

Anticoagulation efficacy of dabigatran etexilate for left atrial appendage thrombus in patients with atrial fibrillation by transthoracic and transesophageal echocardiography

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Abstract

To evaluate the anticoagulation efficacy of dabigatran etexilate for left atrial appendage (LAA) thrombus resolution in patients with atrial fibrillation by transthoracic echocardiography and transesophageal echocardiography, and to investigate the anticoagulation factors.

A total of 58 atrial fibrillation patients with LAA thrombus in our hospital were enrolled. After dabigatran etexilate anticoagulation for 3 months, the patients were divided into the effective group and ineffective group according to dissolution of thrombosis. The baseline data and the left atrial diameter (LAD), left atrial ejection fraction (LAEF), left ventricular ejection fraction, LAA flow velocity (LAA-v), and LAA thrombus size before and after anticoagulation treatment were recorded, and the measurement index were statistically analyzed.

After the patients received anticoagulation treatment for 3 months, 15 patients had complete dissolution, thrombus in 21 patients reduced significantly, and the complete dissolution rate was 25.9% (15/58), the effective rate of dissolution was 62.1% (36/58). Compared with the ineffective group, the proportion of persistent atrial fibrillation and LAD in effective group were lower than those in the ineffective group, the LAEF and LAA-v in the effective group were higher than those in the ineffective group, and the differences were statistically significant ($P < .05$). Multivariate logistic regression analysis on the baseline data and each ultrasound index showed that the type of atrial fibrillation, LAD, LAEF, and LAA-v were independently associated with the efficacy of anticoagulation ($P < .05$).

Dabigatran etexilate is effective in dissolution of LAA thrombus in patients with atrial fibrillation, and the atrial fibrillation type, LAD, LAEF, and LAA-v are significantly related with the efficacy of anticoagulation.

Abbreviations: AF = atrial fibrillation, LAA = left atrial appendage, LAA-v = LAA flow velocity, LAD = left atrial diameter, LAEF = left atrial ejection fraction, LVEF = left ventricular ejection fraction, TEE = transesophageal echocardiography, TTE = transthoracic echocardiography.

Keywords: anticoagulation, atrial fibrillation, dabigatran etexilate, left atrial appendage thrombu

1. Introduction

Atrial fibrillation (AF) is the most common and sustained cardiac arrhythmia, which occurring in 1% to 2% of the general population,^[1] while thrombotic disease is its main complication, and AF is associated with high morbidity and mortality.^[2-4] Due to the growing prevalence and the incidence of AF across the world, the emergence of this disorder has been confirmed as a

global epidemic through recent epidemiologic statistics.^[5] In 2010, it was estimated that about 33.5 million individuals, or 0.5% of the world's population, had AF.^[6] The increasing in the epidemiology of AF is expected to be continued with the aging of societies worldwide.^[7] Until 2009, Warfarin and other vitamin K antagonists were the only available oral anticoagulants. In recent years, many new oral anticoagulants, such as dabigatran etexilate, have been approved for anticoagulation in patients with nonvalvular AF, and it may reduce the risk of bleeding while anticoagulation.^[8] However, the research data about antithrombotic efficacy is very small. The purpose of this study was to evaluate the anticoagulation efficacy of dabigatran etexilate on left atrial appendage (LAA) thrombus in patients with AF by a combination of transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE), and to explore the factors influencing anticoagulant efficacy in order to provide evidence for clinical treatment.

2. Materials and methods

2.1. Research subjects

A total of 58 patients with AF who treated in the department of cardiovascular medicine in our hospital from June 2016 to May 2017 were enrolled in this study. TEE was used as the gold standard for detecting LAA thrombus. A total of 58 patients with

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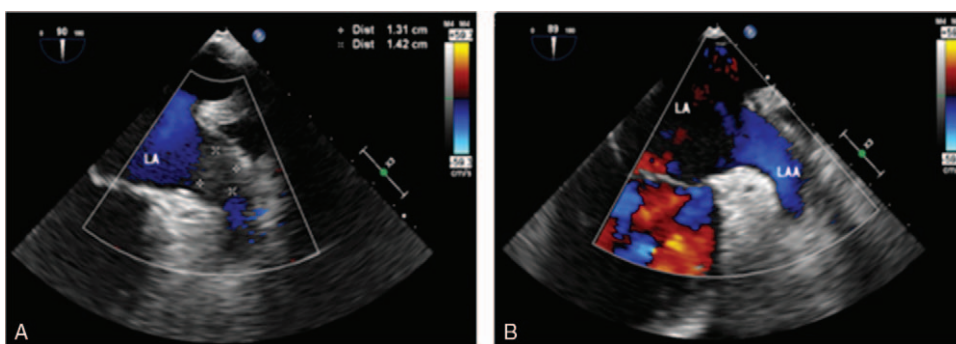


