Effect of Diltiazem Hydrochloride on Cardiac Function and Prognosis in Patients with Atrial Fibrillation–Mediated Cardiomyopathy

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Research Article

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Abstract

Background

In previous studies, faster heart rates in patients with atrial fibrillation combined with heart failure have been associated with poor long-term patient prognosis. However, the classical pharmacological regimen of beta-blockers has not reduced mortality in patients with atrial fibrillation combined with heart failure. Therefore, in patients with atrial fibrillation combined with heart failure with an ejection fraction >40%, we further screened patients with a diagnosis of atrial fibrillation cardiomyopathy and compared the combination of diltiazem with standard anti-heart failure drug therapy.

Objective:

To observe the effect of diltiazem hydrochloride on cardiac function and prognosis in patients with Atrial Fibrillation–Mediated Cardiomyopathy.

Methods:

A total of 186 patients diagnosed with atrial fibrillation–mediated cardiomyopathy who were admitted to the First Affiliated Hospital of Zhengzhou University from August 2018 to June 2020 were randomly divided into two groups: 93 cases in the experimental group and 93 cases in the control group, both groups were given standardized pharmacological treatment for heart failure (diuretics, digoxin, β-blockers, perindopril), and the experimental group was given diltiazem 30 mg on the basis of standardized treatment, 3 times a day. The patients were followed up for 30 days to observe the target heart rate <110 beats/min, left ventricular ejection fraction, proBNP, the rate of decrease in activity tolerance during the treatment period, and readmission rate within 30 days.

Results:

After the addition of diltiazem, the attainment rate of target heart rate was significantly higher in the experimental group than in the control group ($p<0.05$) . The improvement of left ventricular ejection fraction and proBNP was more significant in the experimental group than in the control group ($p<0.05$). The incidence of decreased activity tolerance during the follow-up period was higher in the experimental group than in the control group, but the difference was not statistically significant ($p>0.05$). The readmission rate for heart failure within 30 days was significantly lower in the experimental group than in the control group ($p < 0.05$).

Conclusion

Diltiazem hydrochloride is effective in improving cardiac function and prognosis in patients with atrial fibrillation–mediated cardiomyopathy, and is a safe and effective method.

Background:

Atrial fibrillation–mediated cardiomyopathy, as a subtype of patients with heart failure combined with atrial fibrillation, is essentially reversible heart failure mediated by a single cause, atrial fibrillation. It is now believed that patients with atrial fibrillation under prolonged rapid and irregular cardiac cycles can lead to heart enlargement and reduced ejection fraction, which in turn leads to heart failure. When the patient's heart rhythm is restored or the ventricular rate is tightly controlled, heart failure can be partially improved or even completely corrected. The development of atrial fibrillation–mediated cardiomyopathy can lead to exacerbation of pre-existing heart failure or cardiomyopathy, and some studies have shown that atrial fibrillation–mediated cardiomyopathy accounts for approximately 10% of patients with dilated cardiomyopathy[1]. Although most patients receive standard anti-heart failure treatment, the attainment rate of target heart rate (<110 beats/min at rest) in patients with atrial fibrillation–mediated cardiomyopathy is still suboptimal in clinical work-up, and faster heart rate in patients with atrial fibrillation–mediated cardiomyopathy is associated with poor long-term patient prognosis[2]. Therefore, strict control of ventricular rate in patients with atrial fibrillation–mediated cardiomyopathy would be an important goal to improve the prognosis of atrial fibrillation–mediated cardiomyopathy.

