

Heart failure as an independent predictor of thrombus persistence in nonvalvular atrial fibrillation: a transesophageal echocardiography-based study

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KEY WORDS

left atrial appendage thrombus, left atrial thrombus, thrombus resolution

ABSTRACT

INTRODUCTION Formation of left atrial (LA) thrombus is one of the most serious complications in patients with atrial fibrillation (AF).

OBJECTIVES The aim of our study was to determine the predictors of LA thrombus resolution among patients with AF receiving oral anticoagulation.

PATIENTS AND METHODS After a retrospective analysis of 1877 transesophageal echocardiographic examinations (TEEs) performed in our department between January 2009 and June 2013, we included 64 patients (women, 36%; mean age at diagnosis, 64 ± 8.8 years) with nonvalvular AF and LA thrombi on TEE into the study. All patients received oral anticoagulation and underwent follow-up TEE within a few months since diagnosis.

RESULTS After a mean follow-up period of 88 ± 107 days, thrombus resolution was observed in 30 patients (47%). The univariate Cox proportional regression model showed that heart failure and reduced left ventricular ejection fraction were associated with the persistence of LA thrombus (hazard ratio [HR], 2.72; 95% confidence interval [CI], 1.32–5.61; $P = 0.007$ and HR, 0.97; 95% CI, 0.94–0.99; $P = 0.04$; respectively). The international normalized ratio and CHA₂DS₂-VASC score were not prognostic for thrombus resolution (HR, 0.64; 95% CI, 0.37–1.1; $P = 0.1$ and HR 1.10; 95% CI, 0.91–1.33; $P = 0.3$; respectively). In a multivariate analysis, heart failure was the only independent factor predicting unsuccessful resolution of LA thrombus ($P = 0.04$).

CONCLUSIONS Heart failure is an independent negative predictor of LA thrombus resolution in patients with AF receiving oral anticoagulation.

INTRODUCTION Formation of left atrial (LA) thrombus is an unfavorable scenario in patients with atrial fibrillation (AF). Patients referred for cardioversion and diagnosed with LA thrombus undergo intensive anticoagulant treatment for at least 3 to 4 weeks, followed by repeated transesophageal echocardiography (TEE).¹ However, such a strategy does not guarantee thrombus resolution—the reported prevalence of LA thrombi assessed by TEE in a population of patients with AF receiving oral anticoagulation ranges from 1.1% to 8.8% (depending on whether the international normalized ratio [INR] levels were optimal or subtherapeutic),^{2–5} and the success rate

is 90%.^{6,7} To our knowledge, there have been no studies providing information about predictors of LA thrombus resolution.

PATIENTS AND METHODS **Study population** Based on a retrospective analysis of 1877 TEEs performed in our department between January 2009 and June 2013, we identified 74 patients with LA thrombus (3.9%). The final study sample included 64 patients with nonvalvular AF and LA thrombi detected on TEE (23 women, 41 men) who subsequently received oral anticoagulant therapy and underwent follow-up TEE in our institution. The main indications for baseline

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Received: January 1, 2015.

Revision accepted: March 25, 2015.

Published online: March 27, 2015.

Conflict of interest: none declared.

Pol Arch Med Wewn. 2015;

125 (5): 358–362

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TABLE 1 Baseline characteristics of the study population (n = 64)

Variable	Value
age, y	64 ± 8.8
follow-up, d	88 ± 107
male sex	41 (64)
left atrial appendage thrombus	59 (92)
heart failure	27 (42)
arterial hypertension	35 (55)
mitral valve stenosis	0 (0)
mitral valve insufficiency, grade I (mild)	22 (34)
mitral valve insufficiency, grade II (moderate)	7 (11)
diabetes mellitus	14 (22)
coronary artery disease	18 (28)
obesity	18 (28)

Data are presented as mean ± standard deviation or number (percentage).

TEE were AF, suspected heart failure or chronic heart failure, and stable coronary artery disease. The past medical history, baseline clinical characteristics on admission to the hospital, and 12-lead electrocardiography findings were obtained from medical charts archived in our database. Heart failure was defined clinically in accordance with the European Society of Cardiology (ESC) guidelines.⁸ After the diagnosis of LA thrombus, all patients received oral anticoagulation with vitamin K antagonist (acenocumarol, warfarin) and underwent follow-up TEE and INR measurements.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Patients gave written informed consent before each TEE.

