

# Trimetazidine hydrochloride as a new treatment for patients with peripheral vascular disease – an exploratory trial

Y.-S. CHU, D.-X. LI, M. ZHANG, T.-M. JIANG

Department of Cardiology, Affiliated Hospital of Logistical College of Chinese People's Armed Police Forces, Tianjin, Tianjin, China

**Abstract. – OBJECTIVE:** To evaluate the therapeutic effect of trimetazidine hydrochloride in peripheral vascular disease patients who had Rutherford classification grade 2-3.

**PATIENTS AND METHODS:** 72 patients with Rutherford classification grade 2-3 in peripheral vascular were recruited successfully, they were randomly assigned to control group (35 cases) and trimetazidine group (37 cases), patients in control group received conventional treatment and trimetazidine group received conventional treatment plus trimetazidine hydrochloride for 6 months. Their ankle brachial index (ABI), maximum walking distance, pain onset time and the maximum walking time were compared before and after the treatment.

**RESULTS:** After 6 months' treatment, the ABI, maximum walking distance, pain onset time and the maximum walking time in two groups were both improved of when compared with before treatment ( $p < 0.05$ ). The maximum walking distance, pain onset time and the maximum walking time in trimetazidine group were improved better than control ( $p < 0.05$ ) while no evident improvement in ABI between the 2 groups ( $p > 0.05$ ).

**CONCLUSIONS:** Conventional therapy plus trimetazidine hydrochloride could significantly improve the clinical symptoms of patients with Rutherford classification Grade 2-3 in peripheral vascular.

*Key words:*

Peripheral vascular disease, Rutherford classification, Trimetazidine hydrochloride, Patients.

## Introduction

Peripheral artery disease (PAD, also called peripheral arterial disease) is a common circulatory problem occurred in lower extremities; in which formation of atherosclerotic plaque narrowed arteries, reduce blood flow<sup>1,2</sup>. PAD could result ischemia and necrosis in limb, is a part of atherosclerosis in whole body<sup>3,4</sup>. PAD is a common

cause of morbidity and mortality in worldwide, it is estimated that over 200 million people are affected by PAD<sup>5</sup>, and the incidence of PAD is gradually increasing. The early symptoms of the PAD mainly are intermittent claudication and rest pain caused by lower limb ischemia<sup>6</sup>. Untimely intervention could cause the severity of lower extremity artery stenosis even occlusion, increased ischemia in lower limb further lead to foot ulceration or gangrene, in severe cases, amputation is need and PAD even threaten the patient's life<sup>7</sup>.

PAD seriously affects the patients' quality of life, the PAD patients demonstrate impaired performance on a range of lower extremity performance tests, including poorer walking endurance, slower walking velocity, and reduced lower limb strength, etc<sup>5</sup>. Rutherford classification is commonly used in clinical evaluation of peripheral arterial disease; The Rutherford classification criteria were also widely used in clinical treatment guidelines<sup>8</sup>. Patients with Rutherford classification Grade 2-3 mainly refer to patients with peripheral artery stenosis, and claudication effect their living or working.

The primary goal of conservative clinical management of PAD is to minimize disease progression and optimize performance. Drugs contribute importantly in the treatment of PAD. Early treatment of PAD mainly focuses on anti-platelet, expanding blood vessel, improving collateral circulation. Few mechanisms involved in skeletal muscle energy metabolism, Trimetazidine hydrochloride is a new long chain 3-ketoacyl coenzyme inhibitor (3-KAT inhibitors), trimetazidine hydrochloride exerts its therapeutic effect through oxidation of glucose in the myocardial energy metabolism instead of fatty acid metabolism. Whether trimetazidine could improve the energy metabolism of skeletal muscle in PAD patients is unclear. In this study, patients with Rutherford classification Grade 2-3 were recruited to observe the therapeutic effect of trimetazidine to peripheral vascular disease.

## Patients and Methods

### Patients

Consecutive patients were recruited from April to October in 2013 at our hospital. This study was approved by the Ethic Committee of Affiliated Hospital of Logistical College of Chinese People's Armed Police Forces. All subjects signed written informed consent form. All works were undertaken following the provisions of the Declaration of Helsinki. The study was registered at Center for Drug Evaluation of China Food and Drug Administration (<http://www.chinadrugtrials.org.cn>).

