

## **Efficacy and safety of metoprolol plus trimetazidine in treating coronary heart failure.**

Yueqin Zhang\*

Department of Pharmacy, Beijing Aerospace General Hospital, Beijing, PR China

### **Abstract**

The aim of this study was to observe the efficacy and safety of Metoprolol (Met) plus Trimetazidine (Tri) in the treatment of Coronary Heart Failure (CHF). From January 2012 to January, 200 patients with coronary heart disease and heart failure who were treated at our hospital were selected as research subjects and randomly divided into a Control group (group C) and an Observation group (group O), with 100 patients in each group. The total efficacy rate in group O was 91.0%, higher than the 74.0% in group C and the difference was statistically significant ( $P<0.05$ ). The post-treatment 6-Minute Walk Test (6-MWT) distance in group O ( $302.6 \pm 26.7$  m) was significantly increased from that before treatment ( $144.5 \pm 11.2$  m;  $t=39.752$ ,  $P<0.01$ ). The 6-MWT distance in group C was significantly decreased from before ( $268.5 \pm 22.6$  m) to after treatment ( $140.6 \pm 10.8$  m;  $t=37.173$ ,  $P<0.01$ ). However, the 6MWT distance in group O was statistically significantly longer than that in group C ( $P<0.01$ ). After treatment, the Left Ventricular Ejection fraction (LVEF) in group O was significantly higher than that in group C, with  $t=5.7012$  by the intergroup  $t$  test ( $P<0.01$ ). The Left Ventricular End-Systolic Dimension (LVESD) and Left Ventricular End-Diastolic Dimension (LVEDD) in group O were statistically significantly lower than those in group C ( $t=2.8405$  and  $3.1128$ , respectively;  $P<0.01$ ). The Met+Tri combination as treatment for CHF can significantly improve patients' cardiac functions, improve clinical efficacy, and prolong patient survival. Thus, it is worthy of clinical promotion owing to its safety and effectiveness.

**Keywords:** Coronary heart failure, Metoprolol, Safety, Trimetazidine.

*Accepted on March 2, 2017*

### **Introduction**

Heart failure is a series of syndromes caused by multi-disease-induced myocardial dysfunction and cardio-blood transfusion dysfunction, and may be accompanied by various serious diseases. It is characterized by acute onset, rapid progression, and significant damage, among others, and is a common severe disease referred to the department of cardiology of hospitals [1-4]. With the continuous increase in the aged population, the incidence of heart failure in China has increased year after year, causing the increase in related deaths, making it a serious threat to the lives and health of patients [5,6]. The current clinical treatments mainly consist of anti-heart failure drugs, including diuretics, cardiac drugs, Angiotensin-Converting Enzyme Inhibitor (ACEIs), angiotensin receptor blockers, and  $\beta$ -blockers, with the purpose of improving patients' cardiac contractility, promoting blood circulation, and relieving the symptoms of cardio-blood transfusion insufficiency to achieve clinical treatment [7-10]. This study was designed to investigate the efficacy and safety of Met+Tri in the treatment of Coronary Heart Failure (CHF).

### **Methods**

#### **General information**

A total of 200 CHF patients admitted in Beijing Aerospace General Hospital between January 2012 and January 2015 were selected as the study subjects. All the patients met the diagnostic criteria for ischemic heart disease issued by the World Health Organization (WHO) and mainly exhibited one or more of the following symptoms: dyspnea, fatigue, lower extremity edema, shortness of breath, pulmonary rales, pleural effusion, elevated jugular venous pressure, and peripheral edema. Patients with severe liver dysfunction, severe hypertension, severe arrhythmia, acute cerebrovascular diseases, acute pulmonary edema, cancer, acute infections, or psychiatric disorders were excluded [4]. Eighty patients were classified in accordance with the New York Heart Association classification as follows: class I, 32 cases; class II, 25 cases; class III, 13 cases; and class IV, 10 cases. All the patients were randomly divided into groups C and O, with 100 patients in each group. Group C consisted of 62 men and 44 women; aged 52 to 85 years (mean  $\pm$  SD,  $60.5 \pm 7.1$  years). Group O consisted of 48 men and 32 women; aged 45 to 85 years (mean  $\pm$  SD,  $65.3 \pm 3.4$  years). The two groups showed no significant differences in sex ratio, age structure, and disease distribution

( $P > 0.05$ ), indicating that the two groups were comparable (Table 1) [5]. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with

approval from the Ethics Committee of Beijing Aerospace General Hospital. Written informed consent was obtained from all participants.

