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Original Article

The effect of controlling the heart rate on the heart failure index and on heart function in heart failure patients with atrial fibrillation

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Abstract: Objective: To explore the effect of controlling the heart rate on the heart failure index and on heart function in patients with heart failure and atrial fibrillation. Methods: 82 patients with heart failure and atrial fibrillation were divided into a control group (n=41) and a study group (n=41). The patients in the control group underwent conventional treatment. In addition to the conventional treatment, the patients in the study group were administered metoprolol to actively control their heart rates and to decrease their resting heart rates down to 55-60 beats/min as the target heart rate. After three months of treatment, the heart function, the levels of N terminal pro B type natriuretic peptide (NT-proBNP), and the inflammatory factors were compared between the two groups. At the same time, the readmission rates and prognoses were calculated. Results: After the treatment, the left ventricular ejection fraction (LVEF) and the cardiac output (CO) levels in the two groups were increased, and the levels in the study group were higher than the levels in the control group; there were opposite trends in the left ventricular end-systolic diameter (LVESD) levels, the left ventricular end-diastolic dimension (LVEDD) levels, and the NT-proBNP, serum CRP, TNF-α and IL-6 levels (all $P<0.05$). After a six month follow up, the readmission and heart failure rates, and the incidence of adverse events in the study group were lower than they were in the control group (all $P<0.05$). Conclusion: The effective control of the ventricular rate can more significantly benefit the heart failure symptoms and atrial fibrillation, alleviate the inflammatory response, and thus improve the heart function and prognoses of heart failure patients with atrial fibrillation.

Keywords: Heart rate control, heart failure, atrial fibrillation, heart function

Introduction

Heart failure is the end stage of various heart diseases. Some patients with heart failure may also have atrial fibrillation. Once atrial fibrillation occurs, the ventricular rate can be significantly increased, and a too fast ventricular rate can affect atrial systolic function, reduce cardiac output (CO), and aggravate heart failure [1]. Thus, it can increase the treatment difficulty of heart failure patients with atrial fibrillation, so the prognosis of most patients is poor [2]. One study found that, in addition to other factors, atrial fibrillation is an extremely significant cause of death in patients with heart failure [3]. Richter et al. pointed out that for heart failure patients with atrial fibrillation, the level of ventricular rate control can directly affect the prognosis, so it is considered that the control of the ventricular rate is particularly important for the treatment of such patients [4]. At present, there are four common methods of clinical heart rate control: β-receptor blockers (metoprolol, bisoprolol, etc.), calcium antagonists (diltiazem and verapamil), membrane inhibitors (amidoprocain, propafenone, quinidine, etc.), potassium channel blockers (amiodarone), of which β-blockers are the most commonly used [5].

Metoprolol is a β1 receptor blocker. It can slow down the heart rate, inhibit cardiac contractility, reduce cardiac automaticity and delay atrioventricular conduction. It is widely used to treat patients with arrhythmia [6]. However, there are few published studies on the use of metoprolol to control the heart rates of heart failure

Table 1. Comparison of the baseline data between the two groups (n, $\bar{x} \pm sd$)

Index	Study group (n=41)	Control group (n=41)	χ^2/t	P
Gender (n)			0.785	0.376
Male	24	20		
Female	17	21		
Age (years)	53.3±6.4	54.1±5.7	0.598	0.552
BMI (kg/m^2)	23.20±2.77	23.11±2.81	0.146	0.884
Course of chronic heart failure (years)	9.1±2.1	8.5±1.9	1.357	0.179
Duration of atrial fibrillation (years)	2.2±0.4	2.4±0.7	1.588	0.116
NYHA-FC (n)			1.220	0.543
Grade II	14	10		
Grade III	20	21		
Grade IV	7	10		
LVEF (%)	43.09±3.28	43.74±3.81	0.943	0.349

Note: BMI: body mass index; NYHA-FC: New York Heart Association Functional Classification; LVEF: left ventricular ejection fraction.

patients with atrial fibrillation or on its short-term efficacy and effect on short-term heart function. Our report is as follows.

Materials and methods

Baseline data

82 heart failure patients with atrial fibrillation treated in Xiangyang No. 1 People's Hospital, Hubei University of Medicine from February 2018 to February 2020 were recruited as the study cohort and randomly divided into the study group (n=41) and the control group (n=41). The baseline data were shown in **Table 1**. Inclusion criteria: (1) Patients ranging in age from 20 to 75 years old. (2) Patients who meet the diagnostic criteria for heart failure for atrial fibrillation in the *Pharmacologic Therapy Updates of 2018 Guidelines for the Diagnosis and Treatment of Heart Failure in China* and the *2016 Guidelines for the Management of Patients with Atrial Fibrillation* formulated by the European Society of Cardiology (ESC) [7, 8]. (3) The patients who meet classifications II to IV of the *New York Heart Association Functional Classification (NYHA-FC)* [9]. Exclusion criteria: (1) Patients with blood pressure below 100/60 mmHg. (2) Patients with hypertension, diabetes, whose conditions were poorly controlled by the basic treatment. (3) Patients with an atrioventricular block above second degree. (4) Patients with a history of myocardial infarction within one month before enrollment. (5) Patients who were allergic to the drugs used in this study. (6) Patients with significant liver and kidney dysfunction. This study was reviewed and approved by the medical Ethics Committee of Xiangyang No. 1 People's Hospital, Hubei University of Medicine. All the patients signed the informed consent form for the study.

