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Clinical efficacy of enhanced external counter pulsation plus sacubitril/valsartan in the treatment of patients with chronic heart failure and the effect on ankle-arm index and cardiac function

X.-L. HUANG, X.-J. WANG, B.-T. CHEN, Y.-N. CHEN

Department of Geriatrics, Xi'an Ninth Hospital, Xi'an, China

Abstract. – OBJECTIVE: The aim of this study was to evaluate the clinical efficacy of enhanced external counter pulsation (EECP) plus sacubitril/valsartan in the treatment of patients with chronic heart failure (CHF) and the effect on ankle-arm index and cardiac function.

PATIENTS AND METHODS: In this retrospective study, 106 patients with chronic heart failure treated in our hospital from September 2020 to April 2022 were recruited and randomly assigned to receive either sacubitril/valsartan (observation group) or EECP plus sacubitril/valsartan (combination group) alternately at the point of admission, with 53 patients in each group. Outcome measures included clinical efficacy, ankle brachial index (ABI), cardiac function indices [N-terminal brain natriuretic peptide precursor (NT-proBNP), 6 min walking distance (6MWD), left ventricular ejection fraction (LVEF)], and adverse events.

RESULTS: EECP plus sacubitril/valsartan resulted in significantly higher treatment efficiency and ABI levels *vs.* sacubitril/valsartan ($p<0.05$). Patients receiving combined therapy showed significantly lower NT-proBNP levels than those given monotherapy ($p<0.05$). EECP plus sacubitril/valsartan resulted in longer 6MWD and higher LVEF than sacubitril/valsartan alone ($p<0.05$). No significant differences were observed in the adverse events between the two groups ($p>0.05$).

CONCLUSIONS: EECP plus sacubitril/valsartan substantially improves the ABI levels, cardiac functions, and exercise tolerance of patients with chronic heart failure, with a high safety profile. EECP improves blood supply to myocardial ischemic tissues by increasing ventricular diastolic blood return and blood perfusion to ischemic myocardium, raises aortic diastolic pressure, restores pumping function, improves LVEF, and reduces NT-proBNP secretion.

Key Words:

Enhanced external counterpulsation, Sacubitril/valsartan, Chronic heart failure, Clinical outcomes, Ankle brachial index, Cardiac function.

Introduction

Chronic heart failure (CHF) is a common clinical cardiovascular disease with a high prevalence and rapid progression. There is a significant association between increased morbidity and the aging process and the occurrence of underlying diseases such as hypertension[1]. WHO statistics[2] show that the prevalence of chronic heart failure in Europe is about 10% in people over 65 years of age, with a 5-year mortality rate of 67%. Research[2] has suggested that the development of CHF is associated with the activation of the neuroendocrine system and cytokines in the body and that hemodynamic disorders, cardiomyocyte remodeling, and apoptosis are also linked to the development of CHF[3]. Various cardiovascular diseases can lead to cardiac insufficiency due to prolonged cardiac overload, myocardial injury and weakened systolic function, and CHF is the final outcome of most cardiovascular diseases and one of the most important causes of death. CHF has a long course and is prone to recurrent episodes, requiring frequent hospitalization and imposing a large financial burden on patients. Recurrent disease also aggravates heart failure and compromises prognosis.

Conventional treatment of CHF includes antiplatelet, anti-myocardial ischemia, and coronary prevention medication. However, conventional medication is associated with a poor prognosis[4]. Sacubitril/valsartan is a representative drug of angiotensin receptor enkephalinase inhibitors, and research[5] has confirmed its significant effect on the elevation of endogenous vasoactive peptide levels in CHF patients, which indicated further therapeutic improvement for CHF patients with the rational use of sacubitril/valsartan. Nevertheless, sacubitril/valsartan may result in adverse events such as renal impairment, hyperkalemia, and angioedema[6].