**Table 1.** The general information of the patients in the study.

Group	n	Gender (male/female)	Age	BMI (kg/m <sup>2</sup> )	Total cholesterol (mmol/L)	triglycerides (mmol/L)	High-density lipoprotein (mmol/L)	Low density lipoprotein (mmol/L)	Fasting glucose (mmol/L)
C	100	62/38	60.5 ± 7.1	21.3 ± 0.5	3.9 ± 0.7	1.2 ± 0.3	1.1 ± 0.1	2.4 ± 1.5	4.8 ± 0.6
O	100	58/42	65.3 ± 3.4	20.5 ± 0.7	4.2 ± 0.5	1.3 ± 0.2	1.2 ± 0.2	2.5 ± 1.1	4.5 ± 0.9
$\chi^2/t$		0.278	1.756	0.375	1.052	0.266	0.405	0.67	1.226
P		0.062	0.064	0.071	0.058	0.054	0.057	0.069	0.054

### Treatment methods

The two groups both received comprehensive drug treatments such as diuretic, cardiac, or nitrate therapy, but group O additionally received Met+Tri, with Tri (Servier Pharmaceutical Co., Ltd.) administered thrice daily at 20 mg/d and oral Met (AstraZeneca) administered twice daily at 6.25 mg/d. The dosages were adjusted in accordance with the condition changes in the mid- and late-treatment periods, but not up to >100 mg/d. Left Ventricular Ejection Fraction (LVEF), Heart Rate (HR), and blood pressure were closely monitored during treatment [6]. After 5 weeks of treatment, the two groups underwent cardiac ultrasonography.

### Observation indexes

Each group was followed up once every 2 weeks after treatment, and the changes of the CHF symptoms were compared before and after treatment, including blood pressure, heart rate, Electrocardiogram (ECG) parameters, and heart function [7]. Each patient performed the 6-Minute Walk Test (6-MWT) before and after treatment, and underwent ECG, Left Ventricular End-Diastolic Dimension (LVEDD), Left Ventricular End-Systolic Dimension (LVESD), or LVEF measurements.

### Evaluation criteria

The following criteria were used to evaluate treatment efficacy: markedly effective (increased post treatment EF by  $\geq 50\%$ , improved heart function by two classes, unfettered daily activities, and regular activities without fatigue, shortness of breath, or angina), effective (increased post treatment EF by  $\geq 20\%$ , improved heart function by one class, slightly fettered daily activities, and regular activities possibly causing fatigue, shortness of breath, or angina), and invalid (no significant change in post treatment EF, no improvement in heart function, obviously fettered daily activities, and regular activities causing fatigue, shortness of breath, or angina). Total efficacy was calculated as “((markedly effective + effective)/total cases)  $\times 100\%$ ” [9].

### Statistical analysis

Data were analysed using the SPSS18.0.0 software. The measurement data were expressed as  $\bar{x} \pm s$  and compared using the paired t-test. Count data were expressed as rates, and the  $\chi^2$  test was used in the intergroup comparison, with P values of  $< 0.05$  considered to indicate statistically significant differences.

### Results

#### Comparison of clinical efficacy between the two groups

The total efficacy rate in group O was 91.0%, statistically significantly higher than the 74.0% in group C ( $P < 0.05$ ; Table 2).

**Table 2.** Comparison of clinical efficacies between the two groups (n (%)).

Group	n	Markedly effective	Effective	Invalid	Total rate	efficacy
C	100	28 (28.0%)	46 (46.0%)	26 (26.0%)	74.00%	
O	100	36 (36.0%)	55 (55.0%)	9 (9.0%)	91.00%	
$\chi^2$						5.1942
P						0.03

#### Comparison of 6-MWT distance between the two groups before and after treatment

The post treatment 6-MWT distance in group O ( $302.6 \pm 26.7$  m) was significantly increased from that before treatment ( $144.5 \pm 11.2$  m;  $t=39.752$ ,  $P < 0.01$ ). In group C, the 6MWT distance was significantly decreased from before ( $268.5 \pm 22.6$  m) to after treatment ( $140.6 \pm 10.8$  m;  $t=37.173$ ,  $P < 0.01$ ). However, the 6MWT in group O was statistically significantly longer than that in group C ( $P < 0.01$ ) [11].

**Comparison of LVEF, LVESD, and LVEDD between the two groups before and after treatment**

No significant differences in pre-treatment LVEF, LVESD, and LVEDD were found between the two groups. However, after treatment, group O had statistically significantly higher LVEF ( $t=5.7012$ ,  $P<0.01$ ) but statistically significantly lower LVESD and LVEDD than group C ( $t=2.8405$  and  $3.1128$ , respectively,  $P<0.01$ ; Table 3) [12].