Methods

All the patients were given conventional anti-heart failure treatment. The need and the amount of warfarin treatment were evaluated according to the CHA2DS2-VASc scoring system. The specific therapeutic drugs and medication were as follows: The digitalis cardiotonic agents, diuretics, ACEI, aldosterone antagonists, and other drugs were used to maintain the patients' vital signs. For example, digoxin tablets (Southwest Pharmaceutical Co., Ltd., China, specification: 0.25 mg) were administered at 0.125-0.25 mg/day, 1 time/day. Furosemide tablets (Shanghai Meiyou Pharmaceuticals Co., Ltd., China, specification: 20 mg) were administered at 20-40 mg/day, 1 time/day. Captopril tablets (Shanghai Shikangte Pharmacy Co., Ltd., specification: 12.5 mg) were administered at 6.25 mg/time, 3 times/day. Spironolactone tablets (ShangHai Hengshan Pharmaceutical Industry, specification: 20 mg) administered at 10-20 mg/day, 1 time/day. All of the above drugs were used continuously for 3 months.

Based on the above treatment, the study group was given metoprolol succinate sustained-release tablets (registration number: H20140-

Table 2. Comparison of the heart function between the patients in the two groups before and after the treatment ($\bar{x} \pm sd$)

Groups	Time	LVEF (%)	CO (L/min)	LVESD (mm)	LVEDD (mm)
Study group (n=41)	Before treatment	42.09±3.28	3.46±1.02	44.58±4.30	55.97±2.64
	After treatment	52.03±4.11*,#	4.97±0.94*,#	41.02±3.85*,#	51.64±3.01*,#
Control group (n=41)	Before treatment	42.74±3.81	3.53±0.97	44.89±3.90	56.20±3.10
	After treatment	48.80±3.29*	4.33±0.80*	43.01±3.05*	53.36±2.77*

Note: LVEF: left ventricular ejection fraction; CO: cardiac output; LVESD: left ventricular end-systolic diameter; LVEDD: left ventricular end-diastolic diameter. Compared with before the treatment, *P<0.05; compared with the control group, #P<0.05.

777, AstraZeneca AB, specification: 47.5 mg) to actively control the heart rate. The patients' resting heart rates were reduced to 55 mg/min, which was set as the target heart rate to guide the drug treatment. The recommended initial dose was 23.75 mg/time, 3 times/day. After continuous treatment for 3-5 days, the dose was promptly adjusted according to the patients' heart rate changes. The doses were generally no more than 95 mg/time, 3 times/day. The results were observed after continuous treatment for three months.

Outcome measurement

The main outcomes were: (1) The heart function index of the left ventricular ejection fraction (LVEF), CO, the left ventricular end-systolic diameter (LVESD)/left ventricular end-diastolic dimension (LVEDD) and so on were monitored by color Doppler ultrasound (GE company, USA. Model: Voluson E8 Expert) before and after the treatment. (2) About 5 mL of venous blood was drawn before and after the treatment, 2 mL of which was analyzed using an automatic blood biochemical analyzer (Beckman Coulter Company, USA, model: AU680). The NT-proBNP in the whole blood was measured using enzyme-linked immunosorbent assays (ELISA) to reflect the heart failure improvement. The ELISA kits (item number: mI061452, China) were purchased from Shanghai Enzyme Union Biotechnology Co., Ltd., item number: mI061452. Origin: China.

The secondary outcomes were: (1) The remaining 3 mL of the blood samples were centrifuged at 3,000 rpm/min for 10 min, and the serum inflammatory factor levels such as the CRP, TNF-α, and IL-6 levels were measured using ELISA. The kits (item number: mI057570, mI077385, mI038115, China) were purchased from the Shanghai Enzyme Union Biotechnology Co., Ltd. (2) During the six-month follow-up, the two groups' cardiovascular and cerebrovascular events were compared, and the readmission and mortality rates were calculated. The readmission rate = the number of hospitalized patients/total cases × 100% during the follow-up period. The fatality rate = the number of patients who died of the disease/total number of cases × 100%.

