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Original Research Article

Effect of modified Wenyang Buxin decoction and routine therapy on cardiac function and serum levels of H-FABP, cTnI and Ang-2 in chronic heart failure patients

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Abstract

Purpose: *To investigate the effect of modified Wenyang Buxin decoction and routine therapy on cardiac function and serum levels of heart-type fatty acid binding protein (H-FABP), cardiac troponin-1 (cTnI) and angiopoietin-2 (Ang-2) in chronic heart failure (CHF) patients.*
Methods: *A total of 120 CHF patients admitted to Zhejiang Province Rongjun Hospital (from January 2019 - January 2020) were selected for this study. They were randomly but equally distributed into groups A and B. All patients were given routine therapy such as diuretic treatment and detumescence, while those in group A received 150 mL of modified Wenyang Buxin decoction daily, in addition to routine therapy. At 2 months after therapy, cardiac function indices, serum H-FABP, cTnI and Ang-2 levels, hemorheology indices, traditional Chinese medicine (TCM) syndrome scores, and Chinese questionnaire of quality of life in cardiovascular patients (CQQC) scores of the two groups were evaluated.*
Results: *After therapy, cardiac function indices, serum H-FABP, cTnI and Ang-2 levels, hemorheology indices as well as TCM syndrome score and CQQC score were significantly improved in group A, when compared with corresponding values in group B ($p < 0.05$).*
Conclusion: *Modified Wenyang Buxin decoction and routine therapy improves serum biomarker levels, cardiac function and quality of life, and relieves clinical symptoms of CHF in patients. Therefore, this treatment approach may be useful in the management of CHF patients.*

Keywords: *Wenyang Buxin decoction, Heart-type fatty acid binding protein (H-FABP), Cardiac troponin-1 (cTnI), Angiopoietin-2 (Ang-2), Chronic heart failure (CHF), Cardiac function*

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INTRODUCTION

Chronic heart failure (CHF) is the end-stage state of cardiovascular disease characterized by ventricular remodeling with symptoms such as asthma, poor breathing and fluid retention. The treatment of CHF in China starts mostly with diuretic therapy and cardiotonics. However, digitalis and other drugs produce slow effects, and they have many contraindications. Clinical practice has shown that the average survival of CHF patients at 2 years after diagnosis is only 66 % [1]. Thus, conventional therapy cannot comprehensively improve the survival of patients

[2]. Compared with conventional therapy, traditional Chinese medicine (TCM) pays more attention to the combined treatment of multiple organs. Recent studies have shown that CHF affects the neuroendocrine system of patients and makes levels of a variety of biomarkers abnormal. Biomarkers such as cTnI and Ang-2 in renin-angiotensin-aldosterone system, natriuretic peptide system, and neuroendocrine system are closely related to multiple organ functions [3]. There is no research on the effect of TCM on the neuroendocrine system of CHF patients. However, from the perspective of pharmacology, *Salvia miltiorrhiza*, *Radix astragali*, safflower and other drugs normalize the levels of these biomarkers, thereby attenuating ventricular remodeling, improving heart and kidney functions, and enhancing blood circulation, leading to improved therapeutic effectiveness [4]. In this study, *Wenyang Buxin* decoction consisting of drugs such as *Radix codonopsis, Radix astragali, Salvia miltiorrhiza* and *Safflower* were selected as the adjunctive treatment to investigate the effect of the modified decoction and routine therapy on treatment of CHF.

METHODS

General profile of patients

A total of 120 CHF patients who were on admission for one year were chosen as research subjects, and were equally assigned to groups A and B using random number Table. General basic data were comparable in the 2 groups. This research received approval from the ethical body of *Zhejiang Province Rongjun Hospital* (approval no. 20181176), and it followed the guidelines of Declaration of Helsinki [5]. All included subjects submitted signed written informed consents to participate in the study.

