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Original Article

Different doses of atorvastatin combined with trimetazidine for left heart insufficiency in elderly patients with coronary heart disease

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Abstract: Objective: The influences of different doses of atorvastatin combined with trimetazidine on left ventricular dysfunction (LVD) in senile patients with coronary heart disease (CHD) and its effects on hemodynamics and adverse reactions were studied. Methods: A total of 160 senile patients with LVD were collected and treated with atorvastatin and trimetazidine. According to the dosage of atorvastatin, they were assigned to a high-dose group (HD group, n = 82) and a low-dose group (LD group, n = 78). Results: There was no significant difference between the two groups in the total effective rate (P > 0.05). After treatment, the hemodynamics of both groups was improved, and the LD group showed significantly lower fibrinogen, plasma specific viscosity, and whole blood low shear viscosity, as well as red blood cell specific volume than the LD group (P < 0.05). There was no significant difference between the two groups in the whole blood high shear viscosity (P > 0.05), and cardiac function and 6-minute walking distance were significantly improved in both groups. After treatment, the HD group showed significantly better cardiac function index than the LD group (P < 0.05), and no significant difference was observed in 6-minute walking distance between the two groups (P > 0.05). In addition, after treatment, both groups showed lower expression of cardiotrophin-1 (CT-1) and interleukin-6 (IL-6) and higher expression of insulin-like growth factor-1 (IGF-1), and the HD group showed lower serum levels of CT-1 and IL-6 and higher IGF-1 level than the LD group (all P < 0.05). Pearson correlation coefficient analysis revealed a negative correlation of serum IGF-1 with CT-1 and IL-6 and a positive correlation between CT-1 and IL-6. Conclusion: High-dose atorvastatin combined with trimetazidine can effectively and safely treat LVD in senile CHD patients, and it can regulate the levels of IGF-1, CT-1 and IL-6 in serum, and significantly improve hemodynamics and cardiac function.

Keywords: Different doses of atorvastatin, trimetazidine, CHD, LVD, hemodynamics, adverse reactions

Introduction

Cardiovascular disease is the main cause of death in all regions worldwide. Coronary heart disease (CHD) is a common cardiovascular disease. According to the 2015 statistics of the World Health Organization, there were about 17,700,000 deaths for cardiovascular disease, including 7,400,000 deaths for CHD [1-4], and the majority of CHD patients are the elderly [5]. In recent years, although the mortality of CHD is declining, more and more people suffer from the disease [6]. Because of the gradual development of the disease, CHD patients often suffer from left ventricular dysfunction (LVD) and other conditions [7]. The occurrence of the disease will terribly compromise the life quality of the elderly patients, and also poses a great threat to the life safety of the patients. Therefore, the important task of the current clinical research is to find safe and effective treatments to improve the life quality and heart function of the patients [8].

Atorvastatin is well tolerated and belongs to statins. Atorvastatin is considered as one of the first-line drugs in Chinese patients with lipid disorders, which can effectively reduce the incidence and mortality of cardiovascular events. Studies have revealed that in CHD patients, high-dose atorvastatin treatment can lead to the regression of carotid atherosclerotic disease, while low-dose atorvastatin only prevents the progress of the disease [11]. Trimetazidine

is a 3-keto-coa-thiolase (3-KAT) inhibitor, which can adapt to autonomic nerve function, restore heart function, improve myocardial ischemia, and increase the stability of CHD [12]. Many studies have verified that atorvastatin and trimetazidine play a synergistic role in a variety of diseases [13, 14]. However, there is little research on the therapeutic effect of different doses of atorvastatin combined with trimetazidine in the elderly patients with LVD and its impact on hemodynamics.

