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Original Article

Beneficial effects of trimetazidine as a metabolic therapy on cardiac recovery and quality of life for patients with coronary heart disease after percutaneous coronary intervention

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Abstract: Objective: The retrospective study investigated the effect of trimetazidine (TMZ) as a metabolic therapy on cardiac recovery and quality of life (QOL) for patients with coronary heart disease (CHD) after percutaneous coronary intervention (PCI). Methods: We included 100 CHD patients who underwent PCI in the Affiliated Calmette Hospital of Kunming Medical University between January 2016 and June 2016. Patients were randomly assigned to control and experimental groups. Patients in the control group took secondary prevention medications and those in the experimental group were given secondary prevention medications and three-month oral administration of TMZ. The treadmill exercise test, the echocardiogram, the six-minute walking test (6MWT), the MOS 36-Item Short-Form Health Survey (SF-36), and the Seattle Angina Questionnaire (SAQ) were administered to 100 patients. Results: Patients who had taken secondary prevention medications and oral administration of TMZ in the experimental group were compared to those patients who had just taken secondary prevention medications in the control group on metabolic equivalents (METs), left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDd), the SF-36 and SAQ subscale scores: the experimental group exhibited increased METs and LVEF, and decreased LVEDd compared with the control group; there were significant differences in the SF-36 domains of general health, role physical, bodily pain and social functioning between two groups; the 6MWT distance was longer in the experimental group than in the control group; the experimental group had higher SAQ subscale scores of physical limitation, angina stability, treatment satisfaction and disease perception than the control group. Conclusion: Our study provides evidence that oral administration of TMZ as a metabolic therapy may improve cardiac recovery and QOL for CHD patients undergoing PCI.

Keywords: Trimetazidine, coronary heart disease, percutaneous coronary intervention, metabolic therapy, quality of life

Introduction

Coronary heart disease (CHD), a polyfactorial disease, is mainly manifested with atherosclerosis induced by lipid metabolism disorders [1]. CHD is one of the dominating causes of death and disease burden in developed countries and developing countries [2]. CHD mortality of Chinese population in both urban and rural districts has grown since 1980s [3, 4]. Accumulating evidence suggests that CHD has a number of risk factors, such as age, gender, body mass index (BMI), blood pressure, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), cigarette smoking, and diabetes mellitus [5-7]. Percutaneous coronary intervention (PCI) is relatively effective to achieve successful revascularization and to improve heart rate recovery (HRR) in patients with cardiovascular disease [8]. Although PCI shows short-term improvement for heart transplant patients, there is still some disagreement on long-term efficacy of PCT [9]. It is urgent to find alternative and beneficial therapies to improve quality of life (QOL) for CHD patients after PCI.

Table 1. Comparison on baseline characteristics of CHD patients undergoing PCI between control and experimental group

Baseline characteristic	Control group	Experimental group	t/x^2	*P*
Age (year)	62.33 ± 8.08	61.12 ± 7.63	0.770	0.443
Gender			1.967	0.161
Male	30	23		
Female	20	27		
Disease duration (year)			0.518	0.772
≤ 5	15	18		
6~10	29	26		
≥ 10	6	5		
BMI (kg/m^2)			0.271	0.602
18.5~23.9	10	8		
< 18.5 or > 23.9	40	42		
Smoking history			2.361	0.307
Never smokers	3	6		
Former smokers	18	22		
Persistent smokers	29	22		

Note: CHD, coronary heart disease; PCI, percutaneous coronary intervention; BMI, body mass index; continuous data were compared between two groups using *t* test; categorical data were compared between two groups using Chi-square test.

Table 2. Comparison on METs between patients with TMZ treatment in the experimental group and those without in the control group

Group	METs		t	*P*
	Before treatment	After treatment		
Control group	4.91 ± 1.14	5.43 ± 1.06	2.309	0.044
Experimental group	4.97 ± 1.26	5.96 ± 1.03	4.396	< 0.001
t	0.266	2.353		
P	0.956	0.039		

Note: METs, metabolic equivalents; TMZ, trimetazidine; continuous data were compared using *t* test.