Corresponding Author: X.-J. Wang, MD; e-mail: yuejing20282@126.com

Ziad et al[7] indicated that reasonable and effective cardiac rehabilitation training was associated with significant therapeutic benefits for CHF patients. In recent years, with the continuous development of medical technology in China, enhanced external counterpulsation (EECP) rehabilitation training has been gradually introduced into the clinical management of cardiovascular diseases. Enhanced external counter pulsation (EECP) is an extracorporeal noninvasive circulatory assist device that increases diastolic aortic pressure by sequential pressurization of the limb, thereby improving coronary perfusion and myocardial blood supply and effectively ameliorating cardiac function[8]. However, the combination of EECP and sacubitril/valsartan for CHF management has been marginally studied.

The treatment of chronic heart failure in traditional Chinese medicine (TCM) has become a major topic of attention in recent years. Coronary heart disease is classified as "edema", "asthma" and "palpitations" in TCM and is caused by damage to heart Qi, deficiency of heart yang, inability of blood flow or stagnation of Qi and blood stasis, resulting in irregular heart veins and stagnation of blood and water. Treatment is based on the general principle of warming Yang, benefiting Qi, activating blood circulation, resolving blood stasis, and relieving water retention. However, the combination of TCM with EECP and sacubitril/valsartan has been less studied. To this end, the present study was conducted to evaluate the clinical efficacy of EECP plus sacubitril/valsartan in the treatment of patients with chronic heart failure and the effect on ankle-arm index and cardiac function.

Patients and Methods

Participants

In this retrospective study, 106 patients with chronic heart failure treated in our hospital from September 2020 to April 2022 were recruited and randomly assigned alternatively at the point of admission to receive either sacubitril/valsartan (observation group) or EECP plus sacubitril/valsartan (combination group), with 53 patients in each group. Clinical baseline profiles included sex, age, BMI, systolic blood pressure, diastolic blood pressure, heart rate, New York Heart Association (NYHA) functional class, and comorbid underlying disease.

The randomization was carried out using an online web-based randomization tool (freely available at http://www.randomizer.org/). For concealment of allocation, the randomization procedure and assignment were managed by an independent research assistant who was not involved in screening or evaluation of the participants.

The original sample size calculation estimated that 50 patients in each group would be needed to detect a 3-point difference between groups in a 2-sided significance test with a power of 0.8 and an alpha error level of 0.05.

The study was done in accordance with standards of Good Clinical Practice and the Declaration of Helsinki. Ethics number: MKYU20200908.

Inclusion and Exclusion Criteria

Inclusion criteria: 1) patients were diagnosed with chronic heart failure according to the Diagnostic Criteria for Heart Failure[9]; 2) patients were classified as class II-III by NYHA[10]; 3) patients had normal mental state and normal communication skills; 4) patients and family members were informed about the study and voluntarily participated in the study. 5) ECG showed myocardial ischemia, conduction block, and ventricular hypertrophy; 6) Chest radiograph showed pulmonary stasis, enlarged heart shadow, and left ventricular ejection fraction (LVEF) ≤45%. Exclusion criteria: 1) patients with severe cardiac arrhythmias; 2) with severe organic dysfunction; 3) with severe visceral diseases; 4) with psychiatric disorders or communication disorders; 5) with Ankle-brachial index (ABI) levels >1.3.

Treatment Methods

Patients in both groups received conventional treatment, including β-blockers, angiotensin-converting enzyme inhibitors/Angiotension II receptor blockers (ACEI/ARB), aldosterone receptor antagonists, diuretics, nitrates and anti-platelet drugs, followed by oxygenation and maintenance of water-electrolyte balance according to the actual situation of the patients.

Observation group: patients in the observation group received 49/51 mg of sacubitril/valsartan sodium tablets (Beijing Novartis Pharmaceutical Co., Ltd., Beijing, China, State Pharmacopoeia J20190002) twice daily, and the dose was increased according to the patient's tolerance. The highest dose was 97/103 mg/dose, and patients were monitored for 14 days following each dose increase, primarily to

monitor substantial renal impairment, higher blood potassium, and reduced blood pressure. The duration of therapy was one week.

Combination group: patients in the combination group received sacubitril/valsartan sodium tablets (the administration approach was identical to that in the observation group) plus EECP. The treatment device for EECP was a P-ECP/TI type oxygen saturation monitoring extracorporeal counter pulsation device, with a balloon pressure of 0.35-0.45 kg/cm^2. The EECP treatment was performed for 1 h once daily, with an interval of 1 d between every 6 d. One course of treatment lasts 36 h, and the duration of treatment was three courses.

