

Xuefu Zhuyu Decoction on Heart Failure Patients with Middle-Range Coronary Heart Disease with Ejection Fraction

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Yan *et al.*: Impact of Xuefu Zhuyu Decoction on Heart Failure Patients

To investigate the impact of Xuefu Zhuyu decoction on cardiac remodeling and quality of life of patients with heart failure and middle-range coronary heart disease with ejection fraction is the main objective of the study. 116 heart failure patients with coronary heart disease in the middle range of ejection fraction were divided as observation or control group. Clinical efficacy of both groups was observed and changes in traditional Chinese medicine symptom scores, cardiac function classification, exercise tolerance, cardiac ultrasound indexes and quality of life were compared before and after treatment between both groups. Relative to before treatment, left ventricular ejection fraction of two groups enhanced dramatically ($p < 0.05$) and the left ventricular end-diastolic diameter increased significantly ($p < 0.05$). Serum N-terminal pro-B-type natriuretic peptide and left ventricular end-systolic diameter significantly declined ($p < 0.05$). Relative to before treatment, physical limitation, physical condition, emotional change, social limitation score and total score in each dimension of Minnesota living with heart failure questionnaire scale obviously declined in both groups ($p < 0.05$), compared with control group following treatment. The above scores decreased in observation group relative to control group ($p < 0.05$). Xuefu Zhuyu decoction can significantly enhance cardiac function and exercise tolerance of such cases, inhibit or reverse cardiac remodeling, and be beneficial to the improvement of quality of life.

Key words: Xuefu Zhuyu decoction, coronary heart disease, middle-range heart failure with ejection fraction, cardiac remodeling, quality of life

With further clinical study regarding the Heart Failure (HF) pathophysiological mechanism, middle-range HF with ejection fraction, as a “grey area” of HF has gradually attracted great attention from the cardiovascular academic community^[1,2]. The European Society of Cardiology (ESC) first defined it in 2016 as a special type of HF with clinical features between those with preserved ejection fraction (Left Ventricular Ejection Fraction (LVEF) $< 40\%$) and decreased ejection fraction (LVEF $< 40\%$). Coronary heart disease is one of the most common causes of this type of HF. How to intervene in such patients early is of great significance for inhibiting or reversing cardiac remodeling, improving cardiac function, improving quality of life and reducing mortality. At present, the intervention for HF mainly adopts standardized anti-HF treatment based on the viewpoint of Western medicine and evidence-based medicine. However, the improvement of HF symptoms and cardiac function in some

patients is still not satisfactory. At present, Traditional Chinese Medicine (TCM) treatment has attracted the attention of cardiologists. The drugs in this scheme can play a synergistic effect, promote the cardiac rehabilitation of patients through multi-channel and multi-target effects, and significantly improve the prognosis. This study observed the effects of Xuefu Zhuyu Decoction on cardiac remodeling and patient's life quality. 96 patients with HF with intermediate ejection fraction coronary heart disease admitted to our hospital from January 2021 to December 2021 were chosen to be study objects. Inclusion criteria was as follows. In line with the relevant diagnostic criteria established by the ESC in 2016^[3], symptoms and signs of chronic HF, and echocardiography showed LVEF of 40% to 49% ; the New York Heart Association (NYHA) at the time of inclusion and cardiac function classification is II-IV; the patient's cognitive function is barrier-free, there is no history of mental illness and can cooperate with physicians

