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Clinical effects of combined treatment by optimal dose of furosemide and spironolactone on diastolic heart failure in elderly patients

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Abstract. Diastolic heart failure (DHF) is characterized by symptoms including reduced ventricular relaxation and compliance, resulting in congestion of pulmonary and systemic circulation. The curative effects of regular cardiac agents are ineffective. Thus, new agents are required to treat chronic cardiac failure. The aim of the present study was to examine the clinical effects of the combined treatment by optimal dose of furosemide (20 mg/day) and spironolactone (40 mg/day) on elderly patients with diastolic heart failure (DHF) [New York Heart Association (NYHA) 1-2 grade]. A total of 93 patients diagnosed with DHF between February, 2013 and February, 2014 were enrolled in the present study. The patients were randomly divided into the furosemide group (20 mg/day, n=27), optimal dose group (20 mg/day furosemide+40 mg/day spirolactone, n=36), and large dose group (40 mg/day furosemide+100 mg/day spirolactone, n=30). Following treatment for one month, a comparison and analysis of the NYHA class, left ventricular ejection fraction (LVEF) and left ventricular end diastolic diameter (LVEDD), left ventricular wall segmental motion among the three groups were performed. The re-hospitalization rate of heart failure and incidence of electrolyte disorder among the three groups was compared and their differences analysed. Compared with pretreatment, the NYHA classifications of the three groups after treatment were reduced and differences were statistically significant (P<0.05). By contrast, for the NYHA classification after treatment there was no statistical significance (P>0.05). Compared with pretreatment, LVEF of the optimal dose group increased, LVEDD decreased, and the average systolic myocardial peak velocity and early diastolic myocardial peak velocity of ventricular wall motion were reduced, with differences being statistically significant (P<0.05). By contrast, in the furosemide and large dose groups no statistical significance was identified before and after the treatment (P>0.05). Improvement of the optimal dose group following treatment was more significant than the remaining two groups, and differences were statistically significant (P<0.05). The re-hospitalization rate of heart failure and incidence of electrolyte disorder in the optimal dose group following treatment were significantly less than the other two groups, and differences were statistically significant (P<0.05). In conclusion, the optimal dose (20 mg/day furosemide+40 mg/day spirolactone) significantly improved the clinical symptoms of elderly DHF patients (NYHA 1-2 grade) and ameliorated their long-term prognosis.

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Introduction

Diastolic heart failure (DHF) is a syndrome characterized by symptoms including normal ventricular systolic functions, and reduction of ventricular relaxation and compliance, which leading to an increase in ventricular filling volume and filling pressure, thereby resulting in congestion of pulmonary and systemic circulation (1). Elderly individuals have a higher incidence of hypertension, coronary heart disease and diabetics as well as a higher proportion of DHF in the early stages. Previous findings have shown that the proportion of DHF on elderly patients was 56.4%, which was higher than that of systolic heart failure (SHF) (2). The curative effects of regular cardiac agents, vascular dilation drugs, hydragogue, and neuroendocrine antagonists in treating DHF are inferior to SHF. Furosemide is a type of diuretic drugs that is used long term. Although it did not reduce the death rate, furosemide significantly improved clinical symptoms as well as curative effects (3). In the guidelines issued by Europe and America in 2012, spirolactone was considered a Ia drug and a small dose was recommended for the treatment of chronic cardiac failure (4). In addition, its anti-ventricular remodeling effect was comparable to angiotensin-converting

enzyme inhibitor (ACEI) drugs (4). However, data for the effect of the clinical application of these two types of drugs are not available. Consequently, in this study we analyzed the clinical effects of the combined treatment by optimal dose of furosemide (20 mg/day) and spironolactone (40 mg/day) to elderly patients with DHF [New York Heart Association (NYHA) 1-2 grade] to provide a new approach for clinical treatment.

