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Original Article

Internal Medicine Section

Safety and Efficacy of Enalapril Combined with Metoprolol in Patients of Hypertension Complicated with Coronary Heart Disease: A Randomised Clinical Trial

PING WANG[1], LIJUN WANG[2], ZHIHUI LIU[3], JI FENG[4]

ABSTRACT

Introduction: Enalapril, which inhibits Angiotensin-Converting Enzyme (ACE), is a commonly used drug for the treatment of hypertension. Metoprolol, a β-blocker, is widely prescribed for patients with cardiac diseases. Essential hypertension has been identified as an independent risk factor of Coronary Heart Disease (CHD). Until now, there are few studies and reports on the application of the two drugs in patients with Hypertension and Coronary Heart Disease (HCHD).

Aim: To assess the safety and efficacy of enalapril combined with metoprolol in patients with HCHD.

Materials and Methods: The present single-centre randomised clinical trial was conducted on 109 patients with HCHD at Jingdezhen Municipal First People's Hospital from April 2018 to January 2020. The participants were randomly divided into into two groups, one group on enalapril (n=58), and the other on enalapril and metoprolol combination (n=51). Patients in both groups were treated for eight weeks. The blood pressure, cardiac function index, serum C-Reactive Protein (CRP), Homocysteine (Hcy), and Matrix Metalloproteinase-9 (MMP-9) levels were compared between the two groups, and the adverse drug reactions of the two groups were statistically analysed using independent sample t-test or Mann-Whitney U test.

Results: The mean age of enalapril group was 64.78±7.29 years, and the gender ratio was 1:1.42. The mean age of enalapril/metoprolol combination group was 63.90±6.91 years, and the gender ratio was 1:0.96. After treatment, both systolic and diastolic blood pressure of the enalapril/metoprolol combination group were significantly lower than that of enalapril group ($p<0.05$). Enalapril combined with metoprolol significantly improved cardiac function and significantly decreased the levels of serum inflammatory markers (CRP 18.57±3.61 vs 27.50±3.60, $p<0.001$; Hcy 12.14±2.07 vs 13.83±2.17 mmol L^{-1}, $p<0.001$; MMP-9 372.35±12.34 vs 436.69±13.89 pg L^{-1}, $p<0.001$; Transforming Growth Factor ALPHA (TGF-a) 8.18±1.38 vs 10.40±1.44 mmol L^{-1}, $p<0.001$). The overall rate of adverse reactions was not significantly different between the groups (enalapril/metoprolol combination group vs enalapril group, 15.69% vs 10.34%, $p=0.406$).

Conclusion: The combined treatment of enalapril and metoprolol was more effective than enalapril alone in reducing the inflammatory response, reducing blood pressure, and improving cardiac function in patients with HCHD. This combinational therapeutic strategy may be a better choice for patients with HCHD.

Keywords: β-blocker, Angiotensin converting enzyme, Cardiac function, Matrix metalloproteinase

INTRODUCTION

Cardiovascular Diseases (CVDs) are the leading cause of death globally.An estimated 17.9 million people died from CVDs in 2019, representing 32% of all global deaths. Of these deaths, 85% were due to heart attack and stroke [1]. CHD is recognised as one of the most common CVDs in humans [2,3]. The death rate of CHD in China increased by 31.6% from 1990 to 2010, and CHD rose from the seventh place to the second place in the list of causes of premature death in China [4]. Essential hypertension has been identified as an independent risk factor of CHD [5,6]. HCHD can significantly reduce patients'quality of life, for example, symptoms of angina and heart failure [7], activity restrictions, and participation restrictions [8]. Therefore, effective prevention and early detection of hypertension and CHD are imperative.

Enalapril, which is a (S)-1-{N-{1-(ethoxycarbonyl)-3-phenylpropyl}-l-alanyl}-l-proline, inhibits ACE, and reduces the level of angiotensin-II, and results in reduced peripheral resistance without increasing cardiac oxygen demand, and decreases aldosterone secretion and elevates serum renin levels [9]. Metoprolol, a β-blocker, is widely prescribed for patients with cardiac diseases [10]. Metoprolol reduces the excitability of sympathetic nerves, reverses cardiac remodeling and improves myocardial function by attenuating myocardial expression of proinflammatory mediators such as Tumour Necrosis Factor-α (TNF-α) [11]. ACE inhibitors and β-blockers have been combined to treat heart failure [12,13], hypertension [14], diabetes and coronary disease [15], and its safety has been extensively studied [16,17].