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to complete various examinations and can communicate with physicians without barriers. TCM syndrome differentiation refers to the “Guiding Principles of Clinical Research on New Chinese Medicines”^[4], which belongs to “Yang-deficiency and water-flooding syndrome”, the main symptoms include chest tightness, shortness of breath, palpitations and shortness of breath; secondary symptoms include lower extremity edema, pale complexion and fatigue; tongue pulse-white and thin coating, dull tongue, thin and weak pulse. Exclusion criteria include acute HF, valvular heart disease, severe arrhythmia, Acute Myocardial Infarction (AMI), Chronic Obstructive Pulmonary Disease (COPD), cancers and severe infectious diseases. The included patients were classified into two groups in accordance with random number table. Observation group included 28 male and 20 female patients with the age of 52-73 y, with an average age of 61.50±9.41 y; the disease course ranged from 4 to 15 y, with an average of 10.49±9.41 y. There were 48 cases in control group, including 29 male and 19 female patients with the age of 50-74 y, with an average age of 62.39±8.34 y; disease course was 3-14 y, and with an average of 10.16±2.19 y. General data between two groups were comparable ($p>0.05$). The approval of this study was obtained from the hospital ethics committee. The control group received basic Western medicine treatment, actively controlled blood pressure and blood sugar and other risk factors, low-salt and low-fat diet, then given diuretic (hydrochlorothiazide tablets, 20 mg/time, 2 times/d), cardiotonic (digoxin, 0.125 mg/d), antiplatelet (aspirin, 100 mg/d), lipid-regulating drugs (atorvastatin calcium tablets, 20 mg orally every night), crown expansion (isosorbide mononitrate tablets, 20 mg/time, 2 times/d), beta receptor blockers or Angiotensin-Converting Enzyme Inhibitors (ACEI) inhibit ventricular remodeling, etc. Based on the control group, observation group were given Xuefu Zhuyu decoction, which consisted of 20 g of *Salvia miltiorrhiza*, 15 g each of Tinglizi, *Alisma*, Polyporus Radix, 30 g each of *Codonopsis*, *Astragalus*, 12 g each of Poria, *Ophiopogon japonicus* and *Atractylodes* rhizome and cinnamon 6 g. Xuefu Zhuyu decoction of 150 ml was given each time, 2 times/d and the course of treatment is 12 w. Observation indicators were as follows. The TCM symptom scores, NYHA cardiac function classification and exercise tolerance of two groups, pre and post-treatment were recorded. The TCM

symptom score is based on the scoring principles formulated in the Guidelines for Clinical Research on New Chinese Medicines to evaluate the symptoms related to “Yang-deficiency and water-overflowing syndrome”. The scores of TCM symptoms were added up after each symptom score; exercise tolerance was assessed by 6 Min Walking Test (6MWT); cardiac ultrasound indexes (ventricular ejection) were recorded before and after treatment in the two groups. Blood fraction (LVEF), Left Ventricular End-Diastolic Diameter (LVEDD), Left Ventricular End-Systolic Diameter (LVESD), mitral early diastolic maximum velocity/new atrial systolic maximum velocity (E/A)] and serum N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP). The Minnesota Living with Heart Failure Questionnaire (MLHFQ) was adopted for evaluating the life quality of both, pre and post-treatment groups. The scale has 4 dimensions (physical limitation, emotional changes, physical condition and social limitation, including 21 items, and each item is based on 0-5 points for evaluation), with a greater total score indicating the poorer life quality. Efficacy criteria used in the study was explained here. Literature reference was used to formulate efficacy criteria. Clinical control-Clinical symptoms are relieved, NYHA grade is 1 and TCM symptom scores are reduced by >90 % after treatment; markedly effective-clinical symptoms are significantly relieved, NYHA grade is reduced by ≥ 2 grades compared with before treatment and TCM symptom scores are reduced by 70 % after treatment; effective-the clinical symptoms are relieved, the NYHA classification is ≥ 1 grade lower than that before treatment and the TCM symptom score is reduced by 30 %-69 % after treatment; ineffective-the clinical symptoms are not improved or even worsened and the NYHA classification and the TCM symptom score are both reduced to meet the above standards. Overall effective rate=(clinical control+markedly effective+effective)/The number of cases in this group $\times 100$ %. Statistical analysis was carried out on the platform of Statistical Package for the Social Sciences (SPSS) 19.0 statistical software. Besides, the measurement data conforming to normal distribution were expressed as mean \pm Standard Deviation (SD, ($\bar{x}\pm s$)), and t-test was performed for comparison between the two groups; which indicates that the Chi-square (χ^2) test was carried out to compare both groups and $p<0.05$ stood for statistical significance. Table 1 compares clinical efficacy of