Their mainly complaints included lower extremity weakness, cold, rest pain, intermittent claudication and toe or foot pain. The measurement of ankle brachial index (ABI) and peripheral vascular color Doppler were performed in these patients (Figure 1). The inclusion criteria were: 1) ABI index <0.9. 2) Color Doppler flow imaging of peripheral blood vessel confirmed that the diameter of the femoral artery, tibial artery and dorsal artery of the foot was reduced; the intimal thickened; atherosclerotic plaque formation could be seen; blood flow velocity decreased. 3) Rutherford classification of Grade 2-3<sup>9</sup>.

Exclusion criteria: (1) patients complicated with severe kidney, insufficiency liver function or heart function; (2) severe stenosis or occlusion in lower extremity artery confirmed by imaging examina-

tion; (3) patients with severe multiple organ failure or with malignant tumor, severe malnutrition or mental disorders; (4) patients with severe diabetes mellitus or patients with various acute complications or trauma; (5) patients with serious illness or at serious stress state; (6) patients with poor compliance; (7) Patients with tinnitus, vertigo or disturbances in vision; (8) Patients with Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome or other related movement disorders<sup>10</sup>.

### Grouping and Treatment

Recruited patients were asked to follow the improvement therapy in living habits and exercise for 2 weeks, then the patients were divided into 2 groups according to the principle of voluntary: control group patients received conventional treatment including oral antiplatelet agents (aspirin, 100 mg/d), lipid-lowering drugs (statins, mainly Rosuvastatin Calcium, 10 mg/d) and antihypertensive drugs; patients in trimetazidine group received conventional treatment plus trimetazidine hydrochloride tablets (Tianjin Servier Pharmaceutical Co., Ltd., approved number of H20055465 by CFDA) with 20 mg, 3 times a day. The treatment lasted 6 months.

The ABI, the maximum walking distance, pain onset time and the maximum walking time were recorded in both group patients before and after treatment.

### Measurement of ABI Index

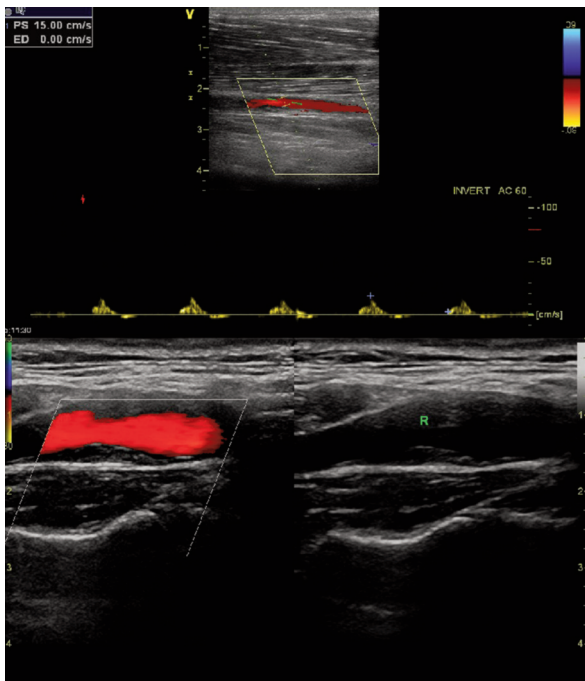
ABI index were measured using bilateral VP-1000 Vascular Profile Device (Omron Healthcare, Inc., Bannockburn, IL, USA). And the low value of ABI at the left and right sides was considered as the ABI value of the patients and been analyzed.

### Demographic Parameters

Demographic parameters were measured at the second day of patients' admission. Venous blood was drawn and their total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), fasting blood glucose (FPG) levels were measured by total automatic biochemical analyzer (Siemens Healthcare Global, Erlangen, Germany).

### Statistical Analysis

All data were analyzed using SPSS18.0 statistical software (IBM, Chicago, IL, USA). The measurement data are expressed as mean  $\pm$  standard deviation. The Count data are expressed as the case number and percent. Differences between cases and controls regarding means and



**Figure 1.** Vascular color Doppler of patient with peripheral artery disease.

proportions were compared by using the *t*-test and the chi-square test, respectively.  $p < 0.05$  was considered statistically significant.