The occurrence of CHD is strongly linked to the metabolic disorder of endogenous substances [15]. Insulin like growth factor-1 (IGF-1), a growth factor, can induce cell growth and proliferation, and lower inflammation [16]. Most researches have revealed that low IGF-1 level is responsible for increased risk of cardiovascular events or death [16-18]. Cardiac Troponin-1 (CT-1) is a proinflammatory cytokine and belongs to the interleukin-6 (IL-6) cytokine family [19]. It has been revealed that CT-1 can promote the production of extracellular matrix, stimulate cell proliferation, thus participating in the reconstruction of damaged blood vessels and heart, leading to cardiovascular hypertrophy and fibrosis [20]. IL-6 is a multi-potent inflammatory cytokine in a variety of cells and organs, which is related to a variety of cardiovascular diseases [21, 22]. It can be used as the main inflammatory mediators to induce acute phase reaction, giving rise to an extensive range of local and systemic changes, including leukocyte recruitment and activation, fever and hemodynamic effects [23]. Hemodynamics can effectively reflect the severity of cardiovascular disease injury [24]. At present, there are few reports about the effects of different doses of atorvastatin combined with trimetazidine on serum factors and hemodynamics.

In this paper, the hemodynamics and IGF-1, CT-1, IL-6 in elderly LVD patients were measured to explore the therapeutic effect and adverse reactions of different doses of atorvastatin combined with trimetazidine.

Method

General information

A total of 160 elderly patients with LVD were treated with atorvastatin and trimetazidine in the First Affiliated Hospital, School of Medicine, Shihezi University. According to the dosage of atorvastatin, the patients were assigned to a high-dose group (HD group, n = 82) and a low-dose group (LD group, n = 78). The HD group consisted of 45 males and 37 females, with a median age of 59.56 ± 8.77 years and a median duration of 13.09 ± 5.28 months. The LD group consisted of 43 males and 35 females, with a median age of 60.11 ± 7.93 years and a median duration of 14.19 ± 6.07 months.

Inclusion criteria: Patients with true and complete clinical data, patients with good compliance, patients without history of mental illness, patients who cooperated with the follow-up investigation voluntarily, patients accompanied by family members at admission to the First Affiliated Hospital, School of Medicine, Shihezi University, and those without history of allergy to treatment drugs.

Exclusion criteria: Patients with communication disorders, patients with severe organic lesions, patients with unconsciousness, patients with life expectancy less than 1 year, patients with malignant tumors, frequent premature beats, liver or kidney dysfunction according to examination, and those who failed to adhere to treatment.

This study was carried out with the permission from the medical ethics committee of the First Affiliated Hospital, School of Medicine, Shihezi University, and in accordance with Helsinki Declaration. All participants and their families were informed of the study and signed informed consent forms for confirmation.

Treatment

All patients were examined and then given routine basic treatment (including diuretics, digitalis, beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers) for cardiac insufficiency. Pulse and blood pressure were monitored. Each patient in the HD group was given trimetazidine tablets orally (Beijing Wansheng Pharmaceutical Co., Ltd., national medicine standard word H20065167), three times a day, 20 mg each time, and was given atorvastatin calcium tablets orally (Beijing Jialin Pharmaceutical Co., Ltd., national medicine standard word H200903819), once a day, 40 mg each time. Each patient in the LD group was given trimetazidine tablets in the same

way as those in the HD group. Patients in the HD group took atorvastatin calcium tablets once a day, 20 mg each time. Both groups took the drugs for one year continuously. If there were rhabdomyolysis, severe drug eruption and liver function decline during the treatment, the drug was stopped immediately, and the patients' condition was followed up and checked regularly.

Serum detection

Elbow venous blood (5 mL) was sampled from each patient by vacuum blood collection needle on an empty stomach before treatment and 1 day after treatment. The blood was centrifuged at 4°C 3000 rpm for 5 min, and then the serum in the test tube was carefully drawn to obtain the serum. The serum was put in the refrigerator at -80°C for analysis. The levels of serum IGF-1, CT-1 and IL-6 were measured by enzyme-linked immunosorbent assay with an mk-3 automatic enzyme labeling analyzer from Shanghai Yilian Medical Instrument Development Co., Ltd., and IGF-1, CT-1 and IL-6 kits from Shanghai Gefan Biotechnology Co., Ltd. (product numbers: hi072, hc090 and hi013) by referring to the manual for specific operation steps. The biochemical analyzer (Beckmann Kurt AU5800) produced by Wuhan Shenkang Medical Instruments Co., Ltd. was used to detect hemodynamic parameters: High and low shear viscosities, fibrinogen, plasma specific viscosity, and erythrocyte specific volume.