Materials and methods

General materials. A total of 93 patients that were diagnosed with DHF at the Department of Cardiology at the Yichang Central People's Hospital between February, 2013 and February, 2014 were enrolled in the study. Of the 93 patients, 49 cases were male and 44 cases female, aged 67-83 years, with an average of 75.8±6.6 years and a course of disease of 2-13 years, with an average of 7.2±1.5 years. Of the 93 patients 28 cases were hypertensive, 16 cases had diabetes, 31 cases had coronary heart disease and 9 cases had cerebral infarction. The diagnosis of DHF was confirmed by the European Society of Cardiology (2012) diagnostic criteria: i) patients were accompanied with obvious cardiac failure clinical performance; ii) patients whose left ventricular systolic functions were impaired; and iii) patients whose left ventricular systolic functions were normal and LVEF >50%. The exclusion criteria for the study were: i) patients with dilated cardiomyopathy, rheumatic valvular heart disease, serious myocarditis and other cardiac organic diseases; ii) patients with severe hepatic renal dysfunction, peptic ulcer and other severe digestive tract diseases as well as malignant electrolyte disorder; and iii) patients with severe arrhythmia, chronic obstructive pulmonary disease, pernicious anemia and patients that declined inclusion for the study.

Approval for the study was obtained from the Ethics Committee of the Central People's Hospital of Yichang. Informed consent was provided by the patients and their relatives. The patients were randomly divided into the furosemide group (20 mg/day, n=27); optimal dose group (20 mg/day furosemide+40 mg/day spirolactone, n=36); and large dose group (40 mg/day furosemide+100 mg/day spirolactone, n=30). Differences with regard to age, gender, disease course and complications betweent the three groups were not statistically significant (P>0.05).

Experimental method. Prior to treatment, the patients were required to accept disease assessment to diagnose cause of heart failure. For the patients with severe myocardial ischemia, revascularization treatment was applied and basic drugs included calcium ion antagonists, ACEI drugs and β-blockers. As for patients with complications such as hypertension and diabetics, proper antihypertensive and hypoglycemic therapy were applied. After treatment for 1 month, the NYHA classification, left ventricular ejection fraction (LVEF), left ventricular end diastolic diameter (LVEDD), and left ventricular wall segmental motion were compared for the three groups and the differences analyzed. The re-hospitalization rate of heart failure and incidence of electrolyte disorder for the three groups were compared and the differences analyzed.

Echocardiography examination was performed as per the suggestion of the American Society of Echocardiography (5). MyLab 50 (Esaote, Shanghai, China) was used and the transducer frequency was set at 4.5-4 MHz, the section on left ventricular long axis was produced and M-mode ultrasonography was used to generate the end diastole at 1 cm under the valvula bicuspidalis. Subsequently, the LVEDDs were observed, a section was made on a standard apical 4-chamber and the anteroposterior (A-P diameter) and superoinferior diameters of the left atrium were measured. The Simpson double method was employed to observe and measure the volume of the left atrium and calculate the LVEF. Doppler imaging was applied to tissues to measure the motion velocity spectrum of the mitral ring along the long axis cardiac muscle tissues in the inferior wall, side wall, ventricular septum and front wall.

Statistical analysis. The statistical software package SPSS 18.0 (SPSS, Inc., Chicago, IL, USA) was used to process the data. Measurement data were presented as means ± standard deviation. Analysis of variance was used for comparisons between groups. Enumeration data were presented as case or percentage. The χ^2 test was used for comparisons between groups. P<0.05 was considered to indicate a statistically significant difference.

Results

Comparisons of NYHA classification, LVEF and LVEDD for the there groups of patients. Comparisons of the differences between NYHA classification, LVEF and LVEDD were carried out for the three groups prior to treatment. No statistical significance was identified (F=0.524, P=0.307, F=0.526, P=0.331, F=0.347, P=0.625, P>0.05). By contrast, the NYHA classifications of the three groups after treatment as compared to the pretreatment values were reduced and differences were statistically significant (furosemide group: 1.2±0.4 vs. 1.6±0.3, t=4.967, P=0.038; optimal dose group: 1.3±0.5 vs. 1.8±0.4, t=5.124, P=0.036; large dose group: 1.3±0.6 vs. 1.7±0.5, t=4.768, P=0.039; P<0.05). Differences in the NYHA classification for the three groups after treatment were not statistically significant (F=0.639, P=0.812, P>0.05). Compared with pretreatment, LVEF of the optimal dose group increased, LVEDD decreased and the differences were statistically significant [(63.8±2.1) vs. (55.7±1.5)%, t=5.124, P=0.036; (56.9±2.3) vs. (63.4±1.5) mm, t=5.524, P=0.034; P<0.05)] whereas comparisons in the remaining two groups prior to and following treatment were not statistically significant (LVEF: furosemide group: t=0.624, P=0.332; large dose group: t=0.754, P=0.421; LVEDD: furosemide group: t=0.421, P=0.213; large dose group: t=0.724, P=0.632; P>0.05). Improvement of the optimal dose group following treatment was more significant than the remaining two groups and differences were statistically significant (F=5.526, P=0.027, F=5.938, P=0.023) (P<0.05; Table I).