## Results

### **Demographic Data Comparisons Before Treatment**

A total of 72 patients with Rutherford classification Grade 2-3 in peripheral vascular were recruited successfully, 35 of them were divided into control group and 37 of them were divided into trimetazidine group. Demographic data showed the age, gender distribution, smoking, hypertension, diabetes, coronary heart disease case number and drug using have statistical difference ( $p > 0.05$ ) between the 2 group; Their systolic blood pressure, diastolic blood pressure, body mass index (BMI), TG, LDL-C, TC and FPG levels in the two groups have no statistical difference too ( $p > 0.05$ ) (Table I).

### **Therapeutic Effect Comparison Before and After Treatment**

Before treatment, there was no significant differences in the levels of ABI index, the maximum walking distance, the pain onset time and the maximal walking time between the 2 groups ( $p > 0.05$ ). After treatment for 6 months, the ABI index, the maximum walking distance, the pain onset time and the maximum walking time were all improved significantly in 2 groups when compared with before treatment ( $p < 0.05$ , Table II).

### **Trimetazidine Improved the Maximum Walking Distance, the Pain Onset Time and the Maximal Walking Time**

The remission of clinical symptoms in trimetazidine group was better than control group, the maximum walking distance, pain onset time and the maximum walking time were obviously better than that the control group with statistical significance ( $p < 0.05$ ). However, there was no significant difference in ABI index between trimetazidine group and control group ( $p > 0.05$ ) after treatment (Table II).

## Discussion

Peripheral artery disease is a local manifestation of systemic arterial occlusive disease occurred in the lower extremities. The mechanism of PAD is the same as that of heart and cerebrovascular disease<sup>11</sup>. PAD seriously threatens to human health. Epidemiological data<sup>12</sup> show that, with the growth of the age, the PAD incidence rate showed an upward trend, the incidence rate in people over age of 70 reach to 15%-20%. PAD can reduce the body function of patients, and it can affect the quality of life.

The treatment of PAD includes conventional therapy such as eliminating the risk factors, exercise, drug therapy, endovascular treatment, surgical treatment and gene therapy. For patient had Rutherford classification grade 4-6, severe rest pain, ulceration or gangrene, timely endovascular treatment or

**Table I.** Demographic data comparisons between control group and trimetazidine group before treatment.

Group	Control	Trimetazidine
Case number	35	37
Age (yr)	58.57 ± 9.47	59.36 ± 8.57
Gender (M/F)	23/12	26/11
Smoking case (n, %)	20 (57.14)	22 (59.46)
Hypertension (n, %)	24 (68.57)	23 (62.16)
Diabetes mellitus (n, %)	22 (62.86)	25 (67.57)
Coronary heart disease (n, %)	17 (48.57)	17 (45.95)
Aspirin user (n, %)	35 (100.00)	37 (100.00)
B receptor blockers user (n, %)	12 (34.29)	11 (29.73)
Calcium antagonist user (n, %)	19 (54.29)	20 (54.05)
ACEI/ARB user (n, %)	19 (54.29)	19 (51.35)
Statin user (n, %)	24 (68.57)	26 (70.27)
Systolic pressure (mmHg)	143.43 ± 18.53	141.38 ± 20.72
Diastolic pressure (mmHg)	82.49 ± 11.36	83.62 ± 10.62
BMI	27.13 ± 3.18	28.15 ± 2.85
TC (mmol/L)	5.03 ± 0.95	5.13 ± 0.91
LDL-C (mmol/L)	3.33 ± 0.95	3.26 ± 0.90
TG (mmol/L)	1.73 ± 0.69	1.75 ± 0.59
FPG (mmol/L)	5.66 ± 0.61	5.79 ± 0.64

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**Table II.** Therapeutic effect comparisons between trimetazidine group and control group before and after treatment.

Group (N)		ABI index	The maximum walking distance (meter)	The maximum walking time (minute)	Pain onset time (minute)
Control (35)	Before treatment	0.69 ± 0.17	112.59 ± 84.22	8.85 ± 2.71	3.53 ± 1.22
	After treatment	0.77 ± 0.15*	192.22 ± 105.44*	12.11 ± 3.08*	7.43 ± 1.72*
Trimetazidine (37)	Before treatment	0.68 ± 0.18	110.49 ± 86.76	9.12 ± 2.74	3.66 ± 1.28
	After treatment	0.78 ± 0.21*	245.74 ± 118.57*#	15.85 ± 2.98*#	9.43 ± 1.81*#

\* $p < 0.05$ , compared with before treatment in same group; # $p < 0.05$ , compared with control after treatment.

surgical treatment should be performed to reconstruct their limb blood. For patient had Rutherford classification grade 3, they have severe intermittent claudication, aggressive medical therapy should be performed, while the surgical treatment should be relatively cautious. For patient had Rutherford classification grade 1-2, the claudication in vast majority of them are stable, exercise and drug therapy are the main choice of treatment<sup>13</sup>.