Efficacy evaluation [8]

Significant effect: After treatment, patients' left ventricular function was significantly relieved, and a series of clinical symptoms such as asthma, edema and panic disappeared significantly or completely. Effective: the left heart function of the patients was basically improved, and the clinical symptoms were basically relieved. Invalid: the left heart function of the patient did not change or worsen, and the clinical symptoms were not relieved. Total effective rate/% = (significant + effective)/total patients × 100%.

Outcome measures

To compare the therapeutic effect and hemodynamic indexes of the two groups; to observe the six minute walking distance, left ventricular end diastolic diameter, left ventricular end systolic diameter, and left ventricular ejection fraction before and after treatment; to compare the changes of serum IGF-1, CT-1 and IL-6 levels before and after treatment; to count the occurrence of adverse reactions during treatment; to analyze the correlation of serum IGF-1 and CT-1 with IL-6.

Statistical analysis

Spss20.0 (IBM Corp, Armonk, NY, USA) was adopted for statistical analyses. The count data was expressed as [n%], and compared between groups through the chi square test. The measurement data was expressed as the mean ± standard deviation (x ± SD), and the mean of clinical data in the two groups was compared using the independent sample t test. Multiple comparisons before and after treatment were conducted by one-way ANOVA, and LSD-t test was applied for post-test. The Pearson correlation coefficient was adopted for bivariate normal distribution data. $P < 0.05$ was statistically significant.

Result

Comparison of general clinical data

Inter-group comparison of general clinical data revealed that no significant difference was found between the two groups in sex, average age, average course of disease, body mass index (BMI), smoking and alcoholism history, NYHA heart function grading, and complications. See **Table 1**.

Comparisons of therapeutic effects between the two groups

The total effective rate of the HD group was 90.24%, slightly higher than that of the LD group (80.77%), but the difference was insignificant ($P > 0.05$). See **Table 2**.

Comparison of hemodynamics between the two groups

Before treatment, no significant difference was found in hemodynamic parameters between the two groups ($P > 0.05$); after treatment, the hemodynamics of both groups improved ($P < 0.001$), and the fibrinogen, plasma specific viscosity, whole blood low shear viscosity WBLSV, erythrocyte specific volume of the HD group

Table 1. Comparison of general clinical data (x ± sd)/n [%]

	HD group (n = 82)	LD group (n = 78)	X^2	P
Gender				
male	45 (54.88)	43 (55.13)	0.001	0.975
female	37 (45.12)	35 (44.87)		
Average age (years)	59.56±8.77	60.11±7.93	0.415	0.678
Average duration (month)	13.09±5.28	14.19±6.07	1.225	0.223
BMI (kg/m^2)	24.11±4.78	24.87±5.03	0.980	0.329
Smoking history or not			0.032	0.859
Yes	43 (52.44)	42 (53.85)		
No	39 (47.56)	36 (46.15)		
Do you drink too much?			0.049	0.825
Yes	34 (41.46)	31 (39.74)		
No	48 (58.54)	47 (60.26)		
NYHA heart function grading			0.261	0.878
Grade II	37 (45.12)	36 (46.15)		
Grade III	38 (46.34)	37 (47.44)		
Grade IV	7 (8.54)	5 (6.41)		
Complication				
Hypertension	25 (30.49)	20 (25.64)	0.465	0.460
Hyperlipemia	21 (25.61)	24 (30.77)	0.526	0.468
Diabetes	31 (37.80)	29 (37.18)	0.007	0.935

Table 2. Comparison of therapeutic effects [%]

	Markedly effective	Effective	Invalid	Total effective rate/%
HD group (n = 82)	32 (39.02)	42 (51.22)	8 (9.76)	90.24
LD group (n = 78)	23 (29.49)	40 (51.28)	15 (19.23)	80.77
X^2				3.267
P				0.071

were significantly lower than those of the LD group (P < 0.05), but no significant difference was found in whole blood high shear viscosity (WBHSV) (P > 0.05). See **Table 3**.