1 Objects And Methods:

1.1 Object:

186 patients admitted for heart failure combined with atrial fibrillation from August 2018 to June 2020, who were clinically diagnosed as atrial fibrillation–mediated cardiomyopathy after ancillary examinations and medical history, were selected and randomly divided into two groups: 93 cases in the experimental group and 93 cases in the control group. Inclusion criteria: 1. Age 35-75 years old, 2. Electrocardiogram suggestive of rapid atrial fibrillation (heart rate >110 beats/min) 3. New York cardiac function classification reached class II-III, left ventricular ejection fraction (LVEF) value >40%, 4. Presence of contraindication to cardioversion or no plan for cardioversion in the short term, 5. In line with the characteristics of atrial fibrillation–mediated cardiomyopathy: (1) able to provide cardiac ultrasound information before the occurrence of atrial fibrillation to confirm normal heart function, (2) and the only cause of this deterioration of cardiac function is atrial fibrillation, other factors that can reduce cardiac function need to be excluded, (3) non-required condition for group enrollment: heart failure can improve or even recover after strict control of ventricular rate in atrial fibrillation. Exclusion criteria: 1. Previous clear history of organic heart disease such as valvular disease, hypertensive heart disease, alcoholic cardiomyopathy, hyperthyroid cardiomyopathy, etc. 2. Presence of contraindications to the use of diltiazem hydrochloride. 3. Severe hepatic and renal insufficiency. Each enrolled patient signed the informed consent form for the trial.

1.2 Methods

1.2.1 Drug treatment. All patients in the group were given standardized drug treatment and anticoagulation for heart failure combined with atrial fibrillation. The dose and method of drug

administration during the 30-day follow-up period were digoxin tablets (Colibri, Sanofi Pharmaceutical Co., Ltd., H3301738) 0.125 mg once daily, bisoprolol tablets (Chengdu Yuan Dong Biopharmaceutical Co. H20083007) 2.5mg once daily, Furosemide for injection (Hainan Huanglong Pharmaceutical Co., Ltd., H20060659) 40mg once daily by sedation, after 2 days of continuous use change to Furosemide tablets (Tianjin Lisheng Pharmaceutical Co., Ltd., H12020163) 20 mg once daily, Spironolactone (Sinopharm Group Rongsheng Pharmaceutical Co. Ltd., H20103382) 4 mg once daily, Rivaroxaban tablets (Bayer Healthcare Ltd., J20180077) 20 mg once daily, warfarin tablets (Qilu Pharmaceutical Co., Ltd., H37021314) titrated with an international normalized ratio (INR) between 2-3 and other drugs. In the experimental group, diltiazem (Zhejiang Asia-Pacific Pharmaceutical Co., Ltd., H33020112) 30 mg 3 times/day was given on the basis of standardized drug treatment, and patients were followed up in the outpatient clinic for 30 days.

1.3 Observation indicators

After 7 days of drug treatment, patients were observed to have a target heart rate <110 beats/min at rest, LVEF values before and after treatment obtained by Philips Heart IE33 cardiac ultrasound using Simpson's method and brain natriuretic peptide precursor values (proBNP) by Getein 1100 immunofluorescence quantitative analyzer, short-term activity tolerance decline in cardiac function during treatment (evaluated by 6-minute walk test), the readmission rate within 30 days.

1.4 Statistical treatment

The measurement data were expressed by ($\bar{\chi} \pm s$) and t-test was used for comparison between groups, and the count data were expressed by percentages and χ^2 test was used for comparison between groups, and the difference was considered statistically significant at $P<0.05$. Each data was analyzed by SASV9 statistic software.

2 Results:

2.1 Baseline information

Comparison of general information between patients in the diltiazem group and the standard treatment group (Table 1): there were no statistically significant differences between the two groups in terms of gender, age, risk factors for cardiovascular disease, clinical manifestations, left ventricular function, blood creatinine level, dose used for standardized drug therapy, and whether or not they smoked.

Table 1
general clinical information x̄ ±s

Projects *P*	Experiment group (93 cases)	Control group (93 cases)	χ^2/t value	*P*
Male, n (%)	57(61.3)	56(60.2)	0,023	0.881
Age, years	64.3 ± 5.3	65.7 ± 5.1	1.836	0.068
Diabetes mellitus, n (%)	0	0	-	-
Hypertension, n (%)	0	0	-	-
Blood creatinine value/(μmol/L)	71.38 ± 8.72	72.83 ± 8.21	1.168	0.245
Hyperlipidemia, n (%)	15(34.9)	16(37.2)	0.039	0.844
Smoking history, n (%)	23(53.5)	25(58.1)	0.112	0.738
LVEF (before treatment), %	46.8 ± 3.7	45.9 ± 3.9	1.614	0.108
Digoxin, n (%)	93(100.0)	93(100.0)	-	-
Furosemide, n (%)	93(100.0)	93(100.0)	-	-
Spironolactone, n (%)	93(100.0)	93(100.0)	-	-
Beta-blockers, n (%)	93(100.0)	93(100.0)	-	-
Perindopril, n (%)	93(100.0)	93(100.0)	-	-
Warfarin, n (%)	15(16.1)	17(18.3)	0.151	0.698
Rivaroxaban, n (%)	78(83.9)	76(81.7)	0.151	0.698
Duration of atrial fibrillation, days	126 ± 34.3	137 ± 29.5	2.345	0.200
proBNP pre-treatment, pg/ml	12382 ± 872.4	11137 ± 1132.7	8.398	0.093
Note: "-" is omitted; LVEF is left ventricular ejection fraction; proBNP is brain natriuretic peptide precursor;				