Inclusion criteria

Patients who were diagnosed with CHF after examination, with the symptoms such as dyspnea, lower extremity edema and abnormal echocardiography [6], patients with cardiac function grades of II - IV [7], and patients with a stable condition within half a year [8], were included in the study

Table 1: Profiles of enrolled patients

Parameter	A	B	λ^2/t	*P*
Gender			0.034	0.854
Male	33	34		
Female	27	26		
Age (years)				
Range	52-74	53-74		
Mean age (years)	62.59±3.54	62.68±3.58	0.138	0.890
Course of disease (years)				
Range	1-6	1-7		
Mean course of disease	4.51±1.11	4.52±1.10	0.050	0.961
Living habits				
Smoking	28	27	0.034	0.855
Alcohol drinking	35	36	0.035	0.853
Basic diseases				
Diabetes mellitus	15	16	0.044	0.835
Pulmonary diseases	14	13	0.048	0.827
NYHA cardiac functional grading				
II	5	6	0.100	0.752
III	35	34	0.034	0.853
IV	20	20	<0.001	1.000
Pathological types				
Hypertensive heart disease	18	19	0.039	0.843
Dilated heart disease	20	21	0.037	0.847
Ischemic heart disease	22	20	0.147	0.702
Education levels			0.035	0.853
High school and below	24	25		
College and above	36	35		
Monthly income (yuan)			0.039	0.843
≤ 3500	18	19		
>3000	42	41		

Exclusion criteria

The excluded patients were mentally-challenged subjects, those with communication problems [9], those who had other organic illnesses, severe arrhythmia, and abnormal hematopoietic function; patients who had received surgical treatment before the study [10], those undergoing other treatments [11], patients with unstable conditions [12], and those who reacted to the medications used in the study.

Treatments

All subjects were given routine therapy such as diuretic therapy and detumescence, while those in group A received modified *Wenyang Buxin* decoction, in addition to routine therapy.

Routine therapy

On admission to the hospital, the patients were instructed to take their medications, and to rest in bed. They were treated with diuretics and β-blockers to correct water and electrolyte disorders. Oxygen inhalation was carried out when necessary, and anti-infection therapy was given to prevent the infection from getting worse. Moreover, appropriate diet plans were formulated. Low-sodium recipes were adopted to strictly control salt intake of patients and make them eat lighter and healthier foods. In addition, the physical sign data of patients were recorded every day, and therapeutic schemes were adjusted according to condition changes.

Wenyang Buxin decoction treatment

The *Wenyang Buxin* decoction prescription contained 13 g of Chinese angelica, cinnamon, achyranthes root, *Pericarpium Arecae*, *Radix codonopsis, Os Draconis*, *Concha ostreae*, *Cornus officinalis*, *Poria cocos*, *Cinnamomum cassia*, large-head *Atractylodes* rhizome and *Radix astragali*; and 5 g of baked licorice. If any patient had obvious blood stasis, *Salvia miltiorrhiza* and safflower were added. If any patient had asthma, Erchen decoction was added. The patients orally took 150 mL of decoction (the above herbs were decocted with water) daily, and they took it in the morning and evening after meals. Both groups were treated for 2 months.

Evaluation of indices

Cardiac function indices

The cardiac function indexes measured in this study were left ventricle ejection fraction (LVEF), left ventricular end-systolic dimension (LVESD), left ventricular end-diastolic dimension (LVEDD) and 6-minute walking distance (6MWD). These indexes (LVEF, LVESD and LVEDD) were determined using color Doppler echocardiography (Xuzhou Belse Electronic Technology Co. Ltd.; Jiangsu Machine Reg no: 20142230583). The time nodes of comparison were before and after therapy.

Serum H-FABP, cTnI and Ang-2 levels

The patients' morning fasting venous blood samples were drawn before and after therapy. Radioimmunoassay (Cobase 411 appliance; SFDA Certified No. 2011: 3402843) was used to determine H-FABP.

Appropriate enzyme-linked immunosorbent assay kits were used to determine cTnI and Ang-2. The whole process was conducted according to the instructions given on the kits. The time nodes of comparison were before and after therapy.