Serum biomarkers have been studied throughout HCHD disease progression, and have a substantial impact on the diagnosis, treatment, and care of patients with HCHD [18]. The rupture of the fibrous cap of the atherosclerotic plaque induces coronary thrombosis and results in acute coronary syndrome. MMP plays an important role in plaque instability. Plaque instability is the most common mechanism of CHD and results in tissue proteolysis, which is an important factor in the thinning and cracking of the hardened atheromatous fibrous cap [19]. The expression of MMP-9 is increased in atherosclerotic plaques and areas of macrophage aggregation. Overexpression of activated MMP-9 can enhance the degradation of Endothelial Cells (ECM), thereby reducing the strength of plaques and promoting plaque rupture [20]. In humans, CRP is a major acute-phase protein whose concentration may increase more than 1,000-fold in severe inflammatory states. CRP may be an atheroprotective molecule, as shown by studies using transgenic CRP in animal models of human-like atherosclerosis

[21,22]. Clinical data have indicated that CRP could be a key predictive factor of atherosclerosis [23-25]. Intraplaque CRP colocalises with oxidised low-density lipoprote in and macrophages in human atherosclerotic lesions. However, MMP-9 has been implicated in plaque rupture [23]. Hcy is a risk factor of atherosclerosis and affects the evolution of carotid intimal-medial thickness in patients with CHD. The degree of vascular disease is positively correlated with Hcy [16,17]. Transforming Growth Factor-α (TGF-a) binds to epidermal growth factor receptor, activates intracellular signal transduction pathways, regulates the activity of transcription factors and cell proliferation, and participates in the pathological process of vascular remodeling [26].

Although enalapril in the treatment of hypertension and metoprolol in the treatment of cardiac diseases have been widely investigated, the literature search of enalapril combined with metoprolol in patients with HCHD indicates that data are scarce [27]. This study sought to determine safety and efficacy of enalapril combined with metoprolol in patients with HCHD. Primary outcome measures were the effect of the drug combination on blood pressure and cardiac function, and the incidence of adverse events in patients with HCHD. Secondary outcome measures were to examine the effect on the concentrations of serum CRP, Hcy, MMP-9, and TGF-α in these patients.

MATERIALS AND METHODS

This was a single-centre, randomised, clinical trial. Patients with HCHD admitted to Jingdezhen Municipal First People's Hospital from April 2018 to January 2020 were selected for participation in this study. All patients gave written informed consent prior to the start of the study. This study was approved by the Medical Ethics Committee of Jingdezhen Municipal First People's Hospital {Code: LIPJ (2018) -01-01 (Ke)}. A parallel-group randomised design was used for this clinical trial.

Sample size calculation: The sample size estimation formula is based on completely random design sample mean comparison:

$$N=n1+n2=(Q_1^{-1}+Q_2^{-1})\left[\frac{(Z_{\alpha/2}+Z_{\beta})^2\sigma^2}{\delta}\right],$$

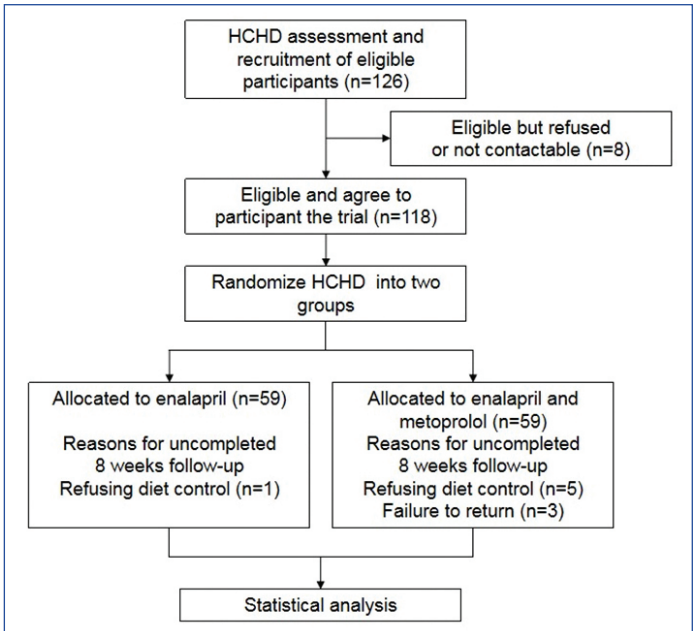
where, α=0.05 and β=0.1, N represents the total sample size of two independent groups, $Z_{\alpha/2}$ representsthe two-sided critical value of the standard normal distribution, Z_{β} representsthe one-sided critical value of the standard normal distribution, Q_1^{-1} represents sample ratio, and Q_1^{-1}=n1/N, Q_2^{-1}=n2/N, and σ represents the standard deviation, and δ represents the between-group difference with clinical significance. Sample size estimation was performed using PASS 2007 software. Calculation produced a suggested sample size of 43 per group. Assuming a 30% dropout rate, the total sample size was finalised at 112 [28].