Figure 1. After anticoagulant therapy, thrombus completely dissolved. (A) Female patient, 52 years old, low echo could be observed at the entrance of left atrial appendage, where the blood flow detours. (B) In the same patient, the thrombus was completely dissolved after dabigatran etexilate anticoagulant therapy for 3 months, blood flow in left atrial appendage was well filled.

AF with LAA thrombus were selected. The age of patients was 41 to 72 years old with a mean age of 59.2 ± 7.7 years. Among them, 28 (48.3%) cases had paroxysmal AF and 30 (51.7%) cases had persistent AF; 40 (69.0%) cases were male and 18 (31%) cases were female; hypertension in 24 (41.4%) cases, and diabetes in 13 (22.4%) cases. All patients were regularly treated with dabigatran etexilate capsule (150mg, orally, 2 per day) anticoagulant therapy for 3 months, and the thrombus shrank to more than 60% as anticoagulant effective, the patients were divided into effective and ineffective group, all selected patients signed informed consent.

Exclusion criteria were: patients with rheumatic heart disease and cardiomyopathy; patients with acute coronary syndromes; and patients cannot tolerate TEE, patients with infectious diseases and patients with severe liver and kidney dysfunction.

2.2. Instruments and methods

Philips EPIQ7C color Doppler ultrasound diagnostic apparatus, transthoracic ultrasound probe X5-1 with the frequency of 1 to 5 MHz; multiplane transesophageal ultrasound probe X7-2t with the frequency of 5 to 9 MHz. During the examination, the left atrial diameter (LAD) and left ventricular ejection fraction (LVEF) were measured in left lateral decubitus position by TTE, and the left atrial ejection fraction (LAEF) on standard apical 4-chamber heart section was measured by Simpson method. Patients were fasting for 12 hours before TEE, and buprenor-

phine hydrochloride gel (10 mL, 300mg) was used for oropharyngeal and esophageal surface infiltration anesthesia 15 to 20 minutes, TEE check was performed to detect the left atrial and LAA thrombosis, and the thrombus size and LAA flow velocity (LAA-v) were measured. All sections were collected in 3 consecutive cardiac cycles and took the average, then stored for analysis.

2.3. Statistical analysis

SPSS 19.0 software was used for statistical analysis of the data. Counting data were expressed as n (%), and Chi-squared test was used. The normally distributed measurement data were expressed as $(x \pm s)$ and *t* test was used. The multivariate logistic regression analysis was performed on baseline data of patients and each ultrasound index to explore the factors that affect the efficacy of anticoagulation. *P* < .05 was considered statistically significant.

3. Results

3.1. Thrombolysis and each ultrasonic indicators self control before and after anticoagulation

Fifty-eight patients with LAA thrombus were treated with anticoagulant therapy for 3 months. Thrombus was completely dissolved in 15 patients (Fig. 1), thrombus was significantly reduced in 21 patients (Fig. 2), thrombus in 22 patients showed

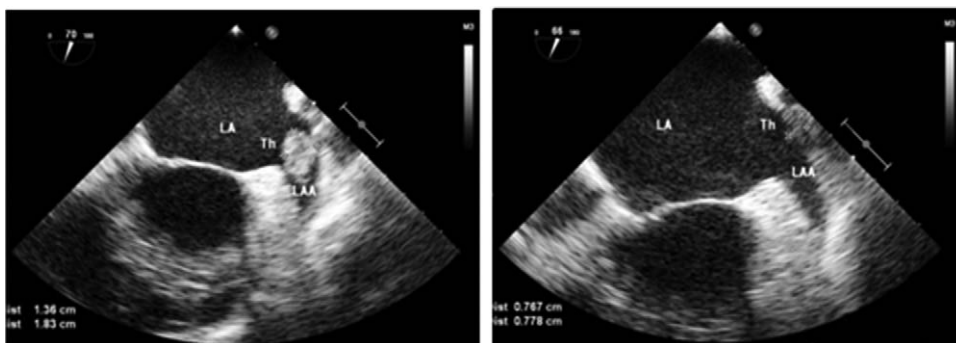


Figure 2. After anticoagulant therapy, thrombus was reduced significantly. (A) Male patient, 52 years old, substantial thrombus image could be observed at the entrance of left atrial appendage. (B) In the same patient, thrombus was significantly reduced and showed in flocculent after dabigatran etexilate anticoagulant therapy for 3 months.