Hemorheology index

The hemorheology indexes selected in this study were hematocrit (HCT), fibrinogen (FIB) and plasma viscosity. Morning fasting venous blood was drawn from each patient before and after therapy, and hemorheology indexes were determined using automated hemorheology analyzer (Shanxi Yasen Industrial Co. Ltd; Shanxi Machine Reg no. 20162400011). The time nodes of comparison were before and after therapy.

Traditional Chinese Medicine syndrome score

The scores were based on *Guiding Principles for Clinical Research of New Traditional Chinese Medicine in the Treatment of Heart Failure* [13]. The main symptoms scored included palpitation, shortness of breath, pain in chest and hypochondrium, abdominal mass and lower extremity edema, while the secondary symptoms included dim complexion and purple lips. The scores were compared before and after therapy.

Chinese questionnaire of quality of life in cardiovascular patients (CQQC) score

The CQQC questionnaire [14] included physical condition, disease condition, medical condition, normal life, socio-psychological status and working state, with a total score of 154 points. The lower the score, the worse the quality of life of patients. The time nodes of comparison were before and after therapy.

Statistical analysis

The selected data processing software for statistics was SPSS 20.0, while GraphPad Prism 7 was applied for generation of Figures. Measurement data are presented as mean ± SD, and were compared with λ^2 test and Student's *t*-test. Significance of differences was assumed at $p < 0.05$.

RESULTS

Cardiac function indices

Table 2 shows that after therapy, there were significantly improved levels of cardiac function indicators in group A, relative to group B.

Serum levels of H-FABP, cTnI and Ang-2

After therapy, the serum levels of H-FABP, cTnI and Ang-2 were significantly better in group A than in group B, as shown in Table 3.

Hemorheology indices

After therapy, the hemorheology indices in group A were significantly better, when compared with group B ($p < 0.05$).

TCM syndrome and CQQC scores

As shown in Figure 1, after therapy, the TCM syndrome and CQQC scores were better in group A than in group B ($p < 0.001$). Before therapy, TCM syndrome scores in the two groups were comparable (30.15 ± 5.21 vs 30.22 ± 5.20, $p > 0.05$). After therapy, the TCM syndrome score was markedly lower in group A than in group B (12.11 ± 3.54 vs 20.63 ± 3.68). Before therapy, CQQC scores in both groups were comparable (50.26 ± 6.11 vs 50.89 ± 6.23, $p > 0.05$). After therapy, the CQQC score was higher in group A than in group B (74.65 ± 7.89 vs 65.11 ± 6.45, $p < 0.001$).

Table 2: Cardiac function indices before and after therapy (mean ± SD)

Index	Group A		Group B		*t*	*P*-value
LVEF	Before	35.12±1.22	Before	35.23±1.20	0.498	0.620
(%)	After	58.98±4.25	After	50.11±4.00	11.772	<0.001
	t	41.799	*t*	27.600		
	P	<0.001	*P*	<0.001		
LVESD	Before	60.12±4.98	Before	60.10±4.55	0.023	0.982
(mm)	After	29.65±4.58	After	40.12±4.26	12.966	<0.001
	t	34.884	*t*	24.830		
	P	<0.001	*P*	<0.001		
LVEDD	Before	70.10±5.98	Before	69.57±5.78	0.494	0.623
(mm)	After	39.56±2.54	After	50.12±3.68	18.293	<0.001
	t	36.411	*t*	21.987		
	P	<0.001	*P*	<0.001		
6 MWD	Before	220.12±20.51	Before	221.89±20.87	0.469	0.640
(m)	After	456.98±35.22	After	325.98±30.45	21.795	<0.001
	t	45.016	*t*	21.841		
	P	<0.001	*P*	<0.001		

Table 3: Comparison of serum levels of H-FABP, cTnI and Ang-2 (mean ± SD)