Because blinding of the dispatching personnel, the paramedics on scene, patients and the physicians is not possible for practical reasons, laboratory personnel, staff of the cardiac function indexes measurements, and outcome assessors remained blinded.

Inclusion criteria: Patients with hypertension based on the 2010 Chinese Hypertension Prevention and Control Guidelines with a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg [29], and at least one main coronary artery lumen stenosis ≥50% on a coronary angiogram; patients who have not taken β-blocker or ACE inhibitors drugs within a month and age ≥18 and age <65-year-old were included.

Exclusion criteria: Rheumatic heart disease, pulmonary hypertension, diabetes mellitus, dilated cardiomyopathy, hypertrophic cardiomyopathy, myocarditis, severe valvular disease, hyperthyroidism, cancer, haematologic disease, left ventricular systolic dysfunction; psychosis or dysgnosia and patients refusing to sign the informed consent were excluded.

The flowchart for the selection procedure of the study participants has been shown in [Table/Fig-1].



[Table/Fig-1]: Flowchart of study participant selection procedure.

Study Procedure

The patients were numbered according to the order in which they were admitted and were divided into- enalapril alone group and an enalapril/metoprolol combination group, using a random number table. The patient's Diastolic Blood Presure (DBP) and Systolic Blood Presure (SBP) were measured in sitting position, and the Left Ventricular End Systolic Diameter (LVEDD), Left Ventricular End Diastolic Diameter (LVESD) and Ventricular Ejection Fraction (LVEF) were measured using echocardiography (IE33 Colour Doppler Ultrasound Diagnostic System, Philips Electronics Co., Ltd., Netherlands). A 5 mL of fasting venous blood was obtained from the patient, and the serum was separated at 3500 r/min, centrifuge radius 8 cm, and centrifuge time 10 minutes. A double antibody sandwich Enzyme-Linked Immunosorbent Assay (ELISA) was used to detect serum CRP, Hcy, MMP-9, and TGF-α levels (CRP, Hcy, MMP-9, TGF-α kits were provided by Wuhan Boster Biotechnology Co., Ltd., MR III microplate reader, Hyperion, USA).

All patients were given routine treatment, including diet control. Patients in the enalapril alone group were treated with enalapril tablets (10 mg/tablet) (Yangtze River Pharmaceutical Group, Jiangsu Pharmaceutical Co., Ltd., specification: 10 mg/tablet), and the dose was adjusted according to the blood pressure level. Patients in the enalapril/metoprolol combination group were treated with oral enalapril and metoprolol tartrate tablets (25 mg/tablet) (Astra Zeneca Pharmaceutical Co., Ltd., specification: 25 mg/tablet). The usage and dosage of enalapril tablets were the same as those in the enalapril alone group. The initial dose of metoprolol tablets was 25 mg/time, 3 times/day, and then gradually increased according to the control of blood pressure and Heart Rate (HR). The maximum dose did not exceed 150 mg QD. All patients were treated for eight weeks. During the treatment, all adverse drug reactions (e.g., bronchospasm, cough [30], dermatitis [31]) were monitored and recorded. After eight weeks, the patient's blood pressure, cardiac function indexes, serum CRP, Hcy, MMP-9, and TGF-α levels were measured.

STATISTICAL ANALYSIS

Data analysis was performed using Statistical package for social sciences (SPSS) (version SPSS 20.0, IBM SPSS Inc, Chicago, IL, USA) for statistical analysis. Percentage (%) was used to represent count data, (x±s) was used to represent measurement data, and the comparison between groups was performed by independent samples t-test. α=0.05 was the test level p<0.05 indicates that the difference is statistically significant, and p<0.01 indicates that the results have significant statistical differences.

