus trimetazidine for treatment of patients with coronary heart disease, examining the effect mechanisms on myocardial and renal function. Methods: Data of 130 patients with coronary heart disease, admitted to the Department of Cardiovasology, were retrospectively analyzed. They were divided into the study group and control group, according to treatment methods, with 65 cases in each group. Both groups were given conventional treatments, including oxygen inhalation, vasodilator, diuretic, anti-platelet aggregation agents, and calcium antagonists. Moreover, the control group was given atorvastatin, orally, and the study group was given oral atorvastatin plus trimetazidine hydrochloride. Concentrations of serum lactate dehydrogenase (LDH), creatine kinase (CK), creatine kinase-MB isoenzyme (CK-MB), blood urea nitrogen (BUN), serum creatinine (Scr), and microalbuminuria (mALB) were measured with the use of an automatic biochemical analyzer, before and after treatment. Concentrations of Serum troponin I (cTnI) and malondialdehyde (MDA), as well as activity of superoxide dismutase (SOD), were measured by enzyme-linked immunosorbent assay (ELISA). Clinical efficacy and incidence of adverse reactions after treatment were also observed. Results: The effective rate in the study group was significantly higher than that in the control group (P=0.008). Incidence of adverse reactions was not significantly different between the two groups (P=1.000). Concentrations of serum LDH, CK, CK-MB, cTnI, and MDA were significantly lower after treatment than before treatment in both groups and were significantly lower in the study group than in the control group (all P<0.001). Serum SOD activity was significantly higher after treatment than before treatment in both groups and significantly higher in the study group than in the control group (both P<0.001). Conclusion: Atorvastatin plus trimetazidine has better clinical efficacy than atorvastatin alone in treating coronary heart disease, maximizing the protective effects for the heart and kidneys. Mechanisms may include anti-oxidative stress response, less release of oxygen free radicals, and improvement of ischemia-reperfusion injury, thereby protecting the myocardium and kidneys.

Keywords: Atorvastatin, trimetazidine, coronary heart disease, myocardial function, renal function

Introduction

Coronary heart disease, a common heart disease, refers to vascular stenosis, obstruction, and paralysis, caused by insufficient blood supply to the myocardium and coronary artery stenosis, results in hypoxia and ischemia in the myocardium, causing myocardial necrosis and myocardial dysfunction. Thus, it is also known as ischemic heart disease [1]. About 95% of coronary heart diseases are caused by coronary atherosclerosis. The severity of this disease is closely related to the number of coronary artery lesions and degree of atherosclerosis and stenosis [2]. The hearts of patients with coronary heart disease are chronically in a state of hypoxia and ischemia. This can cause acidosis of cardiomyocytes and increase blood viscosity, thereby worsening the condition. These result in a series of complications, such as angina pectoris, arrhythmia, heart failure, chronic renal insufficiency, and sudden death [3, 4].

Atorvastatin and trimetazidine are common drugs for ischemic heart disease. Atorvastatin

has favorable effects on anti-inflammation, reducing blood lipids, protecting vascular, inhibiting the formation of low-density lipoproteins and blood lipids, lowering fibrinogen levels, and preventing atherosclerosis [5, 6]. Trimetazidine refers to a kind of piperazine derivatives. It is a novel inhibitor on metabolic regulation that inhibits fatty acid β-oxidation and formation of oxygen free radicals, promotes glucose oxidation and oxygen utilization, maintains mitochondrial function, controls the infiltration of inflammatory cells in the myocardium, and regulates and alleviates myocardial metabolism [7]. Previous studies have shown that atorvastatin and trimetazidine can improve coronary heart disease and inhibit inflammatory factors [8]. However, few studies have investigated the effects of combined therapy of the two drugs on myocardial and renal function in patients with coronary heart disease.

Therefore, atorvastatin plus trimetazidine for treatment of patients with coronary heart disease was conducted in this study, aiming to further observe the therapeutic effects of the two, compare the efficacy between the combination of the two drugs and the use of atorvastatin alone, and examine the effects on myocardial and renal function.