The ESC guidelines<sup>13</sup> recommend that patients with PAD symptom should be treated with anti-platelet agents. Aspirin has clear effect in reducing the event rate of lower extremity revascularization and the risk of bridging vascular blockage after revascularization<sup>14</sup>. Singer indicated that different types of antihypertensive drugs can effectively alleviate the symptoms of intermittent claudication<sup>15</sup>. While other researchers<sup>16,17</sup> are more likely recommending the use of angiotensin converting enzyme inhibitor or angiotensin receptor antagonist. In addition, Statins could significantly improve the pain symptoms in PAD patients with, could improve the time and ability to walk without pain<sup>18,19</sup>, and was recommended for PAD treatment<sup>20</sup>. In the present study, the two group-patients received conventional anti-platelet, blood pressure lowering and lipid lowering treatment, their ABI index, the maximum walking distance, pain onset time and maximum walking time improved significantly, these results are consistent with the above reports, which confirm the above treatment is important for PAD patients.

PAD patient has abnormal energy metabolism of skeletal muscle, the recovery period of high energy phosphate substrate extended in muscle; the exercise tolerance ability of PAD patient is limited, the produced ATP in the skeletal muscle is not sufficient, the anaerobic metabolism is activated, thus lead to deficiency of ATP, and the increased output of lactate and creatine phosphate, which is consistent with acute and chronic ischemic myocardial cells,

The magnetic resonance spectroscopy for skeletal muscle of PAD patients has great difference with normal people. Their adenosine triphosphate (ATP) synthesized by oxidation rate decreased and the proton circulation slowed, these indicate the deficiency of their skeletal muscle oxygen supply and a slowing of the metabolism. This leads to an increase in the body's anaerobic fermentation to compensate deficient ATP, but also produces more lactic acid. For symptomatic PAD patients, their phosphocreatine and pH value in skeletal muscle of lower extremity reduced significantly after exercise<sup>21</sup>. The walking distance of the patients was negatively correlated with the concentration of adenosine diphosphate, and the maximal rate of ATP synthesis in mitochondria of skeletal muscle was positively correlated with their active degree during treadmill exercise<sup>22</sup>. Therefore, improving the energy metabolism of skeletal muscle might be one of the effective methods to improve the clinical symptoms of PAD patients.

Trimetazidine hydrochloride apply its protective effect through direct inhibition of mitochondrial 3-KAT, and made myocardial energy metabolism through oxidation of glucose instead of fatty acid metabolism. Currently, trimetazidine has been widely used in clinical for cardiovascular disease, such as myocardial ischemia, chronic heart failure. But the clinical evidence of trimetazidine improves the energy metabolism of PAD is less. Vitale et al<sup>23</sup> found that trimetazidine could improve the exercise capacity of PAD patients. And our experiment enriches the data.

## Conclusions

In our study, 6 months' treatment of trimetazidine improved the maximum walking distance, pain onset time and the maximum walking time



when compared with control group. But the ABI index improved. This might be because trimetazidine improves the energy metabolism of skeletal muscle in PAD patients, it make full use of the oxygen in the blood, resulting in more ATP, increasing the energy supply of skeletal muscle, thus improve the clinical symptoms of PAD patients. But trimetazidine could only affect the skeletal muscle energy metabolism and has no effect on the expansion of the lower extremity vascular, regression of plaque and the prevention of thrombosis, so the improvement of ABI index is less.

There are some limits of our study: firstly, the case number in this study is limited, this affected the credibility of the studied data; second, the selected subjects of this study were relatively narrow, while in clinical, the PAD patients were most elderly people, their combined disease and drug use was more complicated. Although the above limitation, our study indicated that trimetazidine hydrochloride could improve the clinical symptoms of patients with early PAD. This provides a meaningful reference for clinical medication using of trimetazidine.

#### Conflict of Interest

The Authors declare that there are no conflicts of interest.

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