RESULTS

Characteristics of the patients: A total of 109 patients with HCHD were included in this study (58 in the enalapril alone group and 51 in the enalapril/metoprolol combination group). There was no statistical difference (p>0.05) for gender, age, course of the disease, BMI, HR, SBP, DBP between the two groups, [Table/Fig-2].

Comparison of blood pressure before and after treatment: Before treatment, there was no statistical difference in SBP and DBP between the two groups (p=0.321, 0.395). After treatment, the mean differences of SBP and DBP in the enalapril/metoprolol combination group after treatment were significantly greater than those in the enalapril alone group (p=0.026, 0.013) [Table/Fig-3].

Comparison of cardiac function indexes before and after treatment: Before treatment, there was no statistical difference in HR, LVEDD, LVESD, and LVEF between the two groups (p=0.769, 0.645, 0.737, respectively). After treatment, the decrease of LVEDD and LVESD in the enalapril/metoprolol combination group was significantly higher than that in the enalapril alone group, and the increase of LVEF was significantly higher than that in the enalapril alone group [Table/Fig-4].

Comparison of serum levels of inflammatory factors before and after treatment: Before treatment, the differences in serum CRP, Hcy, MMP-9, and TGF-α between the two groups were not statistically significant (p>0.05). After treatment, the decrease of the markers in the enalapril/metoprolol combination group was significantly greater than that in the enalapril alone group, but there was no significant difference in the decrease of serum TGF-α (p=0.370, >0.05) [Table/Fig-5].

Variables	Enalapril group (n=58)	Enalapril/ Metoprolol combination group (n=51)	p-value
Male (n, %)	34 (58.62)	25 (49.02)	0.818*
Female (n, %)	24 (41.38)	26 (50.98)	
Age (years)	64.78±7.29	63.90±6.91	0.522
Smoking status (yes) (n, %)	19 (32.76)	18 (35.29)	0.783*
Sports activities (>210 min/week) (n, %)	38 (65.52)	30 (58.82)	0.476*
BMI (kg m^{-2})	25.72±1.85	25.24±1.62	0.145
HR (beat min^{-1})	77.22±6.73	76.39±7.07	0.532
SBP (mmHg)	152.91±13.76	150.37±12.84	0.321
DBP (mmHg)	98.45±4.42	99.20±4.72	0.395
Duration of disease (year)	6.98±1.19	6.75±1.16	0.295

[Table/Fig-2]: Patient profiles:enalapril/metoprolol combination group vs enalapril alone group.
BMI: Body mass index; HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; *Using Chi-square test. The rest of variables were calculated using independent-sample t-test

Adverse events assessment: During treatment, there were eight patients with adverse drug reactions in the enalapril/metoprolol combination group were- three intractable dry cough, two rashes, two headache, and one taste alteration. There were six patients with adverse drug reactions in the enalapril alone group- three intractable dry cough, one rash, one taste alteration, and one headache. The total incidence of adverse drug reactions in the enalapril/metoprolol

Item	Enalapril alone (n=58)			Enalapril/Metoprolol combination (n=51)		
	Before treatment	After treatment	Mean difference	Before treatment	After treatment	Mean difference
SBP	152.91±13.76	127.71±11.74	25.21±10.40	150.37±12.84	120.67±7.97	29.71±10.38
DBP	98.45±4.42	78.07±6.36	20.38±5.25	99.20±4.72	75.33±4.46	23.02±5.66
p-value for the intragroup comparison (Independent sample t-test)						
SBP (before vs after)	<0.001			<0.001		
DBP (before vs after)	<0.001			<0.001		
p-value for the intergroup comparison (Independent sample t-test)						
	Before treatment		After treatment		Mean difference	
SBP	0.321		<0.001		0.026	
DBP	0.395		0.10		0.013	