Comparison of heart function improvement between the two groups

The heart function of the two groups before and after treatment was statistically analyzed, as shown in **Table 4**. There was no significant difference between the two groups before treatment (P > 0.05). The heart function of both groups was significantly improved after treatment (P < 0.001). The heart function of the HD group after treatment was significantly better than that of the LD group (P < 0.05). The six-minute walking distance of the two groups after treatment was improved, but the two groups had no significant difference in it (P > 0.05).

Comparison of serum factor levels between the two groups before and after treatment

Before treatment, no significant difference was found in the serum factor expression between the two groups (P > 0.05); after treatment, both groups showed decreased CT-1 and IL-6 levels and increased IGF-1 level (P < 0.001); and as can be seen from **Figure 1**, the HD group showed lower CT-1 and IL-6 levels and higher IGF-1 level than the LD group (both P < 0.05).

Comparison of adverse reactions between the two groups

Statistics of adverse reactions in the two groups during treatment are shown in **Table 5**. The incidence of adverse reactions in the HD group and LD group was 12.20% and 15.38%, respectively. There was no significant difference in the total incidence of adverse reactions between them (P > 0.05).

Correlation of serum IGF-1, CT-1 and IL-6 between the two groups before treatment: The Pearson correlation coefficient analysis revealed a negative correlation between serum IGF-1, CT-1 and IL-6 (r = -0.5601, r = -0.6324, P < 0.05) and a positive correlation between CT-1 and IL-6 (r = 0.6144, P < 0.05) in the HD group before treatment, and also revealed a negative correlation between serum IGF-1, CT-1 and IL-6 (r = -0.5957, r = -0.6694, P < 0.05) and a positive correlation between CT-1 and IL-6 (r = 0.6557, P < 0.05) in the LD group before treatment. See **Figure 2**.

Correlation of serum IGF-1, CT-1, IL-6 in the two groups after treatment: The Pearson correlation coefficient analysis revealed a negative correlation between IGF-1, CT-1 and IL-6 (r =

Table 3. Hemodynamic comparison between the two groups (x ± sd)

	Fibrinogen (g/L)	Specific viscosity of plasma (MPA · s)	WBHSV (MPA · s)	WBLSV (MPA · s)	Hematocrit (%)
HD group (n = 82)					
Before treatment	4.25±0.66	2.09±0.31	6.57±0.85	12.54±1.79	48.76±6.32
After treatment	3.20±0.42	1.32±0.23	4.83±0.45	7.96±1.43	40.57±4.07
t	11.400	15.250	17.410	17.600	9.564
P	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
LD group (n = 78)					
Before treatment	4.35±0.73	2.12±0.42	6.41±0.77	12.39±2.07	49.15±6.04
After treatment	3.49±0.50*	1.55±0.31*	5.02±0.34	8.75±1.26*	42.59±5.24*
t	9.109	11.010	13.560	9.820	7.472
P	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Note: *represents *P < 0.05 vs. the HD group after treatment.

Table 4. Comparison of cardiac function improvement (x ± sd)

	Left ventricular end-diastolic diameter (mm)	Left ventricular end systolic diameter (mm)	Left ventricular ejection fraction (%)	6 min walking distance (m)
HD group (n = 82)				
Before treatment	59.07±4.77	37.69±3.72	41.67±5.34	235.23±67.11
After treatment	41.94±2.42	28.76±1.64	50.76±3.56	475.39±78.64
t	29.830	21.280	12.220	21.570
P	< 0.001	< 0.001	< 0.001	< 0.001
LD group (n = 78)				
Before treatment	58.83±4.42	37.08±3.27	42.08±5.75	238.12±68.34
After treatment	45.39±2.42*	31.41±1.25*	47.87±4.08*	459.98±70.33
t	22.83	13.180	7.594	19.430
P	< 0.001	< 0.001	< 0.001	< 0.001

Note: *P < 0.05 vs. the HD group after treatment.