both groups. Overall effective rate of observation group was notably increased compared with control group ($p < 0.05$). The comparison of TCM symptom score, NYHA cardiac function classification and 6MWT distance between the two groups, pre and post-treatment is presented in Table 2. Compared with before treatment, TCM symptom scores and NYHA cardiac function classification in both groups were evidently declined ($p < 0.05$), and 6MWT distance was increased ($p < 0.05$). Cardiac ultrasound parameters and serum NT-proBNP between the two groups, pre and post-treatment was shown in Table 3. Compared with before treatment, the LVEF and E/A values of both groups obviously elevated ($p < 0.05$), while LVEDD, LVESD and serum NT-proBNP were dramatically decreased ($p < 0.05$). All were superior to control group ($p < 0.05$). The life quality comparison between the two groups, pre and post-treatment was shown in Table 4. Relative to pre-treatment, the scores of each dimension and total score of MLHFQ scale in the both groups notably decreased ($p < 0.05$). HF refers to the terminal stage of diverse Cardiovascular Diseases (CVDs). It represents an important cause of poor exercise tolerance and life quality among middle-aged and elderly people, and has caused a heavy economic and medical burden to the society and patients families. Middle-range HF with ejection fraction is relatively common in coronary heart disease. It belongs to a special type of HF and was previously considered to belong to the clinical category of “diastolic HF”^[4,5]. Relevant epidemiological survey data show that in the whole HF patients, middle-range HF with ejection fraction accounts for about 20 %. Such patients have more cardiovascular risk factors such as diabetes and hypertension, so their prognosis is relatively poor. Relevant studies have shown that cardiac remodeling accounts for an important pathogenesis of HF^[6,7]. Oxidative stress, activation of the neuroendocrine system, inflammatory response, abnormal hemodynamics and overloading of the heart lead to increased ventricular wall pressure. Ischemia and hypoxia, myocardial damage and apoptosis, increased myocardial interstitial fibroblast proliferation and extracellular matrix synthesis, eventually lead to ventricular dilatation and hypertrophy, resulting in cardiac remodeling, deterioration of cardiac function, and decreased exercise tolerance. LVEDD and LVESD reflect the size of the ventricular cavity and are important indicators of cardiac structural abnormalities and cardiac remodeling; E/A reflects

diastolic function; NT-proBNP is a neuroendocrine index of cardiac function and cardiac remodeling. Increased levels often indicate worsening of cardiac function and poor prognosis in patients with HF^[8]. At present, the clinical treatment of HF with coronary heart disease in the middle range of ejection fraction mainly adopts symptomatic treatment such as antiplatelet, coronary expansion, lipid regulation, nutrition of myocardial cells, improvement of myocardial hypoxia-ischemia, cardiac diuresis and inhibition of left ventricular remodeling^[9]. Although the clinical symptoms of patients have been improved to a certain extent and the mortality rate has been reduced, there are still many patients with poor improvement in cardiac function and exercise tolerance, which greatly limits the quality of life of patients. TCM does not have a proper name for coronary HF with intermediate ejection fraction, but it belongs to the categories of “edema”, “chest pain” and “asthma syndrome” according to the characteristics of the disease. The pathogenesis of this disease is the depletion of yang, qi caused by old age, poor mood, overwork and exogenous pathogenic qi, edema and oliguria. This disease belongs to the syndrome of deficiency and deficiency of the heart-yang, blood stasis and phlegm turbidity. The treatment strategy should focus on stimulating blood circulation and removing blood stasis, dredging the veins and benefiting water and nourishing temperature and yang^[10,11]. Based on syndrome differentiation and treatment, the overall concept of TCM and the pathogenesis of specific diseases, this study achieved good results with Xuefu Zhuyu decoction. In the prescription, *Astragalus* and *Codonopsis* can nourish the heart and qi; *Ophiopogon japonicus* moistens the lungs, clears the heart, and nourishes the heart yin; cinnamon warms the meridians, strengthens the heart and strengthens the yang; *Alisma* and other drugs induce diuretic swelling and strengthen qi and spleen. Based on modern pharmacological researches, it was shown that *Astragalus* can nourish cardiomyocytes and inhibit the synthesis of Tumor Necrosis Factor alpha (TNF- α), Matrix Metalloproteinase-9 (MMP-9), and NT-proBNP, thereby blocking myocardial remodeling and local inflammatory response and improve cardiac function. Tinglizi has a certain positive inotropic effect, increases cardiac contractility and cardiac output, and can dilate renal blood vessels and diuresis, thereby reducing cardiac preload and ventricular wall pressure. *Salvia* can dilate arterial blood vessels, decrease peripheral