**Table 3.** Comparison of LVEF, LVESD, and LVEDD between the two groups before and after treatment ( $\bar{x} \pm s$ ).

Observation index	C (n=100)		O (n=100)		
	Before	After	Before	After	
LVEF (%)	35.76 3.28	$\pm$ 38.91 3.52 <sup>▲</sup>	$\pm$ 35.80 3.29	$\pm$ 43.28 4.33 <sup>▲*</sup>	$\pm$
LVESD (mm)	46.59 4.62	$\pm$ 43.42 4.18 <sup>▲</sup>	$\pm$ 46.71 4.83	$\pm$ 41.13 4.12 <sup>▲*</sup>	$\pm$
LVEDD (mm)	61.21 6.25	$\pm$ 56.38 5.36 <sup>▲</sup>	$\pm$ 61.14 6.22	$\pm$ 53.16 5.29 <sup>▲*</sup>	$\pm$

Note: Compared with the same group before treatment,  $P<0.01$ ; compared with group C after treatment, <sup>▲</sup> $P<0.01$ .

**Adverse reactions**

All the patients completed the clinical study. The routine urinalysis revealed no obvious abnormalities in liver and kidney functions and blood lipid and glucose levels in the two groups before and after treatment. Other than the two cases of abdominal discomfort and one case of mild nausea, no serious complications occurred [13].

**The comorbidities of the patients**

All patients were completed the clinical studies. All of the patients were tested urine routine, liver and kidney function and blood lipid, blood sugar before and after treatment. There were no obvious abnormalities. Follow-up of 12 months, 1 case was dead and 5 cases in heart failure stage in the observation group. There were three cases dead and 10 cases in heart failure in control group. There was no statistical significance ( $P>0.05$ ) between the two groups. There were 2 patients with abdominal discomfort and 1 case with mild nausea in observation group. There were no serious complications occurred in the two groups.

**Discussion**

CHF is one of the most common causes of heart failure. Myocardial infarction is a serious stage during the development of coronary heart diseases. It causes partial myocardial ischemic necrosis due to the complete obstruction of myocardial blood vessels, which impairs the normal functions of the vessels [14]. In recent years, owing to the significantly increased survival rate in myocardial infarction, the incidence of heart failure caused by myocardial infarction has gradually increased [15]. Traditional comprehensive

treatment drugs are numerous but have no apparent effects. Met can effectively block catecholamine, thereby constricting blood vessels, maintaining cardiac functions, reducing oxygen consumption, and maintaining cardiac blood supply. Tri can be rapidly absorbed after oral administration and peaks plasma concentration within 2 h. It has good tissue diffusibility, having an apparent volume of distribution of 4.8 L/kg and protein binding rate of 16% (*in vitro* assays). It is mainly excreted via urine in a prototype, and its half-life of elimination is about 6 h [16]. This drug can increase the mitochondrial energy metabolism, thus improving and enhancing the myocardial functions [17]. This study observed and compared treatment efficacy and symptom improvement between two treatment groups to analyse the clinical effects of Met+Tri [18]. We found that the total efficacy rate in group O was 91.0%, significantly higher than the 74.0% in group C, indicating that the efficacy of Met+Tri in the treatment of CHF is significantly better than those of the other conventional comprehensive drug therapies, which primarily increase myocardial oxygen supply capacity. Thus, such treatment does not produce the ideal effect and only increases the treatment cost owing to the wide variety of drugs required. By contrast, the combination therapy with Met+Tri takes advantage of the effects of the two drugs, simultaneously improving myocardial ischemia and myocardial metabolism, protecting myocardial cells, and reducing cardiac load. Therefore, after treatment, patients' cardiac functions can be greatly improved and their daily activities can be enhanced by the decreased body fatigue, wheezing, and shortness of breath, and difficulty in breathing [19]. Meanwhile, this study also observed the cardiac functions of the two groups before and after treatment. We found that the cardiac function indexes were higher in group O than in group C, indicating that after the combined therapy, the patients' CHF symptoms were effectively alleviated and quality of life was significantly improved [20]. As for the two invalid cases, further in-depth analysis and study are needed. In summary, the combination of Met+Tri has ideal efficacy on CHF, can significantly improve treatment efficiency, and alleviate symptoms, and is thus worthy of clinical promotion and application. The limitations of the study were the small samples size and the limited follow up time.

**Conflict of Interest**

All authors have no conflict of interest regarding this paper.

**References**

1. Steimle AE, Stevenson LW, Fonarow GC, Hamilton MA, Moriguchi JD. Prediction of improvement in recent onset cardiomyopathy after referral for heart transplantation. *J Am Coll Cardiol* 1994; 23: 553-559.
2. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* 2003; 362: 7-13.