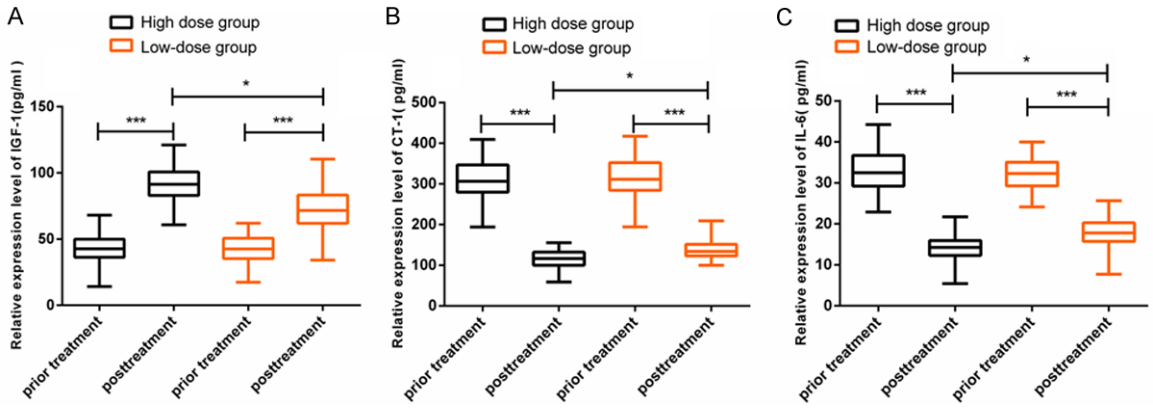

Figure 1. Comparison of serum factor levels before and after treatment between the two groups. Before treatment, no significant difference was found in serum factor expression between them (P > 0.05); after treatment, both groups showed lower CT-1 and IL-6 expression and higher expression IGF-1 (P < 0.001), and the HD group showed lower serum CT-1 and IL-6 levels and higher GF-1 level than the LD group (both P < 0.05). Note: * means the inter-group comparison, *P < 0.05, *** means the inter-group comparison, ***P < 0.001.

Table 5. Comparison of adverse reactions n [%]

	Abdominal pain	Loss of appetite	Gastrointestinal Response	Damage of liver function	Rash	Incidence of adverse reactions/%
HD group	2 (2.44)	2 (2.44)	4 (4.88)	1 (1.22)	1 (1.22)	12.20
(n = 82)	1 (1.28)	3 (3.85)	6 (7.69)	2 (2.56)	0 (0.00)	15.38
LD group						0.385
(n = 78)						0.535