vascular resistance, increase blood flow velocity, strengthen myocardial ischemia and hypoxia, and also inhibit myocardial fibrosis and cardiac hypertrophy. According to our results, the overall effective rate of observation group notably increased relative to control group. After treatment, the TCM symptom scores, NYHA classification, 6MWT

distance, cardiac ultrasound indexes and serum NT-proBNP and MLHFQ scale scores in the observation group increased relative to control group. Therefore, Xuefu Zhuyu decoction can significantly enhance cardiac function and exercise tolerance in such patients, inhibit or reverse cardiac remodeling, and be beneficial to the improvement of quality of life.

TABLE 1: COMPARISON OF CLINICAL EFFICACY BETWEEN THE TWO GROUPS [CASES (%)]

Group	N	Clinical control	Markedly effective	Effective	Invalid	Always valid
Observation group	58	23	25	6	4	54 (93.10)*
Control group	58	20	19	6	13	39 (67.24)

Note: Relative to control group, *p<0.05

TABLE 2: TCM SYMPTOM SCORES, NYHA CARDIAC FUNCTION CLASSIFICATION AND 6MWT DISTANCE OF BOTH PRE AND POST-TREATMENT GROUPS ($\bar{x}\pm s$)

Group	N	Time	TCM symptom score (points)	NYHA cardiac function classification (grade)	6MWT (m)
Observation group	48	Pre-treatment	13.86±4.26	3.18±0.60	325.21±76.28
		Post-treatment	5.74±2.83*#	1.51±0.47*#	412.43±81.41*#
Control group	48	Pre-treatment	14.12±5.19	3.21±0.57	322.27±696.29
		Post-treatment	8.49±3.50*	2.10±0.49*	406.43±78.34*

Note: Relative to pre-treatment, *p<0.05 and relative to control group, #p<0.05

TABLE 3: CARDIAC ULTRASOUND PARAMETERS AND SERUM NT-proBNP OF BOTH PRE AND POST-TREATMENT GROUPS ($\bar{x}\pm s$)

Group	N	Time	LVEF (%)	LVEDD (mm)	LVESD (mm)	E/A	NT-proBNP (ng/l)
Observation group	58	Pre-treatment	45.14±4.20	58.60±5.16	47.38±5.29	0.85±0.26	3177.10±748.61
		Post-treatment	52.61±6.17*#	53.43±5.28*#	42.16±5.41*#	1.08±0.24*#	1256.53±475.83*#
Control group	58	Pre-treatment	44.78±4.31	59.17±6.10	48.27±5.37	0.83±0.25	3201.45±821.45
		Post-treatment	48.54±5.36*	56.20±5.43*	45.33±5.29*	0.95±0.27*	1854.72±521.90*

Note: Relative to pre-treatment, *p<0.05 and relative to control group, #p<0.05

TABLE 4: MLHFQ SCALE SCORES OF BOTH PRE AND POST-TREATMENT GROUPS (POINTS)

Group	N	Time	Physical condition	Physical limitations	Social restrictions	Mood changes	Total score
Observation group	58	Pre-treatment	22.43±6.40	34.44±8.31	16.40±5.61	18.51±6.91	82.34±13.40
		Post-treatment	10.61±3.54*#	15.26±4.10*#	8.21±3.22*#	10.26±3.27*#	44.62±10.19*#
Control group	58	Pre-treatment	23.50±7.19	35.31±9.27	17.54±5.50	19.21±5.32	84.56±13.53
		Post-treatment	15.72±4.37*	21.13±6.19*	12.71±4.80*	14.19±4.50*	62.21±12.87*

Note: Relative to pre-treatment, *p<0.05 and relative to control group, #p<0.05

Conflict of interests:

The authors declared no conflict of interest.

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