Statistical analysis

SPSS 20.0 was used for the data analysis, and the enumeration data were expressed as n% using χ^2 tests. The measurement data were expressed as $\bar{x} \pm sd$, and paired t-tests were used for the before and after treatment comparisons, while the two groups were compared using independent t-tests. P<0.05 indicated that a difference was significant.

Results

Baseline data

The baseline data, such as gender, age, course of the chronic heart failure, duration of the atrial fibrillation and NYHA-FC, showed no significant differences between the two groups (P> 0.05), so the two groups were comparable. The details are shown in **Table 1**.

Heart function

After the treatment, the patients' LVEF and CO levels in the two groups were increased, and the levels in the study group were higher than the levels in the control group. There was opposite trends in the LVESD and LVEDD levels (all P<0.05). The details are shown in **Table 2**.

The NT-proBNP levels and the inflammatory factor levels

The NT-proBNP levels before the treatment in the study group and the control group we-

Table 3. Comparison of the NT-proBNP levels before and after the treatment in the two groups ($\bar{x}$ ± sd)

Groups	Time	NT-proBNP (pg/mL)
Study group (n=41)	Before treatment	3405.58±205.49
	After treatment	1584.50±193.38*,#
Control group (n=41)	Before treatment	3476.08±284.93
	After treatment	2054.40±143.05*

Note: Compared with before the treatment, *P<0.05; compared with the control group, #P<0.05. NT-proBNP: N terminal pro B type natriuretic peptide.

re (3405.58±205.49) pg/mL and (3476.08± 284.93) pg/mL respectively. And the NT-proBNP levels after the treatment in the study group and control group were (1584.50± 193.38) pg/mL and (2054.40±143.05) pg/mL), respectively. After the treatment, the NT-proBNP levels in both groups were decreased, and the level in the study group was lower than the level in the control group (all P<0.05). Similar trends were seen in the serum CRP, TNF-α, and IL-6 levels. The details are shown in **Tables 3**, **4** and **Figure 1**.

Readmission rate

After six months of follow-up, the readmission rate of the patients in the study group was significantly lower than the readmission rate of the patients in the control group (4.88% (2/41) vs. 21.95% (9/41), (P<0.05)). The details are shown in **Figure 2**.

The prognoses and the occurrence of adverse events

After the six months follow-up period, the heart failure deterioration rate and the patients' incidence of adverse events in the study group were lower than they were in the control group (all P<0.05). The details are shown in **Table 5**.

Discussion

For the heart failure patients with atrial fibrillation, whether controlling heart rate can significantly help the patient's heart function and prognosis has been a hot research topic in recent years. Most scholars believe that effectively controlling the heart rate can make the ventricles have a more sufficient filling time. This can significantly eliminate the clinical symptoms of patients with chronic heart failure, so as to improve their heart function and their prognoses [10, 11]. However, some scholars disagree [12]. The effectiveness of heart rate control in the treatment of patients with chronic heart failure and atrial fibrillation is also reaffirmed by the *2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS* [8].

In this study, the control group was given conventional anti-heart failure treatment. In addition to this treatment, the study group was treated with metoprolol to control their heart rates, with their resting heart rates reduced to 55-60 beats/min as the target heart rate. After our comparison, the results showed that the LVEF and CO levels in the patients were increased. After the treatment, the LVESD and LVEDD levels of the patients in both groups were decreased. The changes in the above indexes of the patients in the study group were more significant, suggesting that in addition to conventional anti-heart failure treatment, the effective control of the ventricular rate has a more significant improvement effect on the heart function of heart failure patients with atrial fibrillation. Grande et al. also found that selectively controlling the heart rate is beneficial to the treatment of patients with left ventricular systolic dysfunction and chronic heart failure, as the effect of controlling the ventricular rate on the increase of LVEF is more significant [13]. Ferrari et al. also found that the active control of the heart rate has a positive effect on the prognoses of patients with heart failure [14].

In this study, we found that after the treatment, the NT-proBNP level in the study group was lower than the level in the control group, suggesting that in addition to the conventional anti-heart failure treatment, the effective control of the ventricular rate can more significantly improve the symptoms of heart failure in heart failure patients with atrial fibrillation. Brain natriuretic peptide (BNP) is an important cardiac hormone. It is a vasoactive polypeptide. Although NT-proBNP is a precursor of BNP, the half-life of NT-proBNP is longer than the half-life of BNP, so NT-proBNP is usually used as a diagnostic index of heart failure instead of BNP [15-17]. Li et al. found that after the use of heart rate control drugs in the basic treatment, the ventricular rate and NT-proBNP

Table 4. Comparison of the inflammatory factor levels before and after the treatment in the two groups ($\bar{x} \pm sd$)

Groups	Time	CRP (mg/L)	TNF-α (pg/mL)	IL-6 (ng/L)
Study group (n=41)	Before treatment	28.58±4.40	4.96±1.03	10.04±2.11
	After treatment	15.40±3.28*,#	2.34±1.10*,#	7.13±1.04*,#
Control group (n=41)	Before treatment	29.11±4.93	5.11±1.30	9.97±1.94
	After treatment	20.03±4.44*	3.95±1.22*	8.40±1.57*

Note: Compared with before the treatment, *P<0.05; compared with the control group, #P<0.05.