Materials and methods

General data

Data of 130 patients with coronary heart disease, admitted to the Department of Cardiovasology, from May 2016 to April 2018, were retrospectively analyzed. They were divided into the study group and control group, according to treatment methods, with 65 cases in each group. This study was approved by the Ethics Committee of The Second Affiliated Hospital (Jiande Branch), School of Medicine, Zhejiang University, The First People's Hospital of Jiande.

Inclusion criteria & exclusion criteria

Patients were eligible if they were diagnosed with coronary heart disease, according to the World Health Organization diagnostic criteria (also confirmed by cardiac ultrasounds and electrocardiogram examinations) [9], knew about the protocol and provided informed consent, and had clinical symptoms, such as oppression in the chest, chest pain, palpitations, angina pectoris, and fatigue. Exclusion criteria included pulmonary heart disease, viral myocarditis, arrhythmia, cardiogenic shock, congenital heart disease, left ventricular ejection fraction ≥ 40%, severe electrolyte disorders, dysgnosia or mental illness, severe anemia, coagulation dysfunction, poor medication compliance, incomplete data, and drug allergies.

Therapeutic methods

Both groups were given conventional treatments, including oxygen inhalation, vasodilator, diuretic, anti-platelet aggregation agents, and calcium antagonists [10]. Moreover, the control group was given 10 mg atorvastatin (Pfizer Inc, New York, USA), orally, once a day. The study group was given 20 mg trimetazidine hydrochloride (Tianjin Shiweiya, China), orally, 3 times a day on the control group. Both the study group and control group were treated for 8 weeks.

Outcome measures

Fasting venous blood was collected from all subjects, separated by centrifugation, and stored at -20°C for use.

Myocardial function indices, serum lactate dehydrogenase (LDH), creatine kinase (CK), and creatine kinase-MB isoenzyme (CK-MB), as well as renal function indicators, blood urea nitrogen (BUN), serum creatinine (Scr), and microalbuminuria (mALB), were measured by the AU-5800 automatic biochemical analyzer (Beckman Coulter, Inc, Chaska, MN, USA), before and after treatment, in strict accordance with kit instructions.

Concentrations of serum troponin I (cTnI), as well as oxidative stress parameters, malondialdehyde (MDA) and superoxide dismutase (SOD), were measured by enzyme-linked immunosorbent assay (ELISA), before and after treatment, with reference to kit instructions (all purchased from Shanghai Fanke, China) [11].

Detection method: First, sample wells, standard wells, negative control wells, and positive wells were set for use. They were then added with 100 μL of sample solution, standard solution, negative, and positive control solutions, respectively, into each corresponding reaction well. Afterward, 100 μL of the antibody solution for biological reactions was quickly added into each well, with a membrane as a cover. The solutions were mixed well, then placed for 40

Table 1. Baseline data (n, %; mean ± sd)

Category	Study group (n=65)	Control group (n=65)	t/χ^2	P
Gender			0.528	0.467
Male	39 (60.00)	43 (66.15)		
Female	26 (40.00)	22 (33.85)		
Age (year)	63.52±6.34	62.99±6.93	0.455	0.650
Course of disease (year)	5.63±2.67	5.73±2.87	0.206	0.837
Drinking			1.237	0.266
Yes	25 (38.46)	19 (29.23)		
No	40 (61.54)	46 (70.77)		
Smoking			0.366	0.546
Yes	15 (23.08)	18 (27.69)		
No	50 (76.92)	47 (72.31)		
Complication			1.161	0.281
Diabetes	17 (26.15)	19 (29.23)		
Hypertension	40 (61.54)	43 (66.15)		
Renal insufficiency	8 (12.31)	3 (4.62)		
Body mass index (kg/m^2)	26.01±3.18	26.26±3.47	0.428	0.669
Total cholesterol (mmol/L)	4.76±1.35	4.69±1.73	0.257	0.798
Triglyceride (mmol/L)	1.63±0.83	1.56±0.76	0.502	0.617
Low-density lipoprotein (mmol/L)	2.59±1.05	2.86±1.16	1.391	0.167