[Table/Fig-3]: Comparison of blood pressure levels in two groups (mean±SD,mmHg).
SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Item	Enalapril alone (n=58)			Enalapril/Metoprolol combination (n=51)		
	Before treatment	After treatment	Mean difference	Before treatment	After treatment	Mean difference
HR (beats/min)	89.91±3.72	82.29±3.36	7.62±4.23	90.63±4.37	78.08±2.99	12.55±5.37
LVEDD (mm)	52.67±3.45	46.31±3.63	6.36±1.71	52.86±3.29	44.67±4.32	8.20±3.51
LVESD (mm)	39.78±3.87	34.26±3.93	5.52±1.05	40.12±3.83	32.67±2.90	6.35±0.98
LVEF (%)	43.55±4.01	53.05±4.44	-9.5±2.07	43.80±3.79	54.76±4.30	-10.96±2.00
p-value for the intragroup comparison (Independent sample t-test)						
HR (before vs after)	<0.001			<0.001		
LVEDD (before vs after)	<0.001			<0.001		
LVESD (before vs after)	<0.001			<0.001		
LVEF (before vs after)	<0.001			<0.001		
p-value for the intergroup comparison (Independent sample t-test)						
	Before treatment		After treatment		Mean difference	
HR	0.531		<0.001		<0.001	
LVEDD	0.769		0.033		0.001	
LVESD	0.645		0.017		<0.001	
LVEF	0.738		0.044		<0.001	

[Table/Fig-4]: Comparison of cardiac function index of two groups (mean±SD).
LVEDD: Left ventricular end diastolic dimension; LVESD: Left ventricular end systolic dimension; LVEF: Left ventricular ejection fraction

Item	Enalapril alone (n=58)			Enalapril/Metoprolol combination (n=51)		
	Before treatment	After treatment	Mean difference	Before treatment	After treatment	Mean difference
CRP (mg L-1)	38.40±2.58	27.50±3.60	10.90±4.51	37.69±2.27	18.57±3.61	19.12±4.58
Hcy (mmol L-1)	24.84±3.31	13.83±2.17	11.02±3.42	25.59±3.68	12.14±2.07	13.45±3.21
MMP-9(pg L-1)	786.12±16.86	436.69±13.89	349.43±21.93	785.45±17.01	372.35±12.34	413.10±23.65
TGF-α (ng L-1)	25.45±5.41	10.40±1.44	15.05±5.27	24.14±5.45	8.18±1.38	15.96±5.24
p-value for the intragroup comparison (Independent sample t-test)						
CRP (before vs after)	<0.001			<0.001		
Hcy (before vs after)	<0.001			<0.001		
MMP-9 (before vs after)	<0.001			<0.001		
TGF-α (before vs after)	<0.001			<0.001		
p-value for the intergroup comparison (Independent sample t-test)						
	Before treatment		After treatment		Mean difference	
CRP	0.133		<0.001		<0.001	
Hcy	0.269		<0.001		<0.001	
MMP-9	0.837		<0.001		<0.001	
TGF-α	0.212		<0.001		0.370	

[Table/Fig-5]: Comparison of serum levels of inflammatory factors of two groups (mean±SD).

combination group and the enalapril alone group was 15.69% and 10.34%, respectively, and the difference was not statistically significant (p=0.406).

DISCUSSION

Hypertension is the most common and independent cardiovascular risk factor for coronary artery disease [32]. Cardiovascular risk factors should be managed while regulating blood pressure in the clinical treatment of HCHD [12]. ACE inhibitors used to block the Renin-Angiotensin System (RAS) are effective treatments for hypertension, congestive heart failure, and myocardial infarction. However, studies have found that long-term (13 months) use of ACE inhibitors does not adequately prevent aldosterone production, which results in aldosterone escape [33,34]. Metoprolol is a β-adrenergic receptor blocker, which inhibits the release of angiotensin II by binding to the receptor, thereby reducing blood pressure, regulating HR and prolonging ventricular diastolic time [35].

Clinical studies have shown that metoprolol can increase coronary blood flow, increase left LVEF, and improve cardiac function. At present, it is often used in the clinical treatment of mild to moderate hypertension, tachycardia, angina pectoris, prevents recurrent myocardial infarctions, and arrhythmias [35-37]. Researchers have studied the combined treatment of heart failure [12,13], hypertension, diabetes or coronary disease with ACE inhibitors and β-blockers [15], and its safety [12,13].