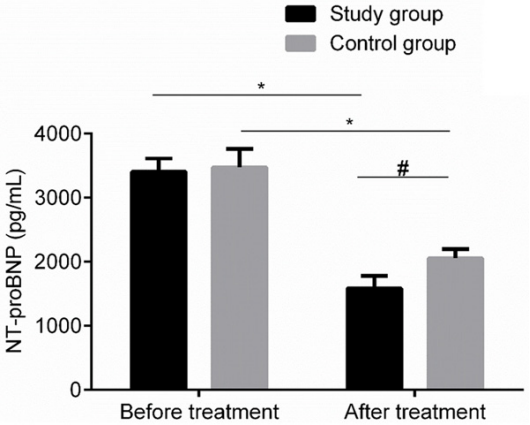

Figure 1. Comparison of the NT-proBNP levels before and after the treatment in the patients in the two groups. NT-proBNP: N-terminal pro-brain natriuretic peptide. Compared with before the treatment, *P<0.05; compared with the control group, #P<0.05.

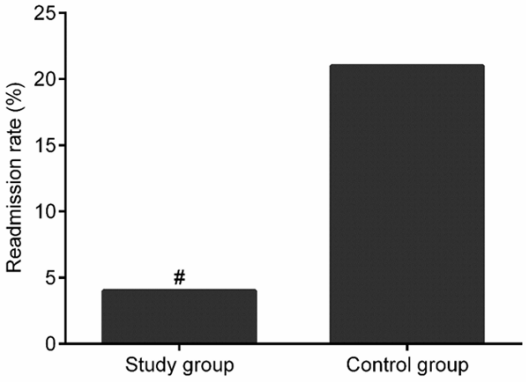

Figure 2. Comparison of the readmission rates between the two groups during the follow-up. Compared with the control group, #P<0.05.

of heart failure patients decreased significantly, suggesting that heart rate control is also very important in the treatment of heart failure [18].

In this study, it was found that after the treatment, the serum CRP, TNF-α, and IL-6 levels in the study group were lower than the levels in the control group after the treatment. This suggests that in addition to the conventional anti-heart failure treatment, the effective control of the ventricular rate can more significantly control the inflammatory state of heart failure patients with atrial fibrillation. The inflammatory factors can induce the inflammatory response, myocardial remodeling, and cardiomyocyte apoptosis, causing varying degrees of damage to heart function [19, 20]. A number of studies have confirmed that a variety of inflammatory factors are expressed at high levels in patients with heart failure, suggesting that their expression levels are closely related to the severity and prognosis of heart failure [21, 22]. Therefore, reducing the inflammatory factor levels is extremely important for preventing the development of heart failure. Pan et al. reported that the levels of a variety of serum inflammatory factors (IL-6, IL-1β, etc.) in patients with heart failure were decreased in varying degrees after the administration of high-dose metoprolol [23]. Most of these inflammatory factors can inhibit myocardial contractility and promote myocardial remodeling. After blocking their expression, the myocardial remodeling was significantly improved, as was the heart function. Finally, this study compared the readmission rates and the prognoses of the two groups during the follow-up, and we found that the readmission rate of the study group was lower than the readmission rate of the control group (4.88% vs. 21.95%), and the deterioration rate of heart failure and the incidence of adverse events were also lower than they were in the control group. This shows that in addition to the conventional anti-heart failure treatment, the effective control of the ventricular rate should improve patient prognosis.

In summary, in addition to the conventional anti-heart failure treatment, the effective control of the ventricular rate can more significant-

Table 5. The prognosis and the occurrence of adverse events in the two groups of patients (n, %)

Groups	The deterioration rate of heart failure	Adverse events			
		Cerebral embolism	Lung infection	Cardiac death	Incidence
Study group (n=41)	1 (2.44)	0 (0.00)	1 (2.44)	0 (0.00)	1 (2.44)
Control group (n=41)	6 (14.63)	2 (4.88)	1 (2.44)	3 (7.32)	6 (14.63)
χ^2	3.905	/	/	/	3.905
P	0.048	/	/	/	0.048

ly alleviate the heart failure symptoms and the inflammatory response, and improve the heart function and the prognosis to a certain extent in heart failure patients with atrial fibrillation. However, our study cohort was small, and the follow-up time was short, so the effect of controlling the ventricular rate on the long-term prognoses of patients with heart failure still needs to be confirmed using a large study cohort and a long-term follow-up study.

Disclosure of conflict of interest

None.

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