The differences of atrial thrombus locations and variable response to anticoagulation in nonvalvular atrial fibrillation with ventricular cardiomyopathy

Hao Zhang MD, PhD1,2 | Miao Yu MD1 | Yu Xia MD1 | Xiaofeng Li MD1 | Jun Liu MD, PhD1 | Pihua Fang MD, PhD1

1Chinese Academy of Medical Sciences and Peking Union Medical College, Fuwai Hospital, Beijing, China
2Department of Cardiology, Chongqing General Hospital, University of Chinese Academy of Sciences, Chongqing, China

Correspondence
Jun Liu, No. 167, Beilishi Road, Xicheng District, Beijing City, China.
Email: liujundoctor@163.com

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Abstract
Objectives: This study aims to research the clinical features of atrial thrombi in patients with nonvalvular atrial fibrillation (AF).

METHODS: This study included 191 patients of AF who had atrial thrombi. One hundred and twenty-eight of them were assigned into nonventricular cardiomyopathy group (non-VCM), and the remaining 63 into ventricular cardiomyopathy group (VCM). After atrial thrombi diagnosed, all patients had taken oral anticoagulant therapy. The resolution rates of thrombi within 12 months were compared between the two groups, as well as the locations of thrombi.

Results: Of all 191 patients, 161 had thrombi only detected in left atrial appendage (LAA), 20 in both left atrium (LA) and LAA, six in LA only, and four in right atrium only. More patients had thrombi out of LAA in the VCM group than in the non-VCM group (30.2% vs 8.6%, P < .001). After propensity score matching, the atrial thrombi were resolved faster in the non-VCM group than in the VCM group (mean time length: 22 ± 2 weeks vs 30 ± 3 weeks, P = .038), and the resolution rate within 12 months was higher in the non-VCM group than in the VCM group (88.7% vs 61.4%, Log-rank, P = .038). In Cox proportional hazards model, absence of ventricular cardiomyopathy was an independent predictor for the resolution of atrial thrombus (hazard ratio: 1.76; P = .035).

Conclusions: The patients of atrial fibrillation with ventricular cardiomyopathies have higher incidence of thrombosis in the body of left atrium or right atrium. And the resolution rate was lower in these patients.

KEYWORDS
anticoagulation, atrial fibrillation, atrial thrombus, location of thrombus, ventricular cardiomyopathy

1 | INTRODUCTION

Atrial fibrillation (AF) is a common cardiac arrhythmia, and the estimated age-standardized prevalence of AF was 0.78% in men and 0.76% in women in a Chinese investigation.1 AF is associated with the development of atrial thrombus, especially in the left atrial appendage (LAA), which is considered the most common source of stroke and systemic embolisms.2,3 However, in...
some patients with AF, the atrial thrombi can take place out of
LAA, and the outcomes of resolution may vary from different
conditions. Consequently, we performed a retrospective study
to research the clinical features and variable responses to anti-
coagulation in AF patients complicated with cardiomyopathy and
ischemic heart disease.

2 | Methods

2.1 | Study population and groups

Consecutive patients were retrospectively assessed from Fuwai
Hospital between May 2011 and June 2018. The criteria for inclusion
were: (1) Nonvalvular atrial fibrillation; (2) Age ≥18 years old; (3) First
time to detect atrial thrombi in Fuwai hospital. The exclusion crite-
rion were: (1) Valvular atrial fibrillation; (2) History of cardiac surgery.
This study was approved by our institutional ethics committee. The
atrial thrombi were diagnosed by at least one of the following imaging
methods: transesophageal echocardiography (TEE), cardiac computed
tomographic angiography, cardiovascular magnetic resonance imaging,
or transthoracic echocardiography (TTE) to diagnose right atrial
thrombus.

Participants in this study were assigned into two groups: ven-
tricular cardiomyopathy group (VCM) and nonventricular cardiomy-
opathy group (non-VCM). Cardiomyopathy is a myocardial disorder
that the heart muscle is structurally or functionally abnormal in the
absence of some secondary disorders as defined by European
Society of Cardiology working group 4. In our study, the VCM group
included patients with these cardiomyopathies and ischemic heart
disease.

2.2 | Comparison of clinical features

The baseline characteristics were compared between the two
groups mentioned above, including left atrial antero-posterior di-
diameter (LAAPD), left ventricular end diastolic diameter (LVEDD)
and left ventricular ejection fraction (LVEF) measured by echo-
cardiography. And CHA2DS2-VASc, CHADS2, HAS-BLED scores
were also collected as well as antithrombotic regimens before
diagnosis.