Comparisons on ventricular wall motion for the three groups of patients. Differences on the average systolic myocardial peak velocity (Sm) and early diastolic myocardial peak velocity (Em) for the three groups prior to treatment were

Table I. Comparisons of the NYHA classification, LVEF and LVEDD for the three groups of patients.

	NYHA classification		LVEF, %		LVEDD, mm	
Group	Pretreatment	Post-treatment	Pretreatment	Post-treatment	Pretreatment	Post-treatment
Furosemide	1.6±0.3	1.2±0.4	56.4±2.3	57.4±1.6	62.6±1.3	61.4±2.1
Optimal dose	1.8±0.4	1.3±0.5	55.7±1.5	63.8±2.1	63.4±1.5	56.9±2.3
Large dose	1.7±0.5	1.3±0.6	55.9±2.1	58.4±1.3	62.9±1.2	61.2±1.8
F-value	0.524	0.639	0.526	2.526	0.347	2.638
P-value	0.307	0.812	0.331	0.027[a]	0.625	0.023[a]

[a]P<0.05 statistically significant. NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter.

Table II. Comparisons of ventricular wall motion for the three groups of patients.

	Average Sm, cm/sec		Average Em, cm/sec	
Group	Pretreatment	Post-treatment	Pretreatment	Post-treatment
Furosemide	12.3±3.1	11.8±1.9	10.4±3.6	9.6±1.4
Optimal dose	13.5±2.4	8.4±2.2	11.5±2.8	7.3±1.5
Large dose	12.6±3.3	11.6±1.8	10.6±2.7	9.2±1.3
F-value	0.634	3.416	0.653	3.624
P-value	0.103	0.012[a]	0.417	0.014[a]

[a]P<0.05 statistically significant. Sm, systolic myocardial peak velocity; Em, early diastolic myocardial peak velocity.

Table III. Comparisons of the re-hospitalization rate of heart failure and incidence of electrolyte disorder for the three groups of patients [case (%)].

Group	Case	Re-hospitalization rate of heart failure	Incidence of electrolyte disorder
Furosemide	27	7 (25.9)	4 (14.8)
Optimal dose	36	5 (13.9)	3 (8.3)
Large dose	30	6 (20.0)	4 (13.3)
χ^2 test		3.104	3.625
P-value		<0.001[a]	<0.001[a]

[a]P<0.05 statistically significant.

not statistically significant (F=0.634, P=0.103, F=0.653, P=0.417; P>0.05). Compared with pretreatment, the average Sm and Em in the optimal group following treatment were greatly reduced and differences were statistically significant (t=6.124, P=0.015, t=6.302, P=0.018; P<0.05). Comparisons in the remaining two groups prior to and following treatment were not statistically significant (average Sm: furosemide group: t=0.825, P=0.424; large dose group: t=0.937, P=0.632; average Em: furosemide group: t=0.535, P=0.257; large dose group: t=0.627, P=0.439; P>0.05). Improvement of the optimal dose group following treatment was more significant than the furosemide and large dose groups and differences were statistically significant (P<0.05; Table II).

Comparisons of the re-hospitalization rate of heart failure and incidence of electrolyte disorder for the three groups of patients. The re-hospitalization rate of heart failure and incidence of electrolyte disorder in the optimal dose group following treatment were significantly less than the furosemide and large dose groups and differences were statistically significant (X^2=6.159, P=0.046, X^2=6.910, P=0.032) (P<0.05; Table III).

