



Effect of the adjuvant milrinone therapy on cardiac function, myocardial remodeling and RAAS system activity in patients with chronic heart failure

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ABSTRACT

Objective: To explore the effect of the adjuvant milrinone therapy on cardiac function, myocardial remodeling and RAAS system activity in patients with chronic heart failure.

Methods: A total of 110 patients with chronic heart failure who were treated in the hospital between January 2015 and January 2017 were divided into control group ($n=55$) and observation group ($n=55$) by random number table method. Control group received conventional therapy for chronic heart failure, and the observation group received milrinone on the basis of conventional therapy. The differences in ultrasound cardiac function and myocardial remodeling index levels as well as serum RAAS index contents were compared between the two groups before and after treatment. **Results:** Before treatment, the differences in ultrasound cardiac function and myocardial remodeling index levels as well as serum RAAS index contents were not statistically significant between the two groups. After treatment, CO and SV levels of both groups of patients were significantly higher than those before treatment while LADd, LVEDd, LVPWT, IVST and LVMI levels as well as serum PRA, Ang II and ALD contents were significantly lower than those before treatment, and CO and SV levels of observation group were significantly higher than those of control group while LADd, LVEDd, LVPWT, IVST and LVMI levels as well as serum PRA, Ang II and ALD contents were significantly lower than those of control group. **Conclusion:** Adjuvant milrinone therapy can effectively enhance the cardiac function, inhibit the myocardial remodeling and decrease the RAAS system activity in patients with chronic heart failure.

1. Introduction

Chronic heart failure is the myocardial damage and myocardial structure function change caused by a variety of reasons, which will eventually result in a decline in ventricular pumping/filling ability, and is mainly characterized by dyspnea, weakness and fluid retention[1,2]. If the chronic heart failure condition is not under control, patients' quality of life can be severely affected, the long-term mortality is higher, and therefore, taking positive and effective therapies to stabilize the illness and optimize the outcome is its

ultimate goal. Cause (hypertension and diabetes) control, symptom improvement (diuresis and cardiotoxic therapy) and so on are the routine therapies for patients with chronic heart failure, but some patients are still in progress, and currently many scholars have recommended milrinone to the overall treatment. Milrinone is a phosphodiesterase inhibitor, and studies have shown that short-term small-dose milrinone can be effective in reducing the cardiac preload and afterload and improving clinical symptoms in patients with chronic heart failure[3–5]. In this study, at the same time of basic treatment, milrinone was added in the overall treatment, and the application value was discussed from the three aspects of cardiac function, myocardial remodeling and RAAS activity, now reported as follows.

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2. Information and methods

2.1 Case information

A total of 110 patients with chronic heart failure who were treated in the hospital between January 2015 and January 2017 were selected as research subjects, and the family members signed informed consent. The patients were divided into control group ($n=55$) and observation group ($n=55$) by random number table method. Control group included 31 men and 24 women that were 57-78 years old; observation group included 29 men and 26 women that were 55-73 years old. The differences in basic data distribution were not statistically significant between the two groups ($P>0.05$), and the hospital ethics committee approved the study.

2.2 Inclusion criteria

(1) Conforming to the diagnostic criteria for chronic heart failure; (2) never accepting milrinone therapy before; (3) cooperating with and finishing the whole treatment, with complete data.

2.3 Exclusion criteria

(1) Allergic to milrinone; (2) combined with severe pulmonary hypertension and pulmonary dysfunction; (3) combined with systemic infectious diseases; (4) combined with severe autoimmune disease.

2.4 Therapy

Control group received routine therapy for chronic heart failure, including reducing blood pressure, lowering glucose, regulating lipid, anti-platelet, vascular dilation and angiotensin converting enzyme inhibitor. Observation group, on the basis of conventional treatment, received adjuvant milrinone therapy, specifically as follows: slow intravenous drip of milrinone injection (Lunan Beite Pharmaceutical Co., Ltd., approved by H10970051) $50 \mu\text{g}/\text{kg}$ within 5-10 min, and then intravenous pumping of the solution of milrinone injection $0.5 \mu\text{g}/(\text{kg} \cdot \text{min})$ and 50 mL saline at 10 mL/h, for continuous 5d of treatment.

Table 1.

Comparison of ultrasonic cardiac function parameter levels between two groups of patients before and after treatment.