Metabolic dyslipidemia is defined by a concomitant increase in triglyceride (TG) levels and a decrease in HDL-C, and may contribute to an increased risk of CHD [10]. Interestingly, metabolic therapy would benefit patients with heart failure through modulating cardiac metabolism but not altering hemodynamics, with the use of metabolic modulators, including trimetazidine (TMZ), perhexiline, ranolazine and etomoxir [11]. CHD also induces congestive heart failure characterized by the failure of sufficient blood and oxygen supply from heart to peripheral tissues and organs [12]. TMZ is a kind of cellular anti-ischemic agent, which is a metabolic compound. It does not influence hemodynamic parameters [13]. More specifically, using TMZ not only improves cardiac function in patients with heart failure, but also has a protective effect against cardiovascular events [14]. Fragasso *et al.* reported that TMZ exerts an anti-ischemic property to improve left ventricular function, without altering the myocardial blood supply and oxygen consumption [15]. The objective of this study was to investigate the effect of TMZ on the cardiac recovery and QOL for CHD patients after PCI.

Materials and methods

Study subjects

A total of 100 CHD patients undergoing PCI in the Affiliated Calmette Hospital of Kunming Medical University between January 2016 and June 2016 were selected as study subjects. Patients consisted of 53 males and 47 females, with a mean age of 61.70 ± 7.88 years. These patients were assigned to a control group and an experimental group at random. Patients were diagnosed as CHD according to the criteria for diagnosis of ischemic heart disease reported by the World Health Organization [16]. Patients were included if they met the following criteria: (1) patients experienced chest discomfort due to exertion, fatigue and physical activity, the symptom was relieved by rest, and there were reversible ischemic electrocardiographic changes at onset; (2) patients had a ST-segment depression of 0.1 mV or more in the exercise electrocardiogram; (3) patients had significant coronary stenosis (greater than 70% lumen diameter) who underwent PCI within recent 6 months. Patients were excluded if they had non-cardiac chest pain caused by lesions of the chest wall, lung and esophagus, and myocardial ischemia caused by peripheral vascular disease; if they were accompanied by severe lesions in the lung, liver, kidney, blood

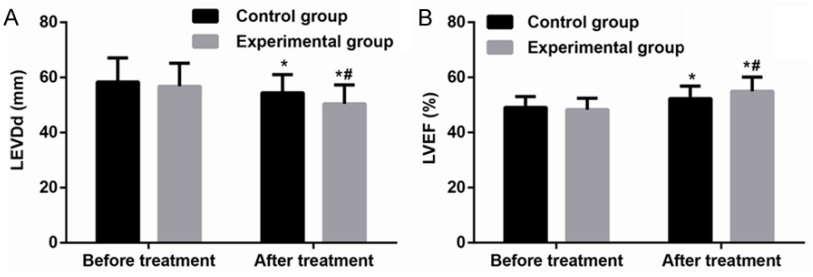

Figure 1. Comparison on LVEDd and LVEF between patients with TMZ treatment in the experimental group and those without in the control group. *, $P < 0.05$ compared with the before treatment; #, $P < 0.05$ compared with the control group. Note: LVEDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; TMZ, trimetazidine.

Table 3. Comparison on scores of SF-36 subscales between patients with TMZ treatment in the experimental group and those without in the control group

Group	Control group		Experimental group	
	Before treatment	After treatment	Before treatment	After treatment
GH	36.67 ± 6.34	50.91 ± 9.14*	37.17 ± 7.42	56.66 ± 8.96*,#
PF	68.45 ± 10.73	74.75 ± 11.87*	68.97 ± 12.36	80.12 ± 11.79*
RP	32.39 ± 20.11	43.59 ± 19.96*	33.03 ± 19.97	53.67 ± 14.13*,#
BP	54.43 ± 19.65	64.43 ± 18.96*	55.74 ± 22.38	75.24 ± 19.56*,#
VT	57.83 ± 15.24	66.54 ± 9.96*	59.12 ± 11.89	67.34 ± 8.99*
SF	60.26 ± 20.31	70.12 ± 16.57*	600.59 ± 18.98	79.67 ± 15.62*,#
RE	36.68 ± 21.34	64.35 ± 19.46*	37.31 ± 25.12	72.14 ± 21.23*
MH	72.13 ± 16.85	77.62 ± 14.76	71.45 ± 16.43	78.34 ± 17.38