The two groups received TCM decoction, and the herbs included 6 g each of *Ginseng* and *Croci Stigma*, 9 g of A*coniti Lateralis Radix Praeparata*, 10 each of *Cassia Twig, Persicae Semen, Salviae Miltiorrhizae Radix et Rhizoma, Chuanxiong Rhizoma, Paeoniae Radix Alba, liquorice root,* and *Aurantii Fructus*, 15 g each of *Angelicae Sinensis Radix, Poria, Pepperweed Seed*, and *Ginger*, and 30 g of *Astragali Radix*.

Outcome Measures

(1) Clinical efficacy: markedly effective: patients' clinical symptoms disappeared, and cardiac function recovered ≥grade 2; Effective: patients' clinical symptoms were all significantly relieved and cardiac function recovered ≥grade 1; Ineffective: patients' clinical symptoms showed no changes.

(2) ABI: The systolic pressure of the brachial artery in the upper arm was measured bilaterally using a Doppler ultrasonography probe while the patient was supine, followed by the systolic pressure of the ankle. The ABI level was calculated by dividing the brachial artery systolic pressure by the ankle systolic pressure on one side. The comparison value was the lower ABI value of the two sides.

(3) Cardiac function indices: the cardiac function indices included in this study were N-terminal brain natriuretic peptide precursor (NT-proBNP), 6 min walking distance (6MWD), and left ventricular ejection fraction (LVEF). 1) NT-proBNP assay: 3 ml of fasting venous blood was collected from patients before and after treatment and centrifuged to obtain the plasma for assay. The NT-proBNP levels were determined using electrochemiluminescence with a Roche E170 immunoassay analyzer (Basel, [Switzerland]). 2) 6MWD: patients were instructed to walk briskly for 6 min in a wide and straight corridor, after which their walking distance for 6 min was measured by the medical personnel of our hospital. 3) LVEF level: before and after the treatment, the patients' left ventricular ejection fraction (LVEF) was measured using a color ultrasound diagnostic instrument (XAR10, Jiangsu Jiahua Electronics Co., Ltd., Xuzhou, Jiangsu, China).

(4) Adverse events: adverse events during treatment in both groups included renal impairment, hyperkalemia, angioedema, and hypotension.

Statistical Analysis

The mean difference between the two groups were tested using student's *t*-test for normally distributed variables and Mann-Whitney U test for non-normal variables. SPSS 22.2 (IBM Corp., Armonk, NY, USA) was used for data management and analyses, and GraphPad Prism 8 (GraphPad Software Inc., La Jolla, CA, USA) was used to plot the graphics. The measurement data were expressed as mean±standard deviation ($\bar{x}$±s) and tested by a *t*-test. The count data were expressed as the number of cases (rate) and tested using the Chi-square test. $p<0.05$ indicates that the difference is statistically significant.

Results

Patient Characteristics

There were 26 male and 27 female patients in the observation group. There were 33 NYHA grade II cases and 20 NYHA grade III cases. There were 18 combination diabetes cases, 20 combined hypertension cases, and 25 combined hyperlipidemia cases. There were 25 male and 28 female patients in the combined group. There were 35 NYHA grade II cases and 18 NYHA grade III cases. There were 16 combination diabetes cases, 21 combined hypertension cases, and 24 combined hyperlipidemia cases. The two groups' patient characteristics were equivalent ($p>0.05$) (Table I).

Clinical Efficacy

The total efficiency of treatment for patients in the observation group was 79.2% (42/53), including 20 cases with markedly effective effects, 22 cases with effective effects, and 11 cases with ineffective effects. The total treatment efficiency for patients in the combination group was 94.3% (50/53), with 24 instances having markedly effective effects, 26 having effective effects, and 3 having ineffective effects. When compared to sacubitril/

Table I. Patient characteristics [$\bar{x}$±s; n (%)].