Groups	<i>n</i>	Time	CO	SV	LADd	LVEDd
Control group	55	Before treatment	5.21±0.57	64.28±7.12	43.28±5.19	63.27±7.19
		After treatment	5.95±0.63*	70.61±8.53*	40.74±4.82*	59.84±6.32*
Observation group	55	Before treatment	5.19±0.58	64.36±7.09	43.17±5.08	63.42±7.31
		After treatment	6.47±0.68**	81.63±9.43**	37.14±4.21**	53.17±6.05**

Note: comparison of indexes within group before and after treatment, * $P<0.05$; comparison of indexes between two groups after treatment, ** $P<0.05$.

2.5 Observation indexes

Before and after treatment, cardiac color Doppler diasonograph (Beijing Xiandai Ouya Medical Equipment Technology Co., Ltd., specifications ESO1) was used to detect cardiac function parameter levels, including cardiac output (CO), stroke volume (SV), left atrial diastolic diameter (LADd) and left ventricular end-diastolic diameter (LVEDd); the levels of myocardial remodeling parameters, including the left ventricular posterior wall thickness (LVPWT), interventricular septal thickness (IVST) and left ventricular myocardial mass index (LVMI). 3.0 mL of fasting cubital venous blood was extracted from two groups of patients, joined by low molecular heparin sodium for anticoagulation and then centrifuged at low speed to get upper serum, and RIA method was used to determine the contents of serum RAAS indexes, including renin (PRA), angiotensin II (Ang II) and aldosterone (ALD).

2.6 Statistical processing

Cardiac function parameters, myocardial remodeling parameters and RAAS indexes belonged to measurement data and were compared by t test. Statistical software was SPSS 25.0. Statistic $P<0.05$ was the standard of statistical significance in differences.

3. Results

3.1 Cardiac function parameters

Comparison of cardiac function parameters CO (mL/min), SV (mL), LADd (mm) and LVEDd (mm) between two groups of patients before treatment and 5d after treatment was as follows: before treatment, CO, SV, LADd and LVEDd levels were not significantly different between the two groups ($P>0.05$); 5 d after treatment, CO and SV levels of both groups of patients were higher than those before treatment while LADd and LVEDd levels were lower than those before treatment, and CO and SV levels of observation group were higher than those of control group while LADd and LVEDd levels were lower than those of control group ($P<0.05$), shown in Table 1.

Table 2.

Comparison of ultrasonic myocardial remodeling index levels between two groups of patients before and after treatment.

Groups	n	Time	LVPWT	IVST	LVMI
Control group	55	Before treatment	9.37±0.98	8.73±0.91	124.38±15.69
		After treatment	8.94±0.93*	8.06±0.84*	115.47±14.35*
Observation group	55	Before treatment	9.41±0.97	8.69±0.89	123.75±14.37
		After treatment	8.17±0.81*#	7.15±0.77*#	98.62±10.17*#

Note: comparison of indexes within group before and after treatment, * $P < 0.05$; comparison of indexes between two groups after treatment, # $P < 0.05$.**Table 3.**

Comparison of serum RAAS index contents between two groups of patients before and after treatment.

Groups	n	Time	PRA	Ang II	ALD
Control group	55	Before treatment	2.18±0.25	254.28±30.19	180.29±21.63
		After treatment	1.83±0.21*	216.38±24.51*	125.38±14.94*
Observation group	55	Before treatment	2.15±0.27	253.67±31.62	181.75±20.74
		After treatment	1.27±0.13*#	154.37±18.23*#	93.26±10.74*#

Note: comparison of indexes within group before and after treatment, * $P < 0.05$; comparison of indexes between two groups after treatment, # $P < 0.05$.

3.2 Myocardial remodeling indexes

Comparison of myocardial remodeling indexes LVPWT (mm), IVST (mm) and LVMI (g/m^2) levels between two groups of patients before treatment and 5 d after treatment was as follows: before treatment, LVPWT, IVST and LVMI levels were not significantly different between the two groups ($P > 0.05$); 5 d after treatment, LVPWT, IVST and LVMI levels of both groups of patients were significantly lower than those before treatment, and LVPWT, IVST and LVMI levels of observation group were lower than those of control group ($P < 0.05$), shown in Table 2.

3.3 RAAS indexes

Comparison of serum RAAS indexes PRA (ng/mL), Ang II (pg/mL) and ALD (pg/mL) contents between two groups of patients before treatment and 5 d after treatment was as follows: before treatment, serum PRA, Ang II and ALD contents were not significantly different between the two groups ($P > 0.05$); 5 d after treatment, serum PRA, Ang II and ALD contents of both groups of patients were significantly lower than those before treatment, and serum PRA, Ang II and ALD contents of observation group were significantly lower than those of control group ($P < 0.05$), shown in Table 3.