minutes. Second, each well was added with 100 μL of streptavidin, with a membrane as a cover. The solutions were again mixed well, then placed for 40 minutes. Third, the solutions were removed. Washing liquid was added to each reaction well for 1 minute of shaking and mixing, then discarded. This was repeated 5 times. Next, each well was added with 100 μL of reaction substrate, reaction solution A, and reaction solution B, with a membrane as cover. They were placed in the dark for 5 minutes. Fourth, 100 μL of stop buffer was added into the reaction well. The optical density value of each well was immediately measured using an enzyme label analyzer (Shenzhen Shengxinkang, China) at 450 nm. Concentrations of cTnI, MDA, and activity of SOD were calculated.

Criteria for efficacy

Markedly effective included disappearance of clinical signs and symptoms and cardiac function ≥ level 2. Effective included significant improvement of clinical signs and symptoms and cardiac function ≥ level 1. Non-effective showed no improvement or aggravation of clinical signs and symptoms [12]. Effective rate = (markedly effective + effective)/total number of cases *100%.

Incidence of adverse reactions was observed in both groups during the treatment period.

Statistical analyses

Statistical analyses were performed using SPSS19.0 (Shanghai Yuchuang, China). Measurement data are expressed as mean ± standard deviation (mean ± sd). They were compared by independent sample t-test between groups and by paired t-test within groups, before and after treatment. Count data are expressed as number of cases and percentage (n, %) and were compared by Chi-squared test. $P<0.05$ indicates statistical significance.

Results

Baseline data

In the study group, there were 39 males and 26 females, aged 51-76 years, with a mean age of 63.52±6.34 years. Course of disease was 1-12 years, with a mean disease duration of 5.63± 2.67 years. There were 17 cases of diabetes, 40 cases of hypertension, and 8 cases of renal insufficiency. In the control group, there were 43 males and 22 females, aged 47-78 years, with a mean age of 62.99±6.93 years. Course of disease 1-11 years, with a mean disease duration of 5.73±2.87 years. There were 19 cases of diabetes, 43 cases of hypertension, 3 cases of renal insufficiency. There were no statistically significant differences between the study group and control group in terms of baseline data, including gender, age, course of disease, drinking, smoking, complications, body mass index, total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) (all $P>0.05$). See **Table 1**.

Clinical efficacy after treatment

In the study group, there were 36 cases (55.38%) of markedly effective, 26 cases (40.00%) of effective, and 3 cases (4.62%) of non-effective, with an effective rate of 95.38%. In the control

Table 2. Comparison of effective rates (n, %)

Group	n	Markedly effective	Effective	Non-effective	Effective rate
Study group	65	36 (55.38)	26 (40.00)	3 (4.62)	62 (95.38)
Control group	65	21 (32.31)	31 (47.69)	13 (20.00)	52 (80.00)
χ^2					7.127
P					0.008

Table 3. Comparison of adverse reactions after treatment (n, %)

Group	n	Nausea	Vomiting	Incidence
Study group	65	2 (3.08)	1 (1.54)	3 (4.62)
Control group	65	1 (1.54)	1 (1.54)	2 (3.08)
χ^2				0.000
P				1.000

Table 4. Changes in serum LDH, CK, and CK-MB concentrations (mean ± sd)

Category	Study group (n=65)	Control group (n=65)
LDH (U/L)		
Before treatment	311.63±32.59	314.75±29.78
After treatment	266.64±25.95[a,b]	289.63±26.93[a]
Difference	44.99±6.83[c]	25.12±3.01
CK (U/L)		
Before treatment	213.76±31.54	221.63±32.79
After treatment	181.63±15.63[a,b]	201.47±16.74[a]
Difference	32.13±14.96[c]	20.16±16.18
CK-MB (U/L)		
Before treatment	39.47±4.63	37.63±5.15
After treatment	21.02±2.14[a,b]	29.63±4.63[a]
Difference	18.45±2.53[c]	8.00±0.56

Note: Compared with before treatment within the group, [a]P<0.001; compared with the control group after treatment, [b]P<0.001; compared with the difference value in the control group, [c]P<0.001. LDH: serum lactate dehydrogenase, CK: creatine kinase, CK-MB: creatine kinase-MB.

group, there were 21 cases (32.31%) of markedly effective, 31 cases (47.69%) of effective, and 13 cases (20.00%) of non-effective, with an effective rate of 80.00%. The effective rate of the study group was significantly higher than the control group (χ^2=7.127, P=0.008). See **Table 2**.