Note: SF-36, MOS 36-Item Short-Form Health Survey; TMZ, trimetazidine; GH, general health; PF, physical functioning; RP, role physical; BP, bodily pain; VT, vitality; SF, social functioning; RE, role emotion; MH, mental health; *$P < 0.05$ compared with data before treatment; #$P < 0.05$ compared with the control group; continuous data were compared among multiple groups using one-way analysis of variance.

and gastrointestinal tract; if they had allergic reactions to medicines; if they were pregnant and lactating women. Patients in the control group took secondary prevention medications and those in the experimental group took secondary prevention medications and three-month oral administration of 20 mg tid TMZ (Vasorel, batch No.: 4J4513, France Les Laboratoires Servier). This study was performed based on the protocols approved by the commitment of our hospital (2016-7). All patients signed written informed consents prior to recruitment.

Treadmill exercise test

The treadmill exercise test was performed using the modified Bruce protocol [17]. Before test, patients were well-informed about the modified Bruce protocol. After having a rest for 15-30 min, patients were trained to run on a treadmill (Diamond pro740SB, Mitsubishi Electric Corporation, Tokyo, Japan) 1 hour before breakfast and 1 hour before dinner (19°C~22°C, 40%~50% of humidity). Metabolic equivalents (METs) of patients were records.

Echocardiogram

All echocardiograms were performed using a Vivid 7 cardiac ultrasound machine (GE Healthcare, Milwaukee, Wisconsin) with a 2~4 MHz transducer, following a standardized protocol. With Simpon's method, left ventricular ejection fraction (LVEF) and left ventricular end-diastolic dimension (LVEDd) were measured to reflect changes of cardiac structure of patients.

The MOS 36-Item Short-Form Health Survey (SF-36) scales

The SF-36 is a brief self-administered questionnaire that generates scores across 36 items describing 8 dimensions: general health (GH), physical functioning (PF), role physical (RP), bodily pain (BP), vitality (VT), social functioning (SF), role emotion (RE) and mental health (MH). Higher scores of the SF-36 subscales indicated better QOL.

Six minute walk test (6MWT)

The 6MWT was performed indoors, along a flat, straight, enclosed, and seldom traveled corridor that had 30 m of length and a hard surface [18]. Before testing, patients were required to adjust environment and were well-informed about the purpose of test. The distance that 100 patients walked in 6 min were measured.

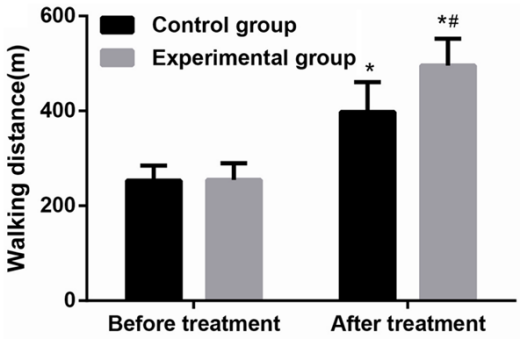

Figure 2. Comparison on the 6MWT distance between patients with TMZ treatment in the experimental group and those without in the control group. *, $P < 0.05$ compared with the before treatment; #, $P < 0.05$ compared with the control group. Note: 6MWT, six minute walk test; TMZ, trimetazidine.

The seattle angina questionnaire (SAQ)

All patients were interviewed by the physician using the SAQ [19] to quantify the physical and emotional effects of CHD. This instrument is a 19-item self-administered questionnaire leading to five scales that measure clinically important dimensions of CHD: physical limitation (PL), angina stability (AS), angina frequency (AF), treatment satisfaction (TS) and disease perception (DP). Higher scores of the SAQ subscales indicated better QOL.

Statistical analysis

The statistical package for the social sciences (SPSS) version 21.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Continuous data were expressed as mean ± standard deviation, with t-test used to compare data between groups. Categorical data were expressed as ratio and percentage, with Chi-square test used to compare data between groups. A *P* valu < 0.05 indicated statistically significant differences.

Results

Baseline characteristics of CHD patients undergoing PCI

One hundred CHD patients undergoing PCI were assigned to a control group and an experimental group. Patients in the control group consisted of 30 males and 20 females, aged 37~72 years and with a mean age of 62.33 ± 8.08 years. Patients in the experimental group comprised 23 males and 27 females, aged 37~72 years and with a mean age of 61.12 ± 7.63 years. No significant difference was found in age, gender, disease duration, body mass index (BMI) and smoking history between control and experimental groups ($P > 0.05$) (**Table 1**). There was no death, case of loss to follow or withdrawal from the study.