4. Discussion

The mortality of patients with chronic heart failure is high, which is caused by poor clinical treatment and heart pumping failure. Glucose and pressure lowering, lipid regulation, antiplatelet, diuresis, vascular dilation and so on are the conventional therapies for chronic heart failure, but some patients are still with persistent increase of cardiac load, the pumping disorder and so on, and drugs with other mechanisms of action are needed to expand the curative effect. Milrinone has been successfully applied in many kinds of heart diseases in recent years, and it can inhibit myocardial phosphodiesterase to increase the intracellular cAMP concentration, promote calcium influx and enhance myocardial contractility, and

can also increase the content of cAMP in vascular smooth muscle cells to exert relaxant effect, which reduce the cardiac preload and afterload together, and optimize the heart pump function to the greatest extent[6-8]. At present, the studies about milrinone treatment of chronic heart failure mostly focus on the overall treatment effectiveness, and the effect of adjuvant milrinone therapy on cardiac function, myocardial remodeling, RAAS activity and other aspects was further explored in this study.

Pumping dysfunction and blood circulation disorder are the root causes of chronic heart failure, color Doppler ultrasound can dynamically reflect the functional status of the human heart, and pumping indexes CO and SV levels decrease while diastolic ability indexes LADd and LVEDd levels increase in the case of cardiac load increase as well as myocardial pumping or diastolic disability, indicating that the heart cannot effectively discharge the physical circulatory blood and it accumulates in ventricle and atrium[9-11]. Changes in cardiac function parameter levels can reflect the illness severity and the effect of clinical treatment in patients with chronic heart failure in real time, and it was found in the study that compared with those before treatment, CO and SV levels of both groups increased while LADd and LVEDd levels decreased after treatment, showing that both therapies can optimize the cardiac function to different extent; Further compared with those of control group, CO and SV levels of observation group were higher while LADd and LVEDd levels were lower after treatment, confirming that the adjuvant milrinone therapy is effective in enhancing the cardiac function of patients with chronic heart failure.

Myocardial remodeling plays a key role in the occurrence and development of chronic heart failure, myocardial fibers reactively thicken to enhance the self contractility when preload and afterload increase, so there is no obvious pumping disorder in early heart failure, but along with the disease progression, the thickened myocardium has been unable to meet the requirement for normal pumping, so the body fluid accumulates[12,13]. There is obvious cardiac hypertrophy in patients with chronic heart failure, which can be quantified from ultrasonography[14,15]. In this study, the differences in myocardial remodeling parameter levels were compared between the two groups of patients, and it was found that compared with those before treatment, LVPWT, IVST and LVMI levels of both groups of patients were lower after treatment,

indicating that both therapies can reverse the myocardial remodeling process in patients with chronic heart failure to different degree; further compared with those of control group, LVPWT, IVST and LVMI levels of observation group were lower after treatment, confirming that adjuvant milrinone therapy can more effectively inhibit myocardial remodeling progress, which is mainly related to the milrinone effect on reducing the cardiac preload and afterload.

The occurrence of chronic heart failure involves changes in neurohumoral indicators, in which RAAS plays an important role. RAAS is activated early after chronic heart failure occurs, which massively secretes PRA, Ang II and ALD, participates in end organ hypoperfusion in heart failure through vasoconstrictive effect, leads to cardiac overload, increased myocardial damage, myocardial and vascular smooth muscle remodeling, and so on, and eventually progresses to irreversible decompensated period[16-18]. The contents of RAAS indexes are closely related to chronic heart failure, which can be used as the effective indicators for the diagnosis of disease and curative effect. In this study, the differences in serum levels of above RAAS indexes were compared between two groups of patients before and after treatment, and it was found that compared with those before treatment, serum PRA, Ang II and ALD levels of both groups of patients were lower after treatment, showing that both therapies are effective; further compared with those of control group, serum PRA, Ang II and ALD contents of observation group were lower after treatment, confirming that adjuvant milrinone therapy can effectively restrain the activity of RAAS, and this also is one of the important mechanisms for it to optimize cardiac function and inhibit myocardial remodeling progress.

Adjuvant milrinone therapy can effectively optimize the cardiac function and inhibit the myocardial remodeling in patients with chronic heart failure, which is directly related to its effect on containing excessive activation of RAAS. Adjuvant milrinone therapy can effectively expand the therapeutic effect of patients with chronic heart failure and is worthy of popularization and application in clinical practice in the future.

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