Table 1

The patient's cardiac structure and function indicators self control before and after anticoagulant therapy.

Item	Before anticoagulant therapy	After anticoagulant therapy	P-value
LAD, mm	40.17 ± 4.28	41.09 ± 5.93	.129
LAEF, %	35.74 ± 10.93	38.58 ± 14.54	.075
LVEF, %	55.15 ± 7.17	54.98 ± 7.08	.906
LAA-v, m/s	0.27 ± 0.06	0.26 ± 0.07	.306

LAA-v = left atrial appendage flow velocity, LAD = left atrial diameter, LAEF = left atrial ejection fraction, LVEF = left ventricular ejection fraction.

no significant change or even increased. The complete dissolution rate was 25.9% (15/58) and the dissolution efficiency was 62.1% (36/58). A total of 19 patients had left atrial or LAA spontaneous echo contrast (was the smoke-shaped low echo shadow expressed in heart chamber under low velocity swirling blood flow noncontrast, generally had no obvious contour, and caused by the larger hematocrit superimposed on each other, is considered to be the prethrombotic state), and the spontaneous echo contrast was disappeared in 5 cases after treatment, reduced in 9 cases. The cardiac structure and function of patients showed no significant change before and after anticoagulant therapy ($P > .05$) (Table 1).

3.2. Comparison of baseline data and ultrasound parameters of patients between effective group and ineffective group before and after anticoagulant therapy

After anticoagulant therapy, the proportion of persistent AF and LAD of patients in the effective group were lower than those in the ineffective group, while the LAEF and LAA-v in the effective group were significantly higher than those in the ineffective group, and the differences were statistically significant ($P < .05$). There were no significant differences in other baseline data and LVEF between 2 groups ($P > .05$) (Table 2).

3.3. Analysis of related factors influencing the dabigatran etexilate anticoagulant therapy

Univariate logistic regression analysis showed that age, type of AF, LAD, LAEF, LVEF, and LAA-v were associated with anticoagulation efficacy ($P < .05$). Multivariate logistic regression

Table 3

Multivariate logistic regression analysis on the factors that influencing the dabigatran etexilate anticoagulation effect.

Item	Wald χ^2	P-value	OR	95% CI
Age	1.77	.183	0.93	0.84–1.03
Atrial fibrillation type	5.72	.017	0.11	0.02–0.67
LAD	4.77	.029	0.83	0.71–0.98
LAEF	6.34	.012	1.21	1.04–1.40
LVEF	1.97	.161	1.09	0.97–1.22
LAA-v	6.66	.010	2.61	7.63–8.93

CI = confidence interval, OR = odds ratio, LAA-v = left atrial appendage flow velocity, LAD = left atrial diameter, LAEF = left atrial ejection fraction, LVEF = left ventricular ejection fraction.

analysis of the above indexes showed that the AF type, LAD, LAEF, and LAA-v were independently related to the anticoagulation efficacy ($P < .05$) (Table 3).

4. Discussion

The AF is an independent risk factor for stroke. For patients with thrombotic AF, the rational use of anticoagulants to prevent thromboembolism is the focus of AF treatment.^[9,10] Warfarin is the first choice of traditional anticoagulants. However, its therapeutic efficacy is sensitive to food and drugs, and its therapeutic window is narrow and its International Normalized Ratio (INR) needs to be monitored on a regular basis, which limits the anticoagulant therapy in some patients.^[11] Since the advent of new oral anticoagulants in 2010, a new drug option has been proposed for anticoagulant therapy in patients with AF. Dabigatran etexilate was first approved for the anticoagulant therapy in patients with nonvalvular AF. Compared with Warfarin, dabigatran etexilate has a short half-life period, rapid onset, is free from other foods and drugs and does not require the monitoring of INR, and is more advantageous in the prevention of stroke in patients with AF.^[12] In this study, 58 AF patients with LAA thrombus were treated with dabigatran etexilate anticoagulant therapy, the thrombosis complete dissolution rate was 25.9%, the effective rate of dissolution was 62.1%, indicating that dabigatran etexilate can effectively dissolve some of the LAA thrombus in patients with AF. Ferner et al^[13] also showed that dabigatran etexilate can reduce or completely dissolve the thrombus in the LAA, and no stroke or thromboembolism occurred during the medication.