2.3 | Follow up

After atrial thrombi diagnosed, patients had taken oral antico-
agulants with either vitamin K antagonist or non-vitamin K oral
anticoagulants (NOACs), which included rivaroxaban and dabi-
gatran in this study. The patients were scheduled to outpatient
clinic at 1, 3, 6, 9 and 12 months, and the same imaging method
was repeated for spotting thrombi, until thrombi resolved.

2.4 | Comparison between the VCM and NON-
VCM groups

Propensity score matching was used to compare the resolution
rate of thrombi between VCM and non-VCM groups. The pro-
ensity score was generated according to potential covariates,
including gender, age, type of AF (paroxysmal or persistent),
BMI, history of stroke, history of congestive heart failure, his-
tory of hypertension, history of diabetes mellitus, CHA2DS2-
VASc scores, LAAPD, LVEF, and concentration of NT-pro-BNP.
Nearest-neighbor matching without replacement was performed.
After matching, Multivariate analysis was used to evaluate in-
dependent risk factors affecting the resolution of atrial thrombi
in both matching groups. Survival curves were compared with
Kaplan-Meier method using a log-rank test, in order to estimate
the time length for thrombi resolution.

2.5 | Statistical analysis

Statistical analyses were conducted using the SPSS version 26 (SPSS
Corp., Armonk, NY, USA). Continuous variables are expressed as
mean ± SD, and using the independent-sample T test. Categorical
variables are expressed as numbers or percentages, using the Chi-
square test or the Fisher’s exact test. A P-value less than 0.05 was
considered statistically significant.

3 | RESULTS

3.1 | Clinical characteristics of participants

We had retrieved 1153 patients diagnosed with atrial fibrillation
and atrial thrombus, and 962 patients were excluded because of
valvular atrial fibrillation or cardiac surgery. One hundred and
ninety-one patients of AF were eligible in our study. There were
128 patients in non-VCM group and 63 in VCM group. The pa-
ients in VCM group had larger LAAPD than in non-VCM group
(48 ± 8 mm vs 43 ± 5 mm, \( P < .001 \)), and LVEF was lower in the
VCM group than in the non-VCM group (49% ± 15% vs 60% ± 6%,
\( P < .001 \)). More patients suffered congestive heart failure in VCM
group than in non-VCM group (60.0% vs 26.2%, \( P < .001 \)), and
the NT-pro-BNP concentration was higher in VCM group than in
non-VCM group (2309.1 ± 3093.8ng/mL vs 964.9 ± 1071.7ng/
ml, \( P = .001 \)). The baseline clinical characteristics and examina-
tion results of these patients are shown in Table 1.

3.2 | Distribution of thrombi site in atrium

Of all 191 patients, 161 had thrombi only detected in left atrial ap-
pendage (LAA). 20 in both left atrium (LA) and LAA, 6 in LA only,
and 4 in right atrium only. More patients had thrombi out of LAA in VCM group than in non-VCM group (30.2% vs 8.6%, \(P < .001\)), and the 4 right atrial thrombi were all from VCM group. The results were shown in Figure 1. Additionally, we stratified the patients by LAAPD into two subgroups: subgroup 1 of LAAPD < 45 mm, and subgroup 2 of LAAPD ≥ 45 mm. More patients with VCM had thrombi out of LAA than non-VCM in subgroup 2 (35.9% vs 12.8%, \(P = .011\)), and similar result was seen in subgroup 1 between two groups (20.8% vs 6.2%, \(P = .047\)) with significance, as shown in Figure 2.

### 3.3 | Anticoagulant therapy

Before the atrial thrombi detected, 55.5% of patients (106/191) did not take any oral anticoagulants, including 31.4% only taking anti-platelet drugs (Table 1). In these 106 patients, 37.7% belonged to the high risk of stroke with CHADS2 score ≥ 2 points, or 70.8% with CHA2DS2-VASc score ≥ 2 points. After atrial thrombi diagnosed, all patients had taken oral anticoagulant therapy. One hundred and six patients took warfarin, 64 patients took rivaroxaban, and the remaining 21 took dabigatran.
3.4 | Follow up of thrombi resolution

After anticoagulant therapy, the median time length for thrombi resolution was 25 ± 1 weeks. The atrial thrombi was resolved faster in non-VCM group than in VCM group (mean time length: 22 ± 1 weeks vs 32 ± 1 weeks, \( P < .001 \)), and the resolution rate in one year was higher in non-VCM group than in VCM group (85.9% vs 61.9%, Log-rank, HR 2.13, 95% CI, 1.44 – 3.14, \( P < .001 \)).