Oral administration of TMZ increased METs of CHD patients undergoing PCI

Before any treatment to CHD patients undergoing PCI, the METs did not differ significantly between control and experimental groups ($P > 0.05$). After taking secondary prevention medications, patients in the control group had increased METs ($P < 0.05$), and after taking secondary prevention medications and oral administration of TMZ, patients in the experimental group also exhibited increased METs ($P < 0.05$). The METs were higher in patients taking secondary prevention medications and oral administration of TMZ compared with those patients just taking secondary prevention medications ($P < 0.05$) (**Table 2**).

Oral administration of TMZ improved cardiac function of CHD patients undergoing PCI

The echocardiogram showed that the LVEDd and LVEF exhibited no significant difference between control and experimental groups before any treatment to CHD patients undergoing PCI ($P > 0.05$). After taking treatments, patients in both control group and experimental group had reduced LVEDd and increased LVEF (all $P < 0.05$). However, LVEDd was dropped and LVEF was increased in a more intense fashion in patients of experimental group compared with those patients of control group (**Figure 1**). The result implied that oral administration of TMZ improved cardiac function of CHD patients undergoing PCI.

Oral administration of TMZ improved QOL of CHD patients undergoing PCI

Scores of SF-36 subscales did not differ significantly between control and experimental groups before treatment ($P > 0.05$). After taking secondary prevention medications, patients in the control group exhibited a remarkable increase in GH, PF, RP, BP, VT, SF and RE scores but did not in MH score ($P < 0.05$). After taking

Table 4. Comparison on scores of SAQ subscales between patients with TMZ treatment in the experimental group and those without in the control group

Group	Control group		Experimental group	
	Before treatment	After treatment	Before treatment	After treatment
PL	52.17 ± 12.34	63.56 ± 14.76*	53.31 ± 18.14	72.43 ± 16.46*,#
AS	45.27 ± 13.65	73.45 ± 16.67*	43.45 ± 14.65	83.42 ± 19.12*,#
AF	55.35 ± 21.34	79.34 ± 14.56*	54.75 ± 18.58	83.32 ± 17.54*
TS	34.77 ± 14.34	59.65 ± 13.34*	35.13 ± 13.53	66.56 ± 11.89*,#
DP	32.49 ± 12.76	44.92 ± 13.45*	33.63 ± 14.95	53.34 ± 15.36*,#

Note: SAQ; Seattle Angina Questionnaire; TMZ, trimetazidine; PL, physical limitation; AS, angina stability; AF, angina frequency; TS, treatment satisfaction; DP, disease perception; *$P < 0.05$ compared with data before treatment; #$P < 0.05$ compared with the control group; continuous data were compared among multiple groups using one-way analysis of variance.

secondary prevention medications and oral administration of TMZ, patients in the experimental group also had increased scores of GH, PF, RP, BP, VT, SF and RE ($P < 0.05$), but did not in MH score ($P > 0.05$). However, SF-36 subscales of GH, RP, BP and SF exhibited higher scores in patients of experimental group than in those patients of control group ($P < 0.05$), but PF, VT, RE, MH subscales did not ($P > 0.05$) (**Table 3**). The result suggested that oral administration of TMZ improved QOL of CHD patients undergoing PCI.

Oral administration of TMZ increased 6MWT distance of CHD patients undergoing PCI

The 6MWT indicated that no significant difference was found in the 6MWT distance between control and experimental groups before treatment ($P > 0.05$). After taking secondary prevention medications, patients in the control group exhibited an increased 6MWT distance ($P < 0.05$), and after taking secondary prevention medications and oral administration of TMZ, patients in the experimental group also showed a significant increase in 6MWT distance ($P < 0.05$). However, the 6MWT distance was longer in patients of experimental group than in those patients of control group ($P < 0.05$) (**Figure 2**).