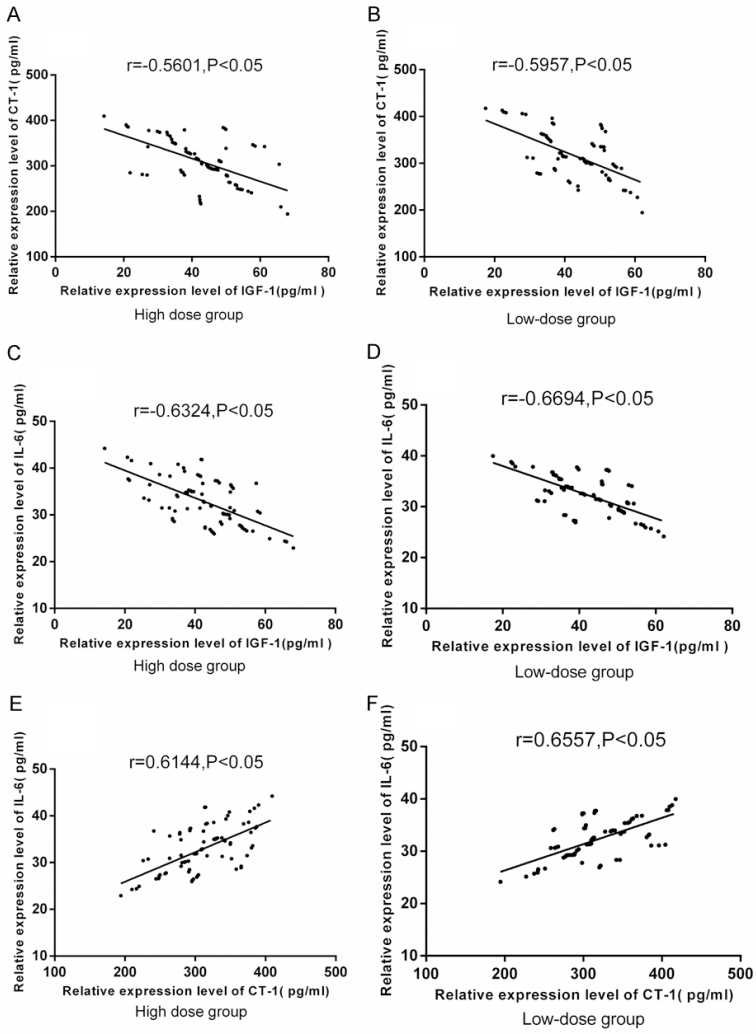

Figure 2. Correlation of serum IGF-1, CT-1 and IL-6 before treatment. According to Pearson correlation coefficient analysis, serum IGF-1 was negatively related to CT-1 and IL-6 (r = -0.5601, r = -0.6324, P < 0.05), CT-1 was positively related to IL-6 (r = 0.6144, P < 0.05), and serum IGF-1 was negatively related to CT-1 and IL-6 (r = -0.5957, r = -0.6694, P < 0.05), CT-1 was positively related to IL-6 (r = 0.6557, P < 0.05).

-0.5986, r = -0.5853, P < 0.05) and a positive correlation between CT-1 and IL-6 (r = 0.6470, P < 0.05) in the HD group, and also revealed a negative correlation between IGF-1, CT-1 and IL-6 (r = -0.5421, r = -0.6150, P < 0.05) and a positive correlation between CT-1 and IL-6 (r = 0.6023, P < 0.05) in the LD group after treatment. See **Figure 3**.

Discussion

CHD is characterized by high mortality, high morbidity, and poor prognosis [25]. The independent risk factors and main diseases of CHD are due to the abnormal performance of lipid metabolism, so it is particularly important to treat and prevent the disease with lipid-lowering medication [26]. Atorvastatin is a new rate-limiting enzyme for cholesterol synthesis, belonging to the intrinsic activity inhibitor of HMG-CoA reductase, which can reduce the synthesis of liver cholesterol by inhibiting the generation of mevalonate through HMG CoA [27]. According to relevant data analysis, atorvastatin can reduce LDL cholesterol by more than 50% at a daily dose of 40 or 80 mg, which can prevent the increase of coronary plaque volume [28]. Trimetazidine has the function of protecting cardiac myocytes, and it is a kind of metabolic medicine, which can effectively stimulate the activity of mitochondria by reducing the metabolism of free fatty acids, enhancing the utilization of lactic acid in cardiac myocytes, reducing the overload of calcium and sodium ions in cells. It can improve the metabolism of mitochondria, and then enhance the utilization of glucose in myocardium, so as to help the body maintain