	Control (n=53)	Combination (n=53)	t/χ^2	*p*
Sex			0.038	0.846
Male	26	25		
Female	27	28		
Age (years)	69.72±7.83	70.04±7.68	-0.212	0.833
BMI (kg/m^2)	25.47±8.86	25.53±8.79	-0.035	0.972
Systolic blood pressure (mmHg)	131.47±21.63	132.06±21.77	-0.14	0.889
Diastolic blood pressure (mmHg)	72.64±14.58	72.47±14.29	0.061	0.951
Heart rate (beats/min)	86.54±21.28	87.12±21.35	-0.14	0.889
NYHA class			0.164	0.685
II	33	35		
III	20	18		
Underlying disease				
Diabetes mellitus	18	16	0.173	0.677
Hypertension	20	21	0.04	0.842
Hyperlipidemia	25	24	0.038	0.846

valsartan alone, EECP with sacubitril/valsartan resulted in considerably greater treatment efficiency (p<0.05) (Figure 1).

ABI Levels

The ABI levels of patients in the observation group before and after treatment were (0.71±0.09 and 0.84±0.12) and in the combination group were (0.74±0.11 and 0.97±0.15). The ABI levels increased in both groups after treatment, with higher levels in the combination group than in the observation group (p<0.05) (Figure 2).

Cardiac Function

Patients who received combination medication had considerably lower NT-proBNP levels than those who received monotherapy. The combination of EECP and sacubitril/valsartan resulted in

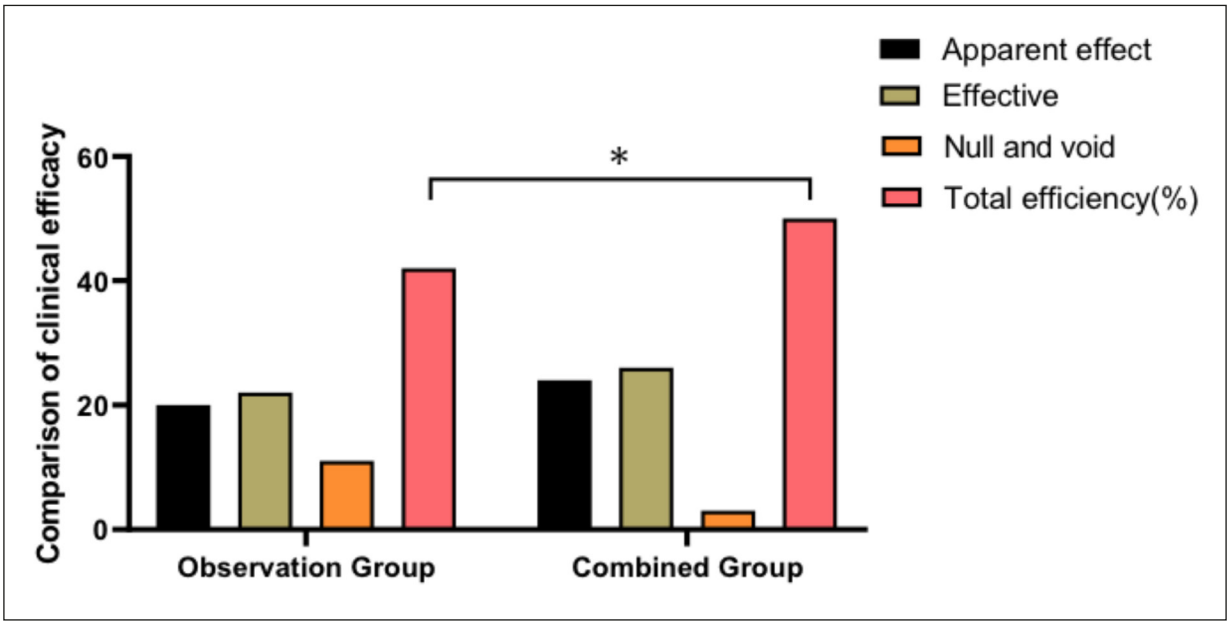

Figure 1. Clinical efficacy [n (%)]. The total efficiency of treatment for patients in the combination group was 94.3% (50/53), including 24 cases with markedly effective effects, 26 cases with effective effects, and 3 cases with ineffective effects. EECP plus sacubitril/valsartan resulted in significantly higher treatment efficiency *vs.* sacubitril/valsartan. *: indicates p<0.05.

a longer 6MWD and greater LVEF than sacubitril/valsartan alone (p<0.05) (Table II).