In the propensity score-matching analysis, 44 patients in the VCM group and 44 patients in the non-VCM group were matched and analyzed. There was no significance in these basic clinical characteristics of 88 patients after PS matching, as shown in Table 2. In Kaplan-Meier analysis of the two matching groups, the
atrial thrombi was resolved faster in non-VCM group than in VCM group (mean time length: 22 ± 2 weeks vs 30 ± 3 weeks, P = .038), and the resolution rate in one year was higher in non-VCM group than in VCM group (88.7% vs 61.4%, Log-rank, P = .038), as shown in Figure 3.

In univariate analysis of these 88 patients, there were less patients with ventricular cardiomyopathy in the thrombus resolution group than in the nonresolution group (27/65 [41.5%] vs 17/23 [73.9%], 95% CI, P = .008). The concentration of NT-pro-BNP was higher in the nonresolution group than in the resolution group (1899.5 ± 1565.6 vs 1334.2 ± 1525.7 pg/mL, P = .133), with more females (13/23 [56.5%] vs 25/65 [38.5%], P = .133) and diabetes mellitus (20/23 [87.0%] vs 44/65 [67.7%], P = .075) patients in the nonresolution group than in the resolution group, but these were not significantly different. In the subsequent multivariate analysis, absence of ventricular cardiomyopathy (hazard ratio: 1.76; P = .035) was an independent predictor for atrial thrombus resolving.

### 4 | DISCUSSION

Few studies had focused on the relationship between atrial thrombus and cardiomyopathy in atrial fibrillation, and the main findings from this retrospective study are as follows:

1. The atrial thrombi tend to arise out of LAA among atrial fibrillation patients with ventricular cardiomyopathy.
2. The atrial thrombi in patients with ventricular cardiomyopathy were more difficult for resolution than those without ventricular cardiomyopathy.
3. Ventricular cardiomyopathy was an independent risk for atrial thrombi existing in AF patients.

#### 4.1 | Difference of thrombosis locations in atrium

LAA is the most common location for thrombosis and a source of cerebral or systemic embolism in AF patients. In patients under regular anticoagulation, the prevalence of left atrial thrombus varies from 1.5% – 3.0%. In a recent meta-analysis, the results showed that left atrial thrombus was identified in up to 9.8% of overall patients with AF, and is associated with a 3.5-fold increased risk of stroke/systemic embolism. As shown in past studies, during AF there is a decrease in LAA contractility and function, which is prone to thrombosis.

However, in our study, 15.7% of cases had thrombi formed in LA body or right atrium, and in patients with ventricular cardiomyopathy, this proportion was up to 30%. We supposed that it may be due to the atrial remodeling in patients with ventricular cardiomyopathy.

In our study, the mean anteroposterior diameter of LA was larger in the ventricular cardiomyopathy group than in the non-cardiomyopathy group, indicating more left atrial remodeling.

Moreover in order to elucidate whether this difference was just due to the enlargement of LA, we conducted the subgroup analysis. And we found that, whether in the subgroup of LA ≥45 mm or LA <45 mm, the proportions of non-LAA thrombi were both significantly higher in the patients with VCM than in non-VCM. These results implied that, the cardiomyopathy may contribute to thrombi formation in the body of LA or right atrium rather than just enlargement of LA.

In some types of cardiomyopathies, such as dilated cardiomyopathy and ischemic heart disease, the pathologic changes (ie fibrosis) were not only manifested in the ventricular myocardium, but also in the atrium. These lesions were possibly linked to the stasis in atrium by inflammation and/or endothelial dysfunction, which may promote thrombosis in the body of LA.

Based on the results, we inferred that, left atrial appendage closure may be unsuitable for some particular patients of AF. As in 2019 AHA/ACC/HRS guideline, left atrial appendage closure may be considered in some selected patients with AF at increased risk to prevent stroke. However, it is a controversial measure for its efficacy. From this study, we found that LAA is not the only one part for thrombosis, while some thrombi could emerge in the right atrium or the body of LA, hence the occlusion of LAA may be unable to reduce thrombosis out of LAA.