Discussion

DHF is a chronic congestive heart failure characterized by reduced ventricular relaxation and compliance (2). It is a clinically independent disease that usually occurs prior to SHF.

Clinical studies have shown that DHF patients account for almost 50% of the total heart failure patients and the majority of these patients are elderly individuals. DHF has seriously affected quality of life of the elderly (6). In the clinical set up, most of the treatment experience was from SHFs and treatment on DHF mainly consisted of SHFs. However, internal mechanisms of the two diseases were markedly different, thus, their curative effects are notably different (7). There is a different frame of reference regarding the application of diuretic furosemide and spirolactone. In one study, in which patients were initially administered a small dose of furosemide, suggested their separate use (8). The dose was gradually increased and spirolactone was administered only to prevent electrolyte disturbances. Although this first-line treatment was safe, the course of treatment was conducted over a long period of time. Results of that study showed that short-term curative effects were not significant, long distance anti-ventricular remodeling effects were weak, symptoms of heart failure occurred repeatedly, the condition of the disease was gradually exacerbated resulting in a poor prognosis (9,10). Other studies recommended administering treatment with a large dose of furosemide and spirolactone to intensify the diuretic effects. Large-dose treatment (40 mg/day furosemide+100 mg/day spirolactone) may exhibit improved diuretic efficacy in liver cirrhosis and ascites. However, this type of treatment may result in severe complications, such as circulating hypovolemia and electrolyte disturbance in elderly DHF patients. Additionally, its anti-ventricular remodeling effects were markedly weak, and in the short term, this may lead to deterioration of the patients' condition. Consequently, its application was limited clinically (11-13).

In the present study, we have analyzed the clinical effects of the combined treatment by optimal dose of furosemide (20 mg/day) and spironolactone (40 mg/day) on elderly patients with DHF (NYHA 1-2 grade). The results showed a statiscally significant decrease in NYHA classifications of the three groups following treatment. Additionally, when compared with pretreatment, LVEF of the optimal dose group increased, LVEDD decreased, and the average Sm and Em of the ventricular wall motion were reduced. The differences were statistically significant while comparisons in the furosemide and large dose groups prior to and following treatment were not statistically significant. Improvement of the optimal dose group following treatment was more significant than the remaining two groups and differences were statistically significant. The re-hospitalization heart failure rate and incidence of electrolyte disorder in the optimal dose group following treatment were significantly less than the remaining two groups and differences were statistically significant. LVEF and LVEDD were used as sensitive indicators of ventricular remodeling. Furosemide, as a loop diuretic, may be used to improve fluid retention in the short term and eliminate sodium and potassium, and its disturbances on kidney, blood fat and blood sugar were relatively weak (14). A review of the literature (12,13) has shown that 20 mg was the optimal dose for diuresis on patients with light and moderate cardiac failure and long-term treatment was safe and effective. ACEI drugs may antagonize stimulation of the renin-angiotension-aldosterone system in heart failure patients in compensated stage and reduce the level of aldosterone. However, recent studies have identified that even a tolerable dose of ACEI drugs may not reduce the level of aldosterone to satisfactory levels. This may be because produce and metabolism of aldosterone had bypassing ways. Therefore, the direct receptor antagonist of aldosterone and spirolactone, was able to produce favorable effects. Findings from the EMPHASIS-HF test have confirmed that the aldosterone receptor antagonist, eplerenone, improved the clinical prognosis of patients with NYHA SHF (15).

The appropriate dose of furosemide and aldosterone may also significantly improve the motion extent, speed and harmony of the left ventricular wall and is favorable for the treatment of heart failures complicated by interventricular heart-block and intraventricular conduction delay. Relevant studies (16) have also shown that a small dose of spirolactone significantly reduces the proportion of heart failure patients required to accept cardiac resynchronization therapy, significantly improve their long-term survival rate, and reduce the extensive economic burden. Although the number of samples in the present study were relatively limited, we concluded that the optimal dose (20 mg/day furosemide+40 mg/day spirolactone) significantly improved the clinical symptoms of DHF in elderly patients (NYHA 1-2 grade) and have good prognosis.

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