Adverse Events

The incidence of adverse reactions in the observation group was 9.4% (5/53), including 1 case of renal impairment, 1 case of hyperkalemia, 1 case of angioedema, and 2 cases of hypotension. The incidence of adverse reactions in the combination group was 7.5% (4/53), including 1 case of hyperkalemia, 2 cases of angioedema, and 1 case of hypotension. No significant differences were observed in the adverse events between the two groups (p>0.05) (Table III).

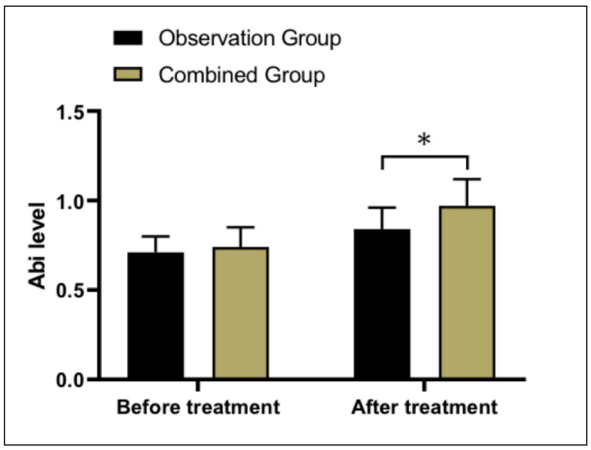

Figure 2. ABI levels ($\bar{x}$±s). The ABI levels increased in both groups after treatment, with higher levels in the combination group than in the observation group. *: indicates p<0.05.

Discussion

CHF is a disease with complex pathogenesis and is associated with a high incidence of hospitalization, rehospitalization and mortality[11]. Research[12] showed that the prevalence of CHF in China is about 0.92% and the mortality is about 4.39%, posing a serious threat to the life safety of people. Sacubitril/valsartan is a commonly used drug for CHF management, and it dilates blood vessels, reverses cardiovascular remodeling, and promotes urinary sodium excretion through two pathways, namely, enkephalinase inhibitor and angiotensin II receptor inhibitor[13]. However, despite its improvement in patient prognosis, research[14] has indicated restricted efficacy of sacubitril/valsartan given the multiple factors of CHF. EECP is a non-invasive treatment for ameliorating symptoms such as myocardial ischemia[15]. It has been frequently reported[16,17] that EECP provided substantial therapeutic benefits for CHF patients.

ABI is the ratio of ankle systolic pressure to forearm systolic pressure and is used for the diagnosis of peripheral arterial disease of the lower extremities. Alsuwailem et al[18] revealed a strong association between ABI levels in CHF patients and the degree of impairment in their walking endurance, while Goernig et al[19] suggested that ABI could be an independent predictor of cardiovascular mortality and adverse events, and that lower ABI levels in patients indicated an increased incidence of adverse

Table II. Cardiac function indices ($\bar{x}$±s).

Indices	Timepoint	Observation (n=53)	Combination (n=53)	t	p
NT-proBNP (ng/L)	Before treatment	3,648±1,022	3,639±1,028	0.045	0.964
	After treatment	941±435	711±105	3.742	<0.001
6MWD (m)	Before treatment	422.39±50.78	420.74±51.29	0.166	0.868
	After treatment	465.58±50.33	515.27±52.67	-4.966	<0.001
LVEF (%)	Before treatment	33.28±7.36	33.32±7.41	-0.028	0.978
0	After treatment	44.68±7.75	52.56±7.87	-5.194	<0.001

Table III. Adverse events [n (%)].

Group	n	Renal impairment	Hyperkalemia	Angioedema	Hypotension	Total incidence (%)
Observation	53	1	1	1	2	9.4% (5/53)
Combination	53	0	1	2	1	7.5% (4/53)
χ^2	-	-	-	-	-	0.121
p	-	-	-	-	-	0.727

cardiovascular events. Both NT-proBNP and BNP are biomarkers of myocardial function and the degree of damage in patients with CHF. The expression of NT-proBNP is closely related to the health of the cardiovascular system[20].