### TABLE 2 Clinical Characteristics of 88 patients after PS matching

| Characteristics                     | Non-VCM group (n = 44) | VCM group (n = 44) | P value |
|-------------------------------------|------------------------|-------------------|---------|
| Age-yrs                             | 59.4 ± 8.6             | 60.2 ± 12.5       | .729    |
| Female-no.(%)                       | 19(43.2)               | 19(43.2)          | 1.000   |
| BMI (kg/m²)                         | 25.1 ± 3.3             | 25.2 ± 3.5        | .843    |
| CHA2DS2-VASc scores                 | 2.9 ± 1.9              | 3.0 ± 1.9         | .782    |
| Has-bled scores                     | 1.6 ± 1.1              | 1.6 ± 1.1         | .853    |
| Non-paroxysmal aF-no. (%)           | 27(61.4)               | 26(59.1)          | .828    |
| NT-pro-bnp (pg/ml)                  | 1359.9 ± 205.0         | 1606.7 ± 1721.5   | .453    |
| laapd (mm)                          | 45 ± 5                 | 46 ± 8            | .795    |
| LVEDD (mm)                          | 49 ± 4                 | 49 ± 11           | .777    |
| LVEF (%)                            | 57 ± 7                 | 56 ± 10           | .710    |
| Prior medical history-no.(%)        |                        |                   |         |
| Congestive heart failure            | 18(40.9)               | 20(45.5)          | .667    |
| Hypertension                        | 19(43.2)               | 20(45.5)          | .830    |
| Diabetes mellitus                   | 31(70.5)               | 33(75.0)          | .632    |
| Ischemic stroke                     | 35(79.5)               | 35(79.5)          | 1.000   |

Note: The propensity score was generated according to potential covariates, including gender, age, type of AF (paroxysmal or persistent), BMI, history of stroke, history of congestive heart failure, history of hypertension, history of diabetes mellitus, CHA2DS2-VASc scores, LAAPD, LVEF and concentration of NT-pro-BNP.
4.2 | Anticoagulation therapy before atrial thrombus detected

In our study, over half of these patients did not take anticoagulants until the atrial thrombi detected. Nearly 25% of the patients were admitted before 2015, during which period, guidelines did not establish the status of CHA2DS2-VASc scoring for stroke risk evaluation, and still considered aspirin for some selective patients with AF.\textsuperscript{16-18} In these patients without anticoagulating, over 60% were stratified into low risk with CHADS2 < 2 points, which may contribute to the deficiency of anticoagulation. By revaluation through CHA2DS2-VASc scoring, up to 70% of the patients without pre-anticoagulation were stratified into high risk of stroke with CHA2DS2-VASc ≥ 2 points. Thus, CHA2DS2-VASc may promote anticoagulation by lifting the risk rating of stroke, thus to decrease atrial thrombosis.

4.3 | Resolution of atrial thrombi

As guidelines recommend, VKA is the most used treatment,\textsuperscript{15,19} and in some trials, NOACs were also proved to be effective for treating atrial thrombi in patients with AF.\textsuperscript{20-22} Wang et al conducted a meta-analysis and found that, the pooled resolution rate of left atrial thrombus from 16 warfarin studies was 63.7%, and two studies in direct-acting oral anticoagulants reported this resolution rates of 89.5% for dabigatran and 41.5% for rivaroxaban.\textsuperscript{23} In our study, the total resolution rate in one year was about 74% after propensity score matching, and the resolution rate in one year was higher in non-VCM group than in VCM group. The difference of resolution rate may be related to the discrepancy of LA size and LVEF between the two groups. As a result, we conducted the univariate and multivariate analysis from the propensity score matching, and made most variates of baseline consistent. The result showed that the absence of VCM was the only independent predictor for thrombi resolution.

As discussed above, the left atrial diameter was greater in VCM group than in non-VCM group, and the atrial contractility declined in some patients with cardiomyopathy. In addition, the patients with cardiomyopathy in our study had lower mean LVEF and higher incidence of heart failure than patients without cardiomyopathy, which could further increase dysfunction of left atrium.\textsuperscript{24,25} All these causes led to slow blood flow in circulation, especially the left atriums, which may increase the difficulty for thrombi resolution.

4.4 | Study limitations

This study was retrospectively conducted in a single center, and the sample size was relatively small, especially in the cardiomyopathy group. Hence, the limited size may overestimate the difference of atrial thrombus locations between the two groups. Moreover about 20% of the participants were diagnosed only by CT. As previous study indicated, CT had a poorer positive predictive value for thrombus in left atrial appendage compared with the gold
standard of TEE. It may include some false-positive thrombi into this study.

CONFLICT OF INTEREST
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ORCID
Hao Zhang https://orcid.org/0000-0001-8362-1926
Jun Liu https://orcid.org/0000-0002-9353-4604

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