This study showed that the combination of enalapril and metoprolol in the treatment of HCHD for eight weeks can significantly reduce SBP and DBP, LVEDD, LVESD, and improve LVEF. However, the long-term efficacy remains to be further studied. This may be due to the synergistic effect of enalapril and metoprolol on reducing cardiac load and pulmonary vascular resistance, increasing coronary blood flow and LVEF, thereby improving cardiacindexes. This study showed that enalapril and metoprolol combination treatment can significantly reduce serum levels of inflammatory factors (CRP, Hcy, and MMP-9) in patients with HCHD.

Fung JW et al.,believe that β-blockade also has a time-limited effect in reducing RAAS activation similar to ACE inhibitors [38]. The effect was present at four weeks, reduced at eight weeks, and not different from baseline at 52 weeks. The experimental plan was to compare the clinical and inflammatory markers levels pretreatment and eight weeks post-treatment. This potential limitation may affect the interpretation of the results of this study.

Many factors may affect the metabolism of Hcy, including several medications widely used in the treatment of CVD [39-41]. Several studies have already shown that thiazide-type diuretics can significantly increase plasma Hcy levels [42], and the β-receptor blocker, metoprolol, decreases plasma Hcy levels [43]. Fan FF et al.,found that enalapril can cause an increase in plasma Hcy levels among hypertensives with low baseline Hcy levels, and there is no significant association of MTHFR C677T genotypes with changes in Hcy levels in response to enalapril among the subjects with essential hypertension [44]. Yet, in the study by Poduri A et al., there was a significant decrease of Hcy levels in mild essential hypertensive patientsafter ramipril treatment (5 mg/d) for six weeks, and they believe the decrease in Hcy induced by β-blockers and ACE inhibitors due to the improvement of endothelial function along with improved renal function [45]. The present results are consistent with the study by Poduri A et al., [45]. The exact mechanism remains to be elucidated.

There was no significant difference in the reduction of serum levels of TGF-α between two groups.This may be due to the relatively small concentrations of TGF-α, or it may be that the number of cases is small, and no significant difference can be found. The sample size will be increased in the future studies. The RAS consists of ACE, the octapeptide product angiotensin II (Ang II), and AT1 and AT2 receptors [46]. MMP activity can be reduced by diminishing RAS signaling [47]. Combining ACE inhibitors and β-blockers increasing the inhibition of RAS signaling may reduce serum levels of MMP-9. The decrease in Hcy induced by ACE inhibitors may be due to the improvement of endothelial function along with improved renal function following ACE inhibitor therapy [48]. A study previously documented that the reduction of plasma Hcy levels by β-blocker therapy in hypertensive patients, however, the mechanism of its action needs to be further studied [45].

The results of this study also showed that the rate of adverse reactions in patients treated with enalapril combined with metoprolol was higher than that of patients treated with enalapril alone, but the difference between groups was not statistically significant. Enalapril combined with metoprolol in the treatment of HCHD did not significantly increase the risk of adverse reactions and had a good safety profile.

Limitation(s)

Although the study design excluded patients who did not take β-blocker or ACE inhibitor drugs within a month, it did not set a wash-out period for participants and did not exclude participants who took anti-platelet aggregation drugs or statins.

CONCLUSION(S)

Enalapril combined with metoprolol is superior to enalapril alone for hypertension complicated with CHD. Although enalapril, was able to significantly reduce serum levels of inflammatory factors (CRP, Hcy, and MMP-9) in patients with HCHD, the magnitude of the reduction in serum levels of inflammatory factors (CRP, Hcy, and MMP-9) with enalapril combined with metoprolol was greater than the reduction with enalapril alone. In the future, researchers need to investigate the molecular mechanism underlying the interaction of ACE inhibitor and β-blocker.

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PARTICULARS OF CONTRIBUTORS:
1. Doctor, Department of Cardiology, Jingdezhen Municipal First People's Hospital, Jingdezhen, Jiangxi, China.
2. Doctor, Department of Cardiology, Jingdezhen Municipal First People's Hospital, Jingdezhen, Jiangxi, China.
3. Doctor, Department of Cardiology, Jingdezhen Municipal First People's Hospital, Jingdezhen, Jiangxi, China.
4. Department of Cardiology, Jingdezhen Municipal First People's Hospital, Jingdezhen, Jiangxi, China.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Ping Wang,
317, North China Road, Jingdezhen City, Jiangxi Province,
China,Jingdezhen, Jiangxi, China.
E-mail: wangping_ys@126.com

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