Oral administration of TMZ alleviate symptoms of angina in CHD patients undergoing PCI

Before any treatment to CHD patients undergoing PCI, there was no significant difference in scores of SAQ subscales between control and experimental groups ($P > 0.05$). After taking secondary prevention medications, patients in the control group had higher scores of SAQ subscales ($P < 0.05$), and after taking secondary prevention medications and oral administration of TMZ, patients in the experimental group also showed higher scores of SAQ subscales ($P < 0.05$). However, SAQ subscales PL, AS, TS and DP scores were all higher in patients of experimental group in comparison to those patients of control group ($P < 0.05$), but the AF score was not ($P > 0.05$) (**Table 4**). The result indicated that oral administration of TMZ alleviated symptoms of angina in CHD patients undergoing PCI.

Discussion

CHD is a large and increasing burden of death in East Asia and its morbidity grew quickly over the past 20 years [2]. By evaluating METs and LVEF, 6MWT distance, SF-36 subscales, SAQ scales of patients receiving oral administration of TMZ following PCI, the study demonstrates that TMZ as a metabolism therapy improves exercise tolerance, cardiac function and QOL, and attenuates angina symptoms.

First of all, the METs and 6MWT distance were increased in patients receiving TMZ treatment compared with those patients without. A meta-analysis that investigates the effect of TMZ on METs in patients with ischemic heart disease (IHD) shows that oral administration of TMZ contributes to improvements in METS, peak oxygen uptake (pVO2), total exercise duration (TED), and 6MWT distance [20]. Vitale *et al.* also suggest that TMZ may improve TED in patients with stable exertional angina [21]. More importantly, TMZ, in part, attenuates myocardial energy metabolic dysfunction, inhibits oxidative stress markers, and suppresses myocardial fibrosis and ventricular remodeling [22]. Additionally, 3-month TMZ treatment improves left ventricular function through reducing whole body energy demand in patients suffering from systolic heart failure [23]. TMZ treated patients show both improved systolic and diastolic cardiac function, and

thereby left ventricular remodeling is prevented [24]. There is an increase in LVEF at 6 and 18 months after TMZ treatment by the improvement of energy production [25]. In this study, we also found the LVEDd was decreased and the LEVF was increased in CHD patients treated with TMZ. In consistent with our results, TMZ therapy reduces LVEDd and increases LVEF, thereby improving cardiac function in several studies [22, 26]. The use of TMZ exhibits a protection against glucose metabolism in cardiomyocytes [27]. TMZ improves myocardial glucose utilization during ischemia by inhibiting fatty acid oxidation, and acts as a metabolic modulator so as to improve left ventricular function [28]. Hence, the addition use of TMZ to PCI in CHD patients improves exercise tolerance and cardiac function.

In additional, this study also shows that the QOL is improved in CHD patients after TMZ treatment. GH, RP, BP and SF scores of patients with TMZ treatment are higher than that of patients without TMZ treatment. As a specific partial inhibitor of fatty acid oxidation, TMZ improves the inflammatory state, left ventricular function and QOL of patients with systolic heart failure [23, 29]. It also appears to improve muscle function with an increased muscle force in the elderly [30]. In elderly patients with ischemic heart disease, TMZ improves the QOL, reduces the occurrence of angina episodes, and also increases skeletal muscle strength [31]. Our results show that scores of PL, AS, TS and DP are significantly increased after oral administration of TMZ, suggesting the reduction in the severity of angina. Peng *et al.* report an anti-anginal effect of TMZ against stable angina pectoris via a metabolic mechanism, reducing the symptoms and improving functional status [32]. César et al. indicates that the effects of TMZ on episodes of angina and QOL are impressive in patients with CHD [33].

In conclusion, the overall results indicate that TMZ therapy increases exercise tolerance, improves cardiac function, and relieves angina symptoms, thereby contributing to better QOL in CHD patients undergoing PCI. This study would provide evidence for the recommendation of the adjunct of TMZ to conventional therapy for CHD patients following PCI. However, the results supporting this finding may be limited by the small size of the study population. Meanwhile, the molecular mechanism underlying TMZ functioning in CHD is wanted in future studies.

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Disclosure of conflict of interest

None.

Ethics statement

This study was conducted based on the protocols proposed by the Ethics commitment of Kunming First People's Hospital (2016-7).

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References

[1] Nakajima T, Honda T, Domon H, Okui T, Kajita K, Ito H, Takahashi N, Maekawa T, Tabeta K, Yamazaki K. Periodontitis-associated up-regulation of systemic inflammatory mediator level may increase the risk of coronary heart disease. J Periodontal Res 2010; 45: 116-22.