Adverse reactions after treatment

In the study group, 2 patients (3.08%) developed nausea and 1 patient (1.54%) experienced vomiting. Incidence of adverse reactions was 4.62%. In the control group, 1 patient (1.54%) developed nausea and 1 patient (1.54%) experienced vomiting. Incidence of adverse reactions was 3.08%. There were no significant differences in incidence of adverse reactions between the two groups (χ^2= 0.000, P=1.000). See **Table 3**.

Myocardial function indices

Before treatment, concentrations of serum LDH, CK, and CK-MB in the study group were not significantly different from those in the control group (all P>0.05). After treatment, serum LDH (t=8.707, P<0.001; t=5.044, P<0.001), CK (t=7.359, P<0.001; t=4.415, P< 0.001), and CK-MB (t=29.160, P<0.001; t=9.313, P<0.001) concentrations were significantly lower in the study group and control group. Also, after treatment, serum LDH, CK, and CK-MB concentrations in the study group were significantly lower than those in the control group (t=4.956, t=6.984, t=13.610, all P<0.001). See **Table 4** and **Figure 1**.

Renal function indices

Before treatment, there were no significant differences in serum BUN, Scr, and mALB levels between the two groups (all P>0.05). After treatment, serum BUN, Scr, and mALB concentrations in the study group were significantly lower than those before treatment (t=5.744, t=4.055, t=4.116, all P<0.001). However, in the control group, the 3 indices were not significantly different from those before treatment (all P>0.05). After treatment, serum BUN, Scr, and mALB in the study group were significantly lower than those of the control group (t=5.251, t=4.065, t=4.136, all P<0.001). See **Table 5** and **Figure 2**.

Serum cTnI and oxidative stress parameters

Before treatment, concentrations of serum cTnI, MDA, and SOD in the study group were not significantly different from those in the control group (all P>0.05). Serum cTnI (t=17.200, P< 0.001; t=6.490, P<0.001) and MDA (t=14.210,