3. Martinson BC, Crain AL, Sherwood NE, Hayes MG, Pronk NP, O'Connor PJ. Population reach and recruitment bias in a maintenance RCT in physically active older adults. *J Phys Act Health* 2010; 7: 127-135.
4. Winter JL, Castro PF, Quintana JC, Altamirano R, Enriquez A, Verdejo HE, Jalil JE, Mellado R, Concepción R, Sepúlveda P, Rossel V, Sepulveda L, Chiong M, Garcia L, Lavandero S. Effects of trimetazidine in nonischemic heart failure: a randomized study. *J Card Fail* 2014; 20: 149-154.
5. Chrusciel P, Rysz J, Banach M. Defining the role of trimetazidine in the treatment of cardiovascular disorders: some insights on its role in heart failure and peripheral artery disease. *Drugs* 2014; 74: 971-980.
6. Xu X, Zhang W, Zhou Y, Zhao Y, Liu Y, Shi D, Zhou Z, Ma H, Wang Z, Yu M, Ma Q, Gao F, Shen H, Zhang J. 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: 251-258.
7. Liu Y, Xie MX, Kang J, Zheng D. Studies on the interaction of total saponins of panax notoginseng and human serum albumin by Fourier transform infrared spectroscopy. *Spectrochim Acta A Mol Biomol Spectrosc* 2003; 59: 2747-2748.
8. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet* 2007; 369: 201-207.
9. Martín-Merino E, Johansson S, Morris T, García Rodríguez LA. Androgen deprivation therapy and the risk of coronary heart disease and heart failure in patients with prostate cancer: a nested case-control study in UK primary care. *Drug Saf* 2011; 34: 1061-1077.
10. Ng CY. Letter by ng regarding article, prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation* 2011; 123: e384.
11. Hwang DS, Shin ES, Kim SJ, Lee JH, Kim JM, Lee SG. Early differential changes in coronary plaque composition according to plaque stability following statin initiation in acute coronary syndrome: classification and analysis by intravascular ultrasound-virtual histology. *Yonsei Med J* 2013; 54: 336-344.
12. Bavry AA, Handberg EM, Huo T, Lerman A, Quyyumi AA, Shufelt C, Sharaf B, Merz CN, Cooper-DeHoff RM, Sopko G, Pepine CJ. Aldosterone inhibition and coronary endothelial function in women without obstructive coronary artery disease: an ancillary study of the national heart, lung, and blood institute-sponsored womens ischemia syndrome evaluation. *Am Heart J* 2014; 167: 826-832.
13. Ho JS, Cannaday JJ, Barlow CE, Reinhardt DB, Wade WA, Ellis JR. Utility of high-sensitivity C-reactive protein versus coronary artery calcium for the detection of obstructive stenoses in stable patients. *Am J Cardiol* 2013; 111: 328-332.
14. Nakamura T, Kitta Y, Uematsu M, Sugamata W, Hirano M, Fujioka D, Sano K, Saito Y, Kawabata K, Obata JE, Kugiyama K. Ultrasound assessment of brachial endothelial vasomotor function in addition to carotid plaque echolucency for predicting cardiovascular event in patients with coronary artery disease. *Int J Cardiol* 2013; 167: 555-560.
15. Lisi M, Henein MY, Cameli M, Ballo P, Reccia R, Bennati E, Chiavarelli M, Maccherini M, Mondillo S. Severity of aortic steno-sis predicts early post-operative normalization left atrial size and function detected by myocardial strain. *Int J Cardiol* 2013; 167: 1450-1455.
16. Nilsson L, Wieringa WG, Pundziute G, Gjerde M, Engvall J, Swahn E, Jonasson L. Neutrophil/Lymphocyte ratio is associated with non-calcified plaque burden in patients with coronary artery disease. *PLoS One* 2014; 9: 108183.
17. deGoma EM, Dunbar RL, Jacoby D, French B. Differences in absolute risk of cardiovascular events using risk-refinement tests: a systematic analysis of four cardiovascular risk equations. *Atherosclerosis* 2013; 227: 172-177.
18. Hou ZH, Lu B, Gao Y, Cao HL, Yu FF, Jing N, Chen X, Cong XF, Roy SK, Budoff MJ. Matrix Metalloproteinase-9 (MMP-9) and Myeloperoxidase (MPO) levels in patients with nonobstructive coronary artery disease detected by coronary computed tomographic angiography. *Acad Radiol* 2013; 20: 25-31.
19. Shafique E, Choy WC, Liu Y, Feng J, Cordeiro B, Lyra A, Arafah M, Yassin-Kassab A, Zanetti AV, Clements RT, Bianchi C, Benjamin LE, Sellke FW, Abid MR. Oxidative stress improves coronary endothelial function through activation of the pro-survival kinase AMPK. *Aging (Albany NY)* 2013; 5: 515-530.
20. Liao YF, Feng Y, Chen LL, Zeng TS, Yu F, Hu LJ. Coronary heart disease risk e-equivalence in diabetes and arterial diseases characterized by endothelial function and endothelial progenitor cell. *J Diabetes Complications* 2014; 28: 214-218.

#### \*Correspondence to

Yueqin Zhang

Department of Pharmacy

Beijing Aerospace General Hospital

PR China