Parameter	Group A		Group B		t	P
H-FABP	Before therapy	8.12±1.11	Before	8.15±1.20	0.142	0.887
(μg/L)	After therapy	4.21±0.51	After	6.00±0.98	12.550	<0.001
	t	24.794	*t*	10.749		
	P	<0.001	*P*	<0.001		
cTnI	Before therapy	0.26±0.05	Before	0.27±0.06	0.992	0.323
(ng/mL)	After therapy	0.09±0.02	After	0.15±0.03	12.890	<0.001
	t	24.453	*t*	13.856		
	P	<0.001	*P*	<0.001		
Ang-2	Before therapy	110.56±25.65	Before	111.68±25.45	0.240	0.811
(pg/mL)	After therapy	68.45±8.54	After	82.68±12.65	7.222	<0.001
	t	12.066	*t*	7.904		
	P	<0.001	*P*	<0.001		

Table 4: Comparison of hemorheology indices before and after therapy (mean ± SD)

Index	Group A		Group B		t	*P*-value
HCT	Before	50.12±4.56	Before	50.56±4.51	0.531	0.596
(μg/L)	After	38.98±3.55	After	46.65±4.14	10.894	<0.001
	t	14.932	*t*	4.947		
	P	<0.001	*P*	<0.001		
FIB	Before	4.12±0.57	Before	4.15±0.59	0.283	0.778
(ng/mL)	After	2.89±0.32	After	3.78±0.55	10.834	<0.001
	t	14.575	*t*	3.553		
	P	<0.001	*P*	0.001		
Plasma viscosity	Before	1.75±0.21	Before	1.73±0.20	0.534	0.594
(pg/mL)	After	1.28±0.11	After	1.50±0.15	9.161	<0.001
	t	15.357	*t*	7.126		
	P	<0.001	*P*	<0.001		

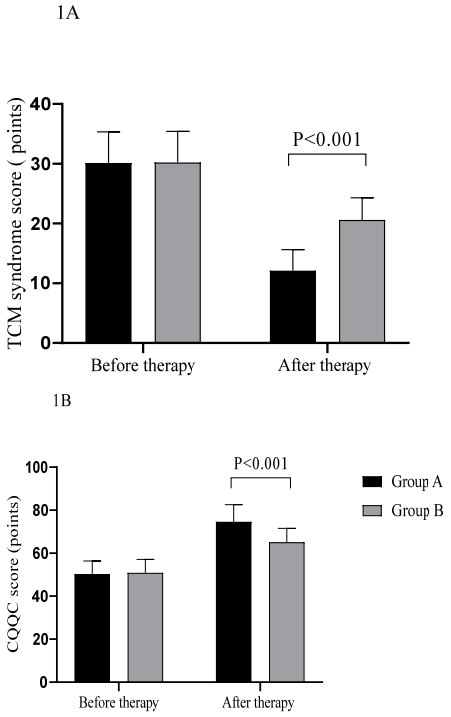

Figure 1: Comparison of TCM syndrome and CQQC scores (mean ± SD, points)

DISCUSSION

In TCM, chronic heart failure (CHF) is classified into the category of edema and asthma. Caused by emotional disorder and *invasion of wind pathogen*, this disease starts in the heart and results in stasis of blood vessels. If it remains uncured for a long time, the spleen and kidney will be affected and *heart qi* will be weakened, which eventually lead to damage of the *meridians* and *collaterals*, and aggravated *qi* deficiency and blood stasis. Therefore, treatment of CHF should start with activating blood circulation and removing blood stasis so as to reduce *deficiency of heart and kidney*, and exert positive effect on *warming yang*, *nourishing heart* and inducing diuresis, thereby alleviating edema. The *Wenyang Buxin* decoction used in this study contained *Radix codonopsis*, *Radix astragali*, *Salviae miltiorrhiza*, and safflower.