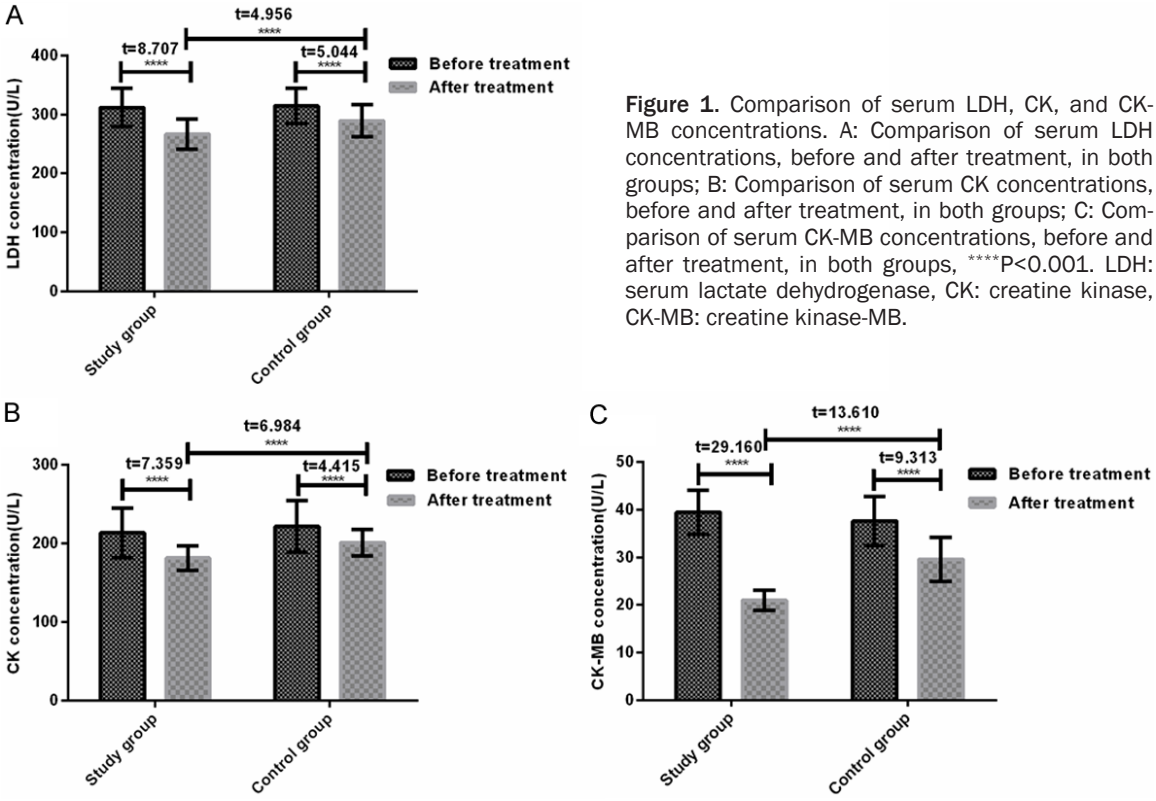

Figure 1. Comparison of serum LDH, CK, and CK-MB concentrations. A: Comparison of serum LDH concentrations, before and after treatment, in both groups; B: Comparison of serum CK concentrations, before and after treatment, in both groups; C: Comparison of serum CK-MB concentrations, before and after treatment, in both groups, ****P<0.001. LDH: serum lactate dehydrogenase, CK: creatine kinase, CK-MB: creatine kinase-MB.

Table 5. Changes in serum BUN, Scr, and mALB concentrations (mean ± sd)

Category	Study group (n=65)	Control group (n=65)
BUN (mmol/L)		
Before treatment	6.74±0.83	6.85±0.93
After treatment	5.98±0.67[a,b]	6.71±1.12
Difference	0.76±0.19[c]	0.14±0.11
Scr (μmol/L)		
Before treatment	85.43±10.34	86.41±9.85
After treatment	78.34±9.58[a,b]	85.57±10.67
Difference	7.09±0.69[c]	0.84±0.89
mALB (mg/L)		
Before treatment	67.19±25.74	65.37±36.68
After treatment	50.15±21.25[a,b]	64.86±19.25
Difference	17.04±4.58[c]	0.48±0.27

Note: Compared with before treatment within the group, [a]P<0.001; compared with the control group after treatment, [b]P<0.001; compared with the difference value in the control group, [c]P<0.001. BUN: blood urea nitrogen, Scr: serum creatinine, mALB: microalbuminuria.

P<0.001; t=8.833, P<0.001) concentrations were significantly lower after treatment in the study group and the control group, while serum SOD activity was significantly higher after treatment in the study group (t=20.090, P<0.001) and control group (t=11.600, P<0.001). Also, after treatment, serum cTnI and MDA concentrations in the study group were significantly lower than those in the control group (t=9.946, P<0.001; t=5.933, P<0.001), while SOD activity was significantly higher in the study group than the control group (t=7.296, P<0.001). See **Table 6** and **Figure 3**.

Discussion

Coronary heart disease has a long course of disease. This can lead to a series of complications as the disease progresses, with heart failure as the most dangerous complication leading to death [13, 14]. Decreased aerobic capacity and productivity of myocardial cells after ischemia are the main causes of heart failure. This can cause a decrease in renal plasma flow and perfusion flow. Hypoxic and ischemic kidneys can release many inflammatory cytokines and oxygen free radicals, causing apoptosis and fibrosis of renal tubular epithelial cells, leading to renal damage and renal failure [15, 16]. Therefore, it is essential to relieve disease progression, improve energy metabolism of cardiomyocytes, and prevent complications, su-