2.2 Comparison of observed indicators

The target heart rate attainment rate of patients in the experimental group (86%) was significantly higher than that of the control group (39.5%), and the difference was statistically significant ($P < 0.05$). The improvement of left ventricular ejection fraction (EF) and ProBNP in the experimental group was significantly better than that in the control group ($P < 0.05$), and the readmission rate within 30 days in the experimental group (4.7%) was significantly lower than that in the control group (20.9%) ($P < 0.05$). The

rates of deterioration of cardiac function during treatment were 11.6% and 9.3% in the experimental and control groups, respectively, but the differences were not statistically significant P > 0.05.

Table 2
comparison of observed indicatorsn,(%)

Projects	Experimental group (93 cases)	Control group (93 cases)	χ^2/t value	*P*
Target heart rate attainment rate, n (%)	80(86.0)	37(39.5)	42.601	0.000
After LVEF treatment, (%)	52.4 ± 3.2	47.3 ± 4.2	6.315	0.000
After proBNP treatment,pg/ml	1542 ± 214.5	2533 ± 282.6	26.937	0.000
Endurance decline rate n (%)	5(11.6)	4(9.3)	0.117	0.733
30-day readmission rate n (%)	2(4.7)	9(20.9)	4.735	0.030
Notes:				

3 Discussion:

The diagnosis of atrial fibrillation–mediated cardiomyopathy is currently difficult, and when atrial fibrillation–mediated cardiomyopathy progresses to the point where the myocardial lesions are irreversible, cardiac function does not improve significantly despite ventricular rate or rhythm control. In addition, in patients with a combination of other types of cardiomyopathy, atrial fibrillation may further worsen cardiac function, and the improvement in cardiac function may be masked in these patients when the ventricular rate is controlled. In some patients, paroxysmal atrial fibrillation is the main manifestation, and because of the short duration of the episodes, they did not seek medical attention in time until they develop cardiac insufficiency. The above reasons make the diagnosis of atrial fibrillation–mediated cardiomyopathy more difficult. Therefore, this study combined with the actual clinical situation, it must be clear that atrial fibrillation is the only cause of unexplained heart failure or causes deterioration of heart failure before the patients are enrolled. It was also combined with the patient's clinical history such as the temporal relationship between new onset of atrial fibrillation or increased atrial fibrillation load and the occurrence of cardiomyopathy: new onset of heart failure after atrial fibrillation that could not be explained by other causes; the simultaneous occurrence of heart failure and atrial fibrillation; the recovery of cardiac function after rhythm or ventricular rate control; the rapid deterioration of cardiac function after the recurrence of atrial fibrillation; and the rapid decrease of BNP level after the restoration of sinus rhythm or ventricular rate control in atrial fibrillation.

There is still controversy about the target heart rate target values in patients with atrial fibrillation–mediated cardiomyopathy. In the RACE II study published in NEJM in 2010 [3], 614 patients with permanent atrial fibrillation were randomly assigned to either a lenient strategy (resting heart rate < 110

bpm) or a strict strategy (resting heart rate < 80 bpm and mild exercise < 110 bpm) with the primary endpoint set at cardiac death, heart failure hospitalization, stroke, systemic embolism, and bleeding with a composite endpoint of fatal arrhythmia. After 3 years of follow-up, 86% of the target heart rate was achieved in the lenient strategy group and only 53% of the target heart rate was achieved in the strict strategy group. The primary endpoint eventually occurred in 12.9% of the lax strategy group and 14.9% of the strict strategy group, with the lax strategy not inferior to the strict strategy (the non-inferiority threshold was set at -2%). In subsequent analyses, cardiac remodeling and quality of life were also not significantly different between the two strategies. Therefore, a more lenient ventricular rate control strategy was adopted in this study, with a target ventricular rate control goal of < 110 bpm at rest, but more stringent ventricular rate control may be considered if patients have significant symptoms, deteriorating left ventricular function, or a CRT in place despite the lenient goal.