Radix astragali nourishes the heart, while *Cinnamomum cassia* removes blood stasis. The combination of the two produces diuretic effect and relieves swelling, as well as lower extremity edema in patients. Usually, *Salviae miltiorrhiza* and safflower are added for patients with severe blood stasis. The two herbs enhance the circulation of blood and eliminate blood stasis, and further repair cardiomyocytes, thereby relieving myocardial ischemia. In patients, CHF is also accompanied by heart-kidney *yang deficiency.* Large-head atractylodes rhizome was also included in *Wenyang Buxin* decoction in order to regulate spleen *qi*. The combination of various herbs produces the good effects of *warming yang* and strengthening *qi* [15].

After treatment with *Wenyang Buxin* decoction, the neuroendocrine indexes of patients in group A were significantly improved, and their serum H-FABP, cTnI and angiopoietin-2 (Ang-2) levels were better, when compared with group B, indicating improvements in multiple organ function and heart failure symptoms. Angiopoietin-2 Ang-2) is an important index that reflects the compensative and repair ability of blood vessels, which are related to neurohumor dysfunction. When the secretion of Ang-2 is abnormal, the degradation of myocardial interstitial collagen is also abnormal, ventricular remodeling is accelerated, and cardiac function is impaired. Therefore, reducing Ang-2 level is beneficial to protecting the myocardial function of the patient. In the study by Zhao *et al*., renal pathological changes in CHF rats treated with *Salvia miltiorrhiza* were mitigated [16]. This is because *Salvia miltiorrhiza* inhibited the expression of angiotensin-converting enzyme and reduced Ang-2 mRNA level, thereby reducing activity of Ang-2. Therefore, *Salvia*

miltiorrhiza improved renal function, prevented decline in cardiac function, and played a crucial role in treating multiple organs in CHF patients.

There is a positive association between cTnI and the ratio of left ventricular mass, indicating that this index is highly sensitive to ventricular remodeling. Research by Wang *et al* showed that the cTnI level of rats treated with *Yiqi Huoxue* decoction (*Radix astragali, Panax ginseng*, *Salvia miltiorrhiza* and safflower) tended to be normal [17]. *Radix astragali* inhibits abnormal proliferation of connective tissues, while *Salvia miltiorrhiza* reduces damage, reverses ventricular remodeling, and exerts an anti-platelet aggregation effect. More than that, large-head Atractylodes rhizome enhances cardiovascular activity, and *Cinnamomum cassia* increases myocardial nutritional blood flow. Thus, *Wenyang Buxin* decoction has the potential to comprehensively improve cardiac function in CHF subjects. After therapy, the cardiac function indexes, overall effect and QoL of patients were better in group A than in group B, and their TCM syndrome score decreased significantly.

Due to the stasis of blood vessels of CHF patients, there were corresponding changes in hemodynamic indexes, indicating higher blood viscosity. High blood viscosity affects the blood perfusion in CHF patients, induces thrombosis, and further exacerbates the disease. Post-treatment hemorheology indexes were better in group A than in group B, which confirmed the positive effects of *Cinnamomum cassia*, *Salvia miltiorrhiza* and safflower in promoting blood circulation and removing blood stasis. In a study by Sui *et al*., it was shown that the plasma viscosity of patients taking *Cinnamomum cassia* was only 1.15 ± 0.23 pg/mL, indicating that *Cinnamomum cassia* had good effect of activating blood [18]. This is similar to the results of the present study. It should be noted that modified amounts of *Salvia miltiorrhiza* and safflower were used in this study. In practice, whether this kind of drug for blood circulation should be indiscriminately applied to all patients still needs further research.

CONCLUSION

Modified *Wenyang Buxin* decoction and routine therapy improves serum biomarker levels, cardiac function and quality of life. Furthermore, it ameliorates the clinical symptoms of chronic heart failure in patients. Therefore, this treatment strategy should be subjected to further clinical trials to ascertain its suitability for use in clinical practice.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Chengsi Qian and Yan Sun conceived and designed the study, collected, analyzed and interpreted the experimental data, drafted the manuscript and revised the manuscript for important intellectual content. Both authors read and approved the final manuscript.

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