[2] Gaziano TA, Bitton A, Anand S, Abrahams-Gessel S, Murphy A. Growing epidemic of coronary heart disease in low- and middle-income countries. Curr Probl Cardiol 2010; 35: 72-115.

[3] Jiang G, Wang D, Li W, Pan Y, Zheng W, Zhang H, Sun YV. Coronary heart disease mortality in China: age, gender, and urban-rural gaps during epidemiological transition. Rev Panam Salud Publica 2012; 31: 317-24.

[4] Zhang XH, Lu ZL, Liu L. Coronary heart disease in China. Heart 2008; 94: 1126-31.

[5] Kavousi M, Elias-Smale S, Rutten JH, Leening MJ, Vliegenthart R, Verwoert GC, Krestin GP, Oudkerk M, de Maat MP, Leebeek FW, Mattace-Raso FU, Lindemans J, Hofman A, Steyerberg EW, van der Lugt A, van den Meiracker AH, Witteman JC. Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. Ann Intern Med 2012. 156: 438-44.

[6] Mooney LA, Franks AM. Impact of health screening and education on knowledge of coronary heart disease risk factors. J Am Pharm Assoc (2003) 2011; 51: 713-8.

[7] Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. Lancet 2011; 378: 1297-305.
[8] Liu J, Xu A, Niu L, Li J. Effect of percutaneous coronary intervention on heart rate recovery in patients with coronary artery disease. Coron Artery Dis 2015; 26: 442-7.
[9] Turner ME, Addonizio LJ, Richmond ME, Zuckerman WA, Vincent JA, Torres AJ, Collins MB. Percutaneous coronary artery revascularization procedures in pediatric heart transplant recipients: a large single center experience. Catheter Cardiovasc Interv 2016; 88: 797-803.
[10] Rana JS, Visser ME, Arsenault BJ, Després JP, Stroes ES, Kastelein JJ, Wareham NJ, Boekholdt SM, Khaw KT. Metabolic dyslipidemia and risk of future coronary heart disease in apparently healthy men and women: the EPIC-Norfolk prospective population study. Int J Cardiol 2010; 143: 399-404.
[11] Palaniswamy C, Mellana WM, Selvaraj DR, Mohan D. Metabolic modulation: a new therapeutic target in treatment of heart failure. Am J Ther 2011; 18: e197-201.
[12] Zittermann A, Koerfer R. Koerfer, Vitamin D in the prevention and treatment of coronary heart disease. Curr Opin Clin Nutr Metab Care 2008; 11: 752-7.
[13] Ikizler M, Erkasap N, Dernek S, Batmaz B, Kural T, Kaygisiz Z. Trimetazidine-induced enhancement of myocardial recovery during reperfusion: a comparative study in diabetic and non-diabetic rat hearts. Arch Med Res 2006; 37: 700-8.
[14] Loiacono F, Alberti L, Lauretta L, Puccetti P, Silipigni C, Margonato A, Fragasso G. [Metabolic therapy for heart failure]. Recenti Prog Med 2014; 105: 288-94.
[15] Fragasso G, Rosano G, Baek SH, Sisakian H, Di Napoli P, Alberti L, Calori G, Kang SM, Sahakyan L, Sanosyan A, Vitale C, Marazzi G, Margonato A, Belardinelli R. Effect of partial fatty acid oxidation inhibition with trimetazidine on mortality and morbidity in heart failure: results from an international multicentre retrospective cohort study. Int J Cardiol 2013; 163: 320-5.
[16] Nomenclature and criteria for diagnosis of ischemic heart disease. Report of the Joint International Society and Federation of Cardiology/World Health Organization task force on standardization of clinical nomenclature. Circulation 1979; 59: 607-9.
[17] Bruce RA. Exercise testing of patients with coronary heart disease. Principles and normal standards for evaluation. Ann Clin Res 1971; 3: 323-32.
[18] Bittner V, Weiner DH, Yusuf S, Rogers WJ, McIntyre KM, Bangdiwala SI, Kronenberg MW, Kostis JB, Kohn RM, Guillotte M, et al. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. SOLVD investigators. JAMA 1993; 270: 1702-7.
[19] Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Prodzinski J, McDonell M, Fihn SD. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. J Am Coll Cardiol 1995; 25: 333-41.
[20] Zhao Y, Peng L, Luo Y, Li S, Zheng Z, Dong R, Zhu J, Liu J. Trimetazidine improves exercise tolerance in patients with ischemic heart disease : a meta-analysis. Herz 2016; 41: 514-22.
[21] Vitale C, Spoletini I, Malorni W, Perrone-Filardi P, Volterrani M, Rosano GM. Efficacy of trimetazidine on functional capacity in symptomatic patients with stable exertional angina--the VASCO-angina study. Int J Cardiol 2013; 168: 1078-81.
[22] Chen A, Li W, Chen X, Shen Y, Dai W, Dong Q, Li X, Ou C, Chen M. Trimetazidine attenuates pressure overload-induced early cardiac energy dysfunction via regulation of neuropeptide Y system in a rat model of abdominal aortic constriction. BMC Cardiovasc Disord 2016; 16: 225.
[23] Lopatin YM, Rosano GM, Fragasso G, Lopaschuk GD, Seferovic PM, Gowdak LH, Vinereanu D, Hamid MA, Jourdain P, Ponikowski P. Rationale and benefits of trimetazidine by acting on cardiac metabolism in heart failure. Int J Cardiol 2016; 203: 909-15.
[24] Lopatin YM, Rosano GM, Fragasso G, Lopaschuk GD, Seferovic PM, Gowdak LH, Vinereanu D, Hamid MA, Jourdain P, Ponikowski P. Effect of trimetazidine on recurrent angina pectoris and left ventricular structure in elderly multivessel coronary heart disease patients with diabetes mellitus after drug-eluting stent implantation: a single-centre, prospective, randomized, double-blind study at 2-year follow-up. Clin Drug Investig 2014; 34: 251-8.
[25] Hu B, Li W, Xu T, Chen T, Guo J. Evaluation of trimetazidine in angina pectoris by echocardiography and radionuclide angiography: a meta-analysis of randomized, controlled trials. Clin Cardiol 2011; 34: 395-400.
[26] Zhang Y, Ma XJ, Shi DZ. Effect of Trimetazidine in Patients Undergoing Percutaneous Coronary Intervention: a meta-analysis. PLoS One 2015; 10: e0137775.
[27] Wei J, Xu H, Shi L, Tong J, Zhang J. Trimetazidine protects cardiomyocytes against hypoxia-induced injury through ameliorates calcium