Although the current CASTLE-AF study, a prospective randomized controlled trial in the field, confirmed[4] that 363 patients with heart failure combined with atrial fibrillation were randomized into catheter ablation and drug treatment groups, the primary composite endpoint (all-cause mortality + heart failure worsening rehospitalization rate) decreased by 16.1% in the catheter ablation group and catheter ablation treatment was superior to drug treatment. However, recurrent recurrences may still exist with rhythm control, whereas ventricular rate control has the advantage of being safe, effective, and easily accepted by patients. Besides, the 2019 ACC/AHA guidelines for the management of atrial fibrillation include ventricular rate control as the first-line treatment option for patients with atrial fibrillation–mediated cardiomyopathy[5]. Therefore heart rate control should be used as a basic treatment for rhythm control. Although β-blockers are the most widely used ventricular rate control agents for atrial fibrillation, some studies have shown that β-blockers do not reduce mortality in patients with atrial fibrillation combined with heart failure[6].

Diltiazem hydrochloride is a non-dihydropyridine calcium channel blocker and is recommended in guidelines as a first-line agent for ventricular rate control along with beta-blockers. Because of the limited use of diltiazem hydrochloride in patients with heart failure with an ejection fraction of less than 40% and the presence of some negative inotropic effects, there is a gap in clinical studies on the prognosis of patients with atrial fibrillation–mediated cardiomyopathy with the use of diltiazem hydrochloride. In the present study, the target heart rate compliance rate, left ventricular ejection fraction, ProBNP improvement and 30-day readmission rate in the experimental group with diltiazem were significantly better than those in the control group, indicating that diltiazem hydrochloride has a protective effect on patients with atrial fibrillation–mediated cardiomyopathy. Although diltiazem hydrochloride has some negative inotropic effects, there was no significant increase in the short-term deterioration rate of cardiac function in the experimental group in this study, which is generally consistent with its safety profile reported in previous similar studies[7]. The mechanism of the protective effect of diltiazem hydrochloride in patients with atrial fibrillation–mediated cardiomyopathy is not well understood, and it may be related to factors such as controlling the rapid ventricular rate by inhibiting the atrioventricular node, increasing myocardial tissue

perfusion, and thus improving diastolic function; improving abnormal calcium regulation and reducing myocardial remodeling through calcium channel blockade.

In this study, a quadruple combination of standardised drug therapy with diltiazem was shown to be superior to the classic three-drug Golden Triangle regimen in patients with atrial fibrillation cardiomyopathy without previous organic heart disease, and significantly improved cardiac function and short-term prognosis in patients with atrial fibrillation cardiomyopathy in the short term. Therefore, the quadruple combination of diltiazem is expected to become a standardised treatment for patients with atrial fibrillation cardiomyopathy in the future. This study also provides a new approach to the clinical management of patients with heart failure combined with atrial fibrillation. Before treating a patient with heart failure combined with atrial fibrillation, we need to first ask the patient about the timing of the onset of atrial fibrillation in relation to the onset of cardiomyopathy in order to initially determine whether the patient has atrial fibrillation cardiomyopathy. If atrial fibrillation cardiomyopathy is present we can offer patients a more individualised quadruple therapy than classical drug therapy.In summary, diltiazem hydrochloride can effectively improve cardiac function and prognosis in patients with atrial fibrillation–mediated cardiomyopathy, and is a safe and effective method.

Declarations:

Compliance with Ethical Standards:

1. The data that support the findings of this study are available from the corresponding author upon reasonable request.

2. Yongrong Liu directly participated in the preparation and design of the experiment, carried out the research and collected data, and completed the writing of the article, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript."

Dan Wang provided support for the work, carried out statistical analysis and reviewed the content.

3. (In case of Funding) Funding:No.

Conflict of Interest:

No.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The trial was approved by the ethics committee at each study center. All the patients provided written informed consent.

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