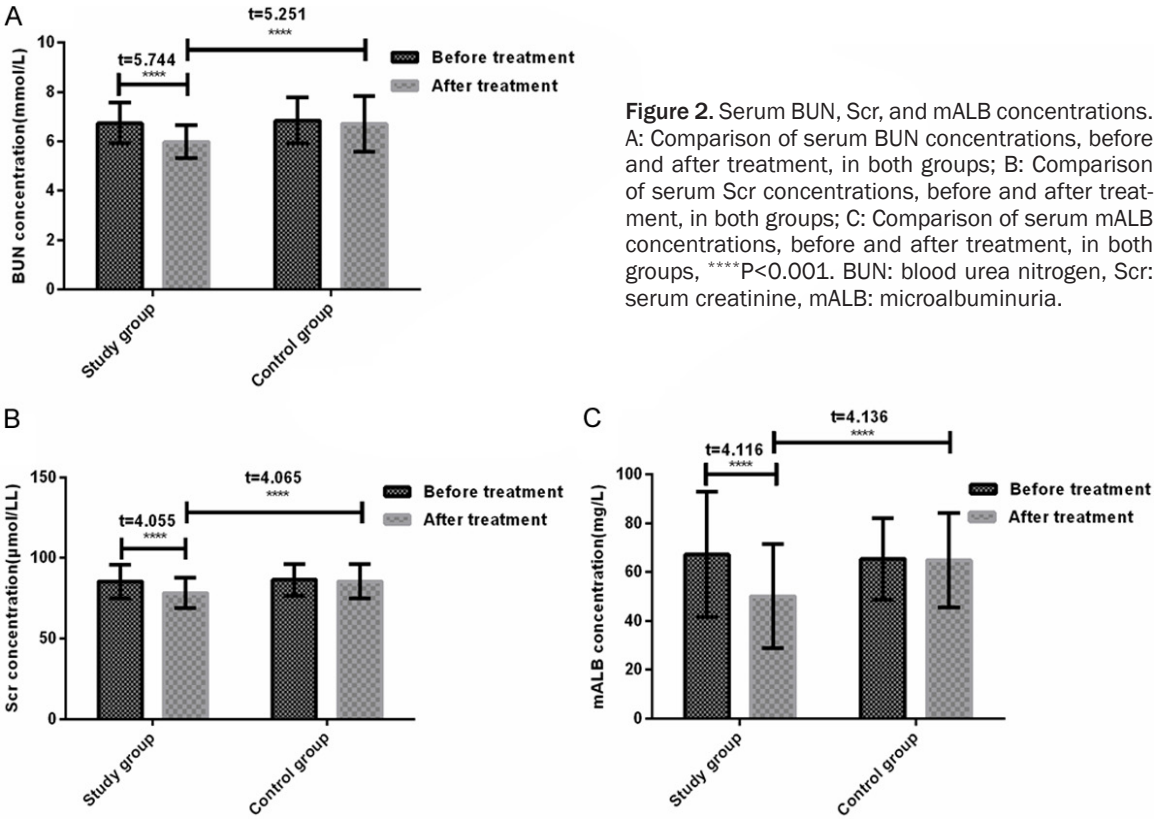

Figure 2. Serum BUN, Scr, and mALB concentrations. A: Comparison of serum BUN concentrations, before and after treatment, in both groups; B: Comparison of serum Scr concentrations, before and after treatment, in both groups; C: Comparison of serum mALB concentrations, before and after treatment, in both groups, ****P<0.001. BUN: blood urea nitrogen, Scr: serum creatinine, mALB: microalbuminuria.

Table 6. Changes in serum cTnI and MDA concentrations, as well as SOD activity (mean ± sd)

Category	Study group (n=65)	Control group (n=65)
cTnI (ng/mL)		
Before treatment	1.41±0.36	1.43±0.37
After treatment	0.51±0.22[a,b]	1.02±0.35[a]
Difference	0.90±0.18[c]	0.41±0.09
MDA (μmol/L)		
Before treatment	8.46±1.42	8.53±1.38
After treatment	5.24±1.15[a,b]	6.49±1.25[a]
Difference	3.22±0.35[c]	2.04±0.18
SOD (kU/L)		
Before treatment	62.37±8.37	61.09±11.08
After treatment	102.34±13.68[a,b]	85.41±12.76[a]
Difference	39.97±5.49[c]	24.32±2.67

Note: Compared with before treatment within the group, [a]P<0.001; compared with the control group after treatment, [b]P<0.001; compared with the difference value in the control group, [c]P<0.001. cTnI: serum troponin I, MDA: malondialdehyde, SOD: superoxide dismutase.

ch as heart failure and renal failure, in the treatment of coronary heart disease.