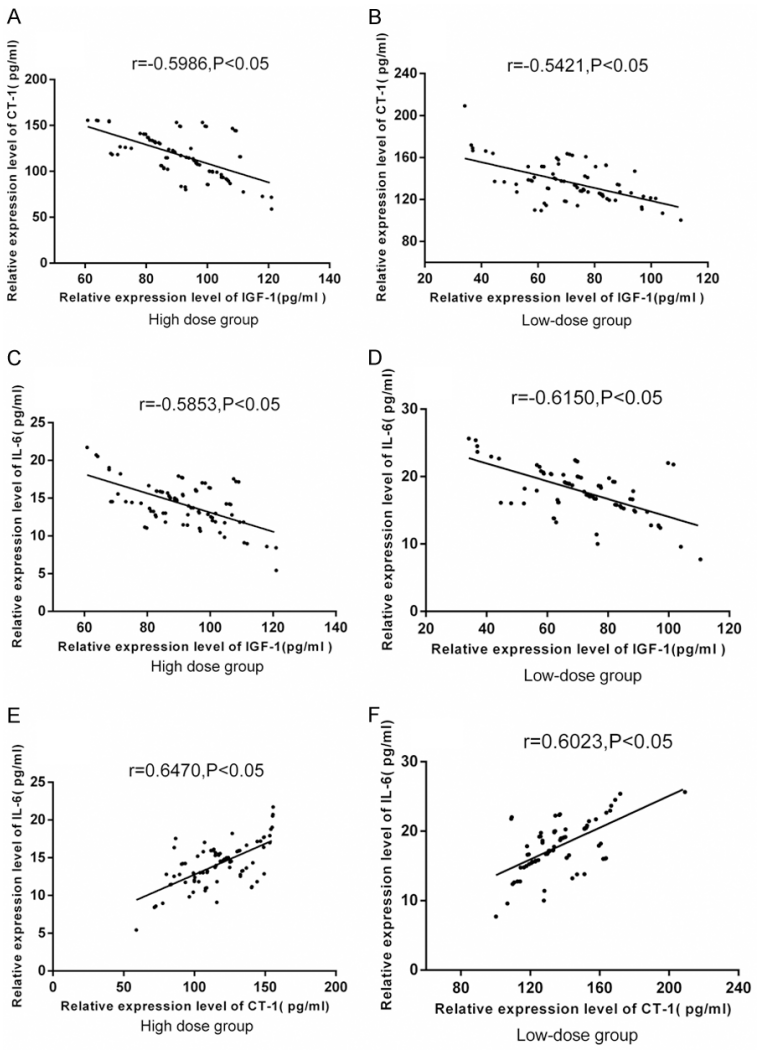

Figure 3. The correlation of serum IGF-1, CT-1 and IL-6 in two groups after therapy. Serum IGF-1 was negatively related to CT-1 and IL-6 ($r = -0.5986$, $r = -0.5853$, $P < 0.05$), CT-1 was positively related to IL-6 ($r = 0.6470$, $P < 0.05$), and serum IGF-1 was negatively related to CT-1 and IL-6 ($r = -0.5421$, $r = -0.6150$, $P < 0.05$), CT-1 was positively related to IL-6 ($r = 0.6023$, $P < 0.05$).

the stability of internal environment and electrolyte balance [29].

CT-1 is highly expressed in cardiac myocytes and cardiac fibroblasts in early embryonic development [30]. Some studies have shown that the expression of CT-1 is strongly linked to the progression of CHD, and the increase of CT-1 level is linked to the severity of CHD [26]. IGF-1 can reduce the burden of atherosclerotic plaques and promote the stability of atherosclerotic plaques [31]. Zhao et al. showed that oral administration of atorvastatin can reduce the level of serum inflammatory cytokine IL-6, thereby alleviating the renal damage of hypertension [32]. In addition, high-dose atorvastatin treatment is linked to the decline of IGF-1 level [33]. This study showed that before treatment, there was no significant difference in the levels of serum IGF-1, CT-1 and IL-6 between groups; after treatment, both groups showed increased IGF-1 level and decreased CT-1 and IL-6 levels, and the HD group showed significantly higher IGF-1 level and lower CT-1 and IL-6 levels than the LD group (both $P < 0.05$). The results suggest that high-dose atorvastatin can significantly improve serum IGF-1, CT-1 and IL-6 levels, and high-dose atorvastatin combined with trimetazidine can effectively reduce inflammation and stabilize plaque in patients with CHD. However, there are few studies in this field, so whether different doses of atorvastatin combined with trimetazidine have different effects on IGF-1, CT-1 and IL-6 levels remains to be further confirmed by experiments. Chiorean et al. suggested that there was a negative correlation between IGF-1 and IL-6 in patients with glioblastomamultiforme ($r = -0.53$, $P < 0.05$) [34]. Moreover, a significant correlation between plasma CT-1 and IL-6 in patients with chronic heart failure (CHF) has been proposed [35]. Through Pearson correlation coefficient analysis, it was found that serum IGF-1 was negatively correlated with CT-1 and IL-6, while CT-1 was positively correlated with IL-6. However, there is no research report on the correlation between IGF-1 and CT-1, so a lot of research is needed to prove it.