6MWD is a commonly used clinical index to assess exercise tolerance of patients, which effectively reflects the recovery of motor function of patients. LVEF is a typical index for assessing patients' cardiac function and is frequently used to examine the improvement of patients' body circulation. In the present study, patients receiving sacubitril/valsartan plus EECP showed significantly higher ABI, 6MWD, and LVEF and lower NT-proBNP levels than those given sacubitril/valsartan alone, suggesting that EECP may further improve patients' cardiac function, increase their exercise capacity, and reduce the risk of cardiovascular death and adverse events. Furthermore, the incidence of adverse events between the two groups was similar, which was consistent with previous research results[21,22]. The reason may be that EECP improves blood supply to myocardial ischemic tissue by increasing ventricular diastolic blood return and blood perfusion to ischemic myocardium, raises aortic diastolic pressure, restores pumping function, increases LVEF, and reduces NT-proBNP secretion. In addition, EECP increases the pumping and filling function of the ventricle, attenuates ultrastructural changes such as endothelial cell atrophy, degradation of cytosolic vacuolation, and nucleus fragmentation, restores ventricular function, reduces cardiac load, affects circulating hemodynamic effects and shear stress on the vessel wall, reduces the apoptotic index of endothelial cells, and prevents exacerbation of symptoms[23,24].

In the herbal formula used in this study, *Astragali Radix* benefits Qi and diuresis to treat deficiency of heart Qi. Modern pharmacological studies in literature have shown that *Astragali Radix* is a non-digitalis positive inotropic drug that increases LVEF and improves left ventricular configuration. The total saponin contained in *Ginseng* can slow down the heart rate, reduce myocardial oxygen consumption, increase myocardial contractility, lower blood lipids, and have a good protective effect against myocardial ischemia and reperfusion injury. *Salviae Miltiorrhizae Radix et Rhizoma* and *Croci Stigma* can activate blood circulation and resolve blood stasis, dilate coronary arteries, improve blood supply to the heart, reduce peripheral vascular resistance, and reduce cardiac afterload. *Pepperweed Seed* diureses the lung, moves fluid, and facilitates diuresis. The combination of TCM and Western medicine has great prospects for treatment.

The mechanism of EECP in the treatment of chronic congestive heart failure is that it regulates blood flow and vascular endothelial status, thereby adjusting the function of damaged vascular endothelial cells, promoting the secretion of substances to resist atherosclerosis, protecting the vascular endothelium after treatment, and rebalancing the blood supply status of the heart. The current study investigated the efficiency of EECP combined with sacubitril/valsartan for CHF, but the treatment of CHF with EECP plus sacubitril/valsartan has not been effectively promoted and popularized due to the lack of clinical CHF management awareness and the limited medical conditions in many hospitals.

Limitations

This study has the following shortcomings: (1) Only 53 patients were included in this study, which is not yet a comprehensive response to the effect of treatment. (2) Only the treatment indexes of patients before and after treatment were comparatively analyzed in the study, and the data comparison should be further refined in the future; (3) Only two groups were listed in the study for efficacy analysis. However, in some patients, extracorporeal counter pulsation treatment was not convenient in some hospitals. These are future directions for further research.

Conclusions

EECP plus sacubitril/valsartan substantially improves the ABI levels, cardiac functions, and exercise tolerance of patients with chronic heart failure, with a high safety profile.

Informed Consent

All researchers have read the manuscript and agreed to publish it. All subjects signed an informed consent form.

Ethics Approval

The study protocol and all amendments were approved by the appropriate ethics body at each participating institution (Ethics number: MK-YU20200908).

ORCID ID

Xiaojing Wang: 0000-0001-9419-4851

Conflict of Interest
All researchers declare no conflict of interest.

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Authors' Contributions
X.-L. Huang: methodology, writing - original draft; X.-J. Wang: data curation, formal analysis, writing - review and editing; B.-T. Chen: investigation, visualization, editing; Y.-N. Chen: conceptualization, project administration, supervision.

Availability of Data and Materials
All the clinical data in this study are authentic and reliable.

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