Atorvastatin, a lipid regulation drug for coronary heart disease, can inhibit the formation of cholesterol in the liver, improve vascular endothelial function, block platelet aggregation and activation, and inhibit inflammatory response [17]. Trimetazidine is for treatment of myocardial ischemia. It can improve energy metabolism disorders of cardiomyocytes caused by insufficient blood supply to coronary arteries, inhibit fatty acid β-oxidation, promote glucose metabolism, and increase the blood supply of cardiomyocytes [18]. Results of the current study showed significantly higher effective rates in the study group than in the control group, with no significant differences in incidence of adverse reactions between the two groups. Results suggest that the combination of atorvastatin and trimetazidine for treatment of coronary heart disease has better clinical efficacy and similar incidence of adverse reactions, compared with atorvastatin alone, in accord with the study of Song et al. [19]. Results indicate that combination treatment for coronary heart disease patients has significant clinical efficacy, improving blood lipid levels and cardiac function.

Progression of coronary heart disease or taking anti-platelet aggregation drugs may cause kidney damage [20]. Athyros et al. showed that

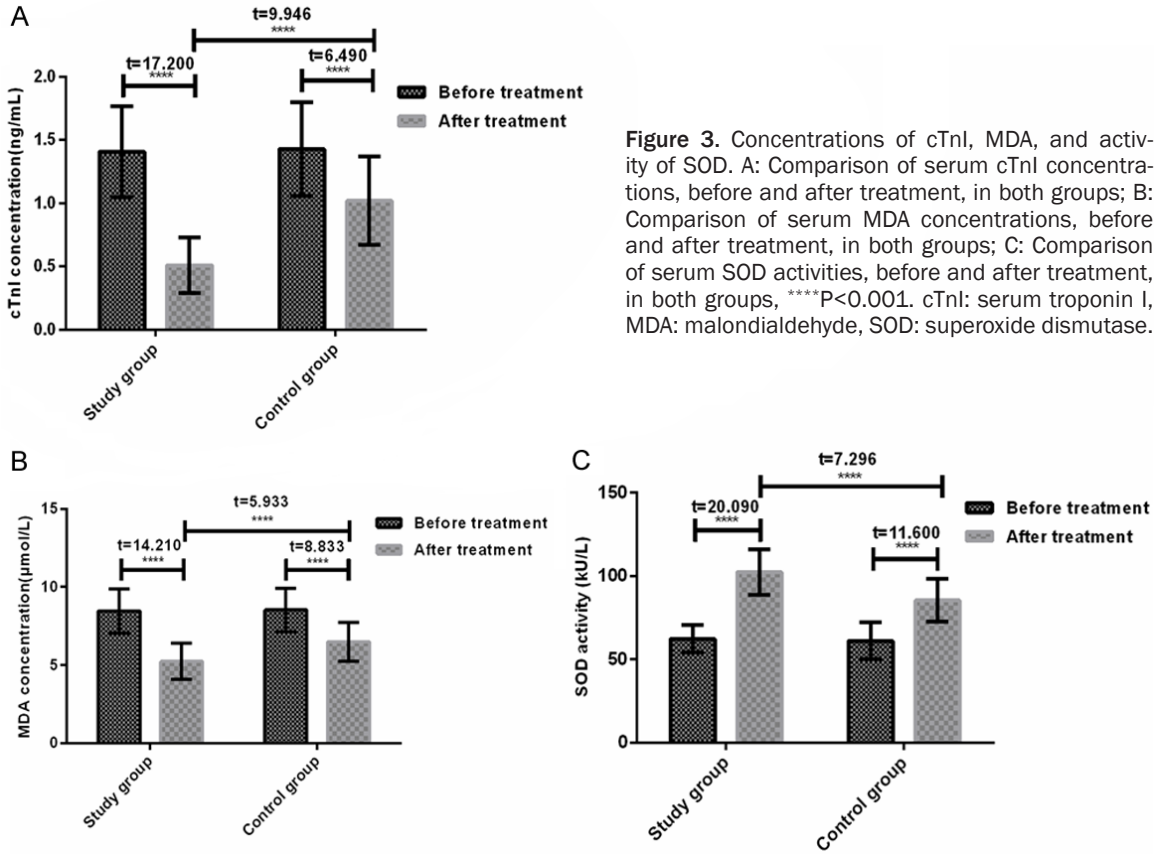

Figure 3. Concentrations of cTnI, MDA, and activity of SOD. A: Comparison of serum cTnI concentrations, before and after treatment, in both groups; B: Comparison of serum MDA concentrations, before and after treatment, in both groups; C: Comparison of serum SOD activities, before and after treatment, in both groups, ****P<0.001. cTnI: serum troponin I, MDA: malondialdehyde, SOD: superoxide dismutase.

atorvastatin can reduce incidence of ischemic cardiovascular events, with promising effects via protecting the heart and kidneys [21]. In this study, serum BUN, Scr, and mALB concentrations in the control group were not significantly different from those before treatment, confirming that atorvastatin may have protective effects on kidneys.

Atorvastatin can reduce ischemia-reperfusion injury and oxidative stress, protect cardiomyocytes, inhibit myocardial remodeling, and improve cardiac function by reducing the deposition of fibronectin and collagen [22]. Trimetazidine can promote the formation of phospholipids by inhibiting the overload of sodium ions and calcium ions during myocardial ischemia-reperfusion, thereby inhibiting the production of oxygen free radicals and reducing myocardial remodeling due to myocardial cell damage [23]. Levels of cTnI can reflect damage to cardiomyocytes. Hypoxia and ischemia can promote neuroendocrine and long-term activation of cytokines, induce cardiomyocytes to initiate specific apoptosis programs, aggravate myocardial damage, and increase cTnI levels [24]. MDA and SOD are important indicators in evaluating lipid peroxidation. MDA is a product of oxidative stress, which can reflect the damage of oxidative stress. SOD activity can reflect the ability of scavenging oxygen free radicals [25]. The present study showed that serum concentrations of LDH, CK, CK-MB, cTnI, and MDA, in both groups, were significantly lower after treatment than before treatment, while serum SOD activity was significantly higher after treatment than before treatment. Additionally, decreases and increases of the indices above were more statistically significant in the study group than in the control group, suggesting that the combination of atorvastatin and trimetazidine may have synergistic effects on the treatment mechanisms of coronary heart disease. Combination of the two drugs can maximize the protective effects on the heart and kidneys, compared with atorvastatin alone. Hao et al. showed that atorvastatin plus trimetazidine can improve unstable angina and myocardial injury during the perioperative period, as well as inhibit inflammatory response [26]. Lin et al. believed that atorvastatin plus trimetazidine in percutaneous coronary intervention for

coronary heart disease could reduce renal oxidative stress and improve renal function, confirming present results [27]. Therefore, atorvastatin plus trimetazidine for coronary heart disease may play a role in protecting the heart and kidneys through various mechanisms, such as anti-oxidative stress, reduction of oxygen free radical release, and improvement of ischemia-reperfusion injury.

However, this study did not follow up the prognosis of patients in either group, with certain limitations. Thus, future studies should extend the study period and follow up the prognosis of patients with coronary heart disease using these two drugs.

In summary, atorvastatin plus trimetazidine has better clinical efficacy than atorvastatin alone in treating coronary heart disease. This combination can maximize the protective effects of the heart and kidneys. Mechanisms may include anti-oxidative stress response, less release of oxygen free radicals, and improvement of ischemia-reperfusion injury, thereby protecting the myocardium and kidneys.

Disclosure of conflict of interest

None.

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