Ma' Study on trimetazidine combined with different doses of atorvastatin in patients with dyslipidemia and angina pectoris revealed no significant difference between the total effective rate of high-dose atorvastatin calcium and

low-dose atorvastatin calcium (P > 0.05) [36]. This study revealed that the HD group showed slightly higher total effective rate than the LD group, but the difference was insignificant, which suggested that different doses of atorvastatin calcium combined with trimetazidine have better effects in the treatment of LVD in CHD. It has been reported that atorvastatin can significantly improve the hemodynamic indexes and hemostatic parameters of patients with chronic cerebrovascular disease after 3 months of treatment [37]. In addition, related studies suggest that trimetazidine treatment can improve the hemodynamic indexes of patients with ischemic heart disease and CHF [38]. However, rare research has been done on the influences of different doses of atorvastatin combined with trimetazidine on hemodynamics. The results revealed that there was no difference in hemodynamic indexes between the two groups before and after the treatment; the hemodynamics of both groups was improved after treatment, and no significant difference was found in WBHSV between the two groups after the treatment (P > 0.05). The plasma specific viscosity, the WBLSV, fibrinogen and the red blood cell specific volume of the HD group after the treatment were significantly lower than those of the LD group (P < 0.05). It is suggested that atorvastatin combined with trimetazidine can strongly improve the hemodynamics of LVD in senile patients with CHD, promote the blood circulation of blood vessels, and high dose of it has a better effect. The results showed that atorvastatin combined with folic acid can improve the cardiac function and 6-min walking distance in patients with CHF. Trimetazidine showed the same effect in the treatment of CHD, and it can regulate myocardial metabolism, inhibit free fatty acid oxidation, and promote phospholipid synthesis, which could significantly improve left ventricular ejection fraction, left ventricular end diastolic diameter and left ventricular posterior wall thickness (P < 0.05) [40]. The results revealed that there was no significant difference between the two groups in heart function index and 6-min walking distance before the treatment, and there was no significant difference between the two groups in terms of 6-min walking distance after treatment (P > 0.05). The results revealed that high-dose or low-dose atorvastatin could significantly improve the 6-min walking distance, while high-dose atorvastatin combined with trimetazidine had a better influence on the left ventricular function of senile CHD patients. One study compared the incidence of adverse events of high-dose and low-dose atorvastatin in patients with stable angina pectoris or acute coronary syndrome, finding that there was no significant difference in primary adverse cardiovascular events between the two groups in one year (P > 0.05) [41], which is similar to the results of our study, implying that high-dose or low-dose atorvastatin is safe in the treatment of LVD in senile CHD patients.

In this paper, the influence of different doses of atorvastatin combined with trimetazidine on LVD in senile patients with CHD and its effect on hemodynamics have been studied. However, the specific mechanism of high-dose atorvastatin in treating LVD in patients with CHD remains unclear. In addition, in the future research, we can study the prognosis and effect factors of high-dose atorvastatin in the treatment of elderly CHD with LVD, in order to provide a more clear reference for the pathogenesis, clinical diagnosis and therapy of elderly CHD with LVD.

In conclusion, high-dose atorvastatin combined with trimetazidine is effective and safe in the treatment of elderly patients with LVD of CHD. It can regulate the levels of IGF-1, CT-1 and IL-6 in serum, and significantly improve hemodynamics and cardiac function.

Disclosure of conflict of interest

None.

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