homeostasis. Chem Biol Interact 2015; 236: 47-56.
[28] Zhao P, Zhang J, Yin XG, Maharaj P, Narraindoo S, Cui LQ, Tang YS. The effect of trimetazidine on cardiac function in diabetic patients with idiopathic dilated cardiomyopathy. Life Sci 2013; 92: 633-8.
[29] Fragasso G, Salerno A, Lattuada G, Cuko A, Calori G, Scollo A, Ragogna F, Arioli F, Bassanelli G, Spoladore R, Luzi L, Margonato A, Perseghin G. Effect of partial inhibition of fatty acid oxidation by trimetazidine on whole body energy metabolism in patients with chronic heart failure. Heart 2011; 97: 1495-500.
[30] Ferraro E, Pin F, Gorini S, Pontecorvo L, Ferri A, Mollace V, Costelli P, Rosano G. Improvement of skeletal muscle performance in ageing by the metabolic modulator Trimetazidine. J Cachexia Sarcopenia Muscle 2016; 7: 449-57.
[31] Marazzi G, Gebara O, Vitale C, Caminiti G, Wajngarten M, Volterrani M, Ramires JA, Rosano G, Fini M. Effect of trimetazidine on quality of life in elderly patients with ischemic dilated cardiomyopathy. Adv Ther 2009; 26: 455-61.
[32] Peng S, Zhao M, Wan J, Fang Q, Fang D, Li K. The efficacy of trimetazidine on stable angina pectoris: a meta-analysis of randomized clinical trials. Int J Cardiol 2014; 177: 780-5.
[33] César LA, Gowdak LH, Mansur AP. The metabolic treatment of patients with coronary artery disease: effects on quality of life and effort angina. Curr Pharm Des 2009; 15: 841-9.