Table 2

Comparison of baseline data and ultrasound parameters of patients after dabigatran etexilate anticoagulant therapy.

Item	Effective group (n=36)	Ineffective group (n=22)	P-value
Gender (male)	26	14	.577
Age (y)	57.88 ± 5.6	61.0 ± 9.94	.341
Hypertension, n (%)	14 (38.9)	10 (45.5)	.430
Diabetes, n (%)	9 (25.0)	4 (18.2)	.554
Atrial fibrillation type			.012
Paroxysmal atrial fibrillation, n (%)	22 (61.1)	6 (27.3)	–
Persistent atrial fibrillation, n (%)	14 (38.9)	16 (72.7)	–
PT, s	13.83 ± 1.23	15.24 ± 2.01	.201
APTT, s	45.28 ± 16.24	41.94 ± 5.67	.664
CREA, $\mu\text{mol/L}$	72.82 ± 29.47	56.99 ± 12.61	.344
LAD, mm	38.50 ± 4.38	43.10 ± 6.25	.027
LAEF, %	46.42 ± 11.76	28.85 ± 10.59	.001
LVEF, %	56.55 ± 5.83	53.82 ± 8.18	.334
LAA-v, m/s	0.30 ± 0.06	0.21 ± 0.05	.003

APTT = activated partial thromboplastin time, CREA = serum creatinine, LAD = left atrial diameter, LAEF = left atrial ejection fraction, LVEF = left ventricular ejection fraction, PT = prothrombin time.

In addition to the reduction or disappearance of thrombus in some patients following anticoagulant therapy, we also observed that in some patients with left atrial or LAA spontaneous echo contrast, the spontaneous echo contrast was disappeared or reduced after anticoagulant therapy. Vestito et al^[14] made a comparative study of the effects of dabigatran and Warfarin on spontaneous echo contrast in LAA of patients with AF, and the results showed that the spontaneous echo contrast was disappeared or reduced in LAA of patients with AF after dabigatran anticoagulant therapy, while after Warfarin anticoagulant therapy, there was no significant change in spontaneous echo contrast. Mahony et al^[15] also observed a decrease in the degree of LA spontaneous echo contrast during antiplatelet therapy. In summary, dabigatran etexilate can reduce the risk factor of thrombus formation in LAA-blood cells spontaneous echo contrast. However, there were no significant changes in LAEF, LVEF, and LAA-v before and after anticoagulant therapy, indicating that dabigatran, as a thrombin factor IIa activity inhibitor, can only affect hematologic parameters, but had no significant effect on hemodynamics.

By comparing the effective group and the ineffective group, LAEF and LAA-v showed significant differences between the 2 groups, and multivariate logistic regression analysis also showed that the anticoagulant effect was independently related to LAEF and LAA-v.

The comparative study between effective group and ineffective group showed that there were significant differences in LAEF and LAA-v between 2 groups, and multivariate logistic regression analysis also showed that the anticoagulation effect was independently related to LAEF and LAA-v. The atrial systolic and diastolic functions were decreased in patients when AF occurred, the LAD was increased, and the state of blood hypercoagulability was aggravated, eventually leading to reducing of left atrial ejection and atrial appendage velocity,^[9] indicating that persistent AF can reduce the efficacy of dabigatran etexilate anticoagulant therapy by affecting the left atrial and LAA function. Due to the special anatomy of the LAA, the pectinate muscle artifact of LAA, or the LAA thrombus whose size is lower than the macroscopic resolution, TEE has certain misdiagnosed rate and omission diagnostic rate in the diagnosis of LAA thrombus.

In this study, among the 58 patients with AF with LAA thrombus, the patients with persistent AF was accounted for 51.7%, after anticoagulant therapy for 3 months, the patients with persistent AF was accounted for 38.9%, while in the ineffective group, the patients with persistent AF was up to 72.7%. Therefore, during anticoagulant therapy, doctors should pay attention in improving the patient's cardiac function, especially the left atrial function, and for the patients with longer duration of AF, the anticoagulation therapy time should be extended accordingly.

5. Conclusion

Dabigatran etexilate, as a direct thrombin inhibitor, can effectively dissolve the LAA thrombus in some patients with AF. The type of AF, LAD, LAEF, and LAA-v are independently associated with the efficacy of anticoagulant therapy for LAA thrombus. TEE can accurately detect the LAA thrombus and can evaluate the efficacy of anticoagulant therapy and its influencing factors.

Author contributions

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