Echocardiographic assessment All patients underwent conventional transthoracic echocardiography and TEE performed with VIVID7 Dimision (GE Vingmed Ultrasound AS, Hurten, Norway) using the harmonic mode. Both examinations were performed by certified echocardiographers. Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson's biplane method. TEEs were focused on the visualization of LA thrombi. Thrombus was defined as a well-circumscribed, intracavitary, echogenic mass distinct from the atrial endocardium or pectinate muscles and visible in multiple planes; the convex contour was used as a criterion for differentiation with spontaneous echocardiographic contrast.^{9,10}

Statistical analysis The MedCalc version 10.4.8.0 statistical software package (MedCalc, Mariakerke, Belgium) was used for all statistical calculations. Continuous variables were presented as mean ± standard deviation and categorical

variables—as percentages. Cox proportional hazard regression models were used to identify predictors of thrombus resolution, and independent predictors were determined by the multiple regression method. A *P* value of less than 0.05 was considered statistically significant.

RESULTS The baseline characteristics of the patients are summarized in **TABLE 1**. The prevalence of reduced LVEF ($\leq 40\%$) was 42%.

After a mean follow-up period of 88 ± 107 days, thrombus resolution was documented in 30 patients (47%). The Cox proportional regression model showed that heart failure and LVEF were predictors of LA thrombus persistence (hazard ratio [HR], 2.72; 95% confidence interval [CI], 1.32–5.61; *P* = 0.007 and HR, 0.97; 95% CI, 0.94–0.99; *P* = 0.04; respectively).

Interestingly, the INR level and CHA₂DS₂-VASc score were not significantly associated with thrombus resolution (HR, 0.64; 95% CI, 0.37–1.1; *P* = 0.1, and HR 1.10; 95% CI, 0.91–1.33; *P* = 0.3; respectively). The prognostic value of the studied variables is summarized in **TABLE 2**. The multiple regression method indicated heart failure to be an independent predictor of unsuccessful LA thrombus resolution (*P* = 0.04).

DISCUSSION Our study indicated that heart failure and low LVEF decrease the chance for thrombus resolution in patients with nonvalvular AF. This is an important finding because there is a paucity of data regarding the prognostic factors for successful resolution of LA appendage thrombus in AF. Our findings can be used to guide clinical decision making in terms of when to initiate short-term high-intensity anticoagulation in patients who are more likely to have their thrombus resolved. The predictive utility of heart failure in thrombus resolution was also documented by Silakur et al.,¹¹ but in a different population. In their study, among 108 patients referred for percutaneous transvenous mitral commissurotomy with diagnosed LA thrombus, the clinical New York Heart Association functional class was found to be an independent predictor.

In our study, the resolution of thrombus after anticoagulant therapy with vitamin K antagonists was reported in 47% of the cases. Previous studies described thrombus resolution even in 62%¹¹ or 80.1%¹² of the patients. These discrepancies may result from the differences in the baseline characteristics of the study populations. Our population was older and more often showed reduced LVEF ($\leq 40\%$).

It should also be noted that 3 weeks of anticoagulant therapy, even with the therapeutic INR level, may not be sufficient for thrombus resolution.¹³ The study of Seidl et al.¹⁴ compared 2 strategies before cardioversion: effective anticoagulation (INR of 2 or 3) lasting at least 3 weeks before cardioversion and TEE-guided cardioversion. The results showed that

TABLE 2 Characteristics of the study subgroups depending on the outcome (group A, patients with thrombus resolution; group B, patients with persistent thrombus) with predictive value of the studied variables (according to logistic regression results)

	Characteristics of study groups		Statistical significance for outcome prediction		
	group A	group B	P value	hazard ratio	odds ratio (95% CI)
spontaneous echo contrast	19 (56)	17 (57)	0.3	0.72	0.3556–1.4416
maximum LA diameter, mm	47.1 ± 6.7	50.5 ± 5.8	0.1	1.05	0.9836–1.1283
LV diastolic diameter, mm	52.1 ± 11.4	57.5 ± 10.4	0.08	1.02	0.9969–1.0596
LV systolic diameter, mm	39.6 ± 2.6	44.7 ± 2.5	0.1	1.02	0.9958–1.0482
mean LVEF, %	44.3 ± 2.8	39.7 ± 15.3	0.04	0.97	0.9442–0.9978
INR	2.07 ± 1.85	2.29 ± 1.3	0.1	0.64	0.3720–1.1044
CHA ₂ DS ₂ -VASc score	2.8 ± 1.8	3.2 ± 1.6	0.3	1.10	0.9093–1.3277
heart failure	9 (30)	18 (53)	0.007	2.72	1.3189–5.6135
diabetes mellitus	6 (20)	8 (23.5)	0.4	1.43	0.6449–3.1646
hypertension	16 (53)	19 (55.9)	0.6	1.18	0.6011–2.3327
vascular disease	9 (30)	13 (38.2)	0.2	1.60	0.8018–3.2004

Data are presented as mean ± standard deviation or number (percentage).

Abbreviations: CI, confidence interval; INR, international normalized ratio; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction

the approaches were not significantly different in terms of patients' outcomes after cardioversion and formed the basis for the American College of Chest Physicians guidelines¹⁵ as well as for the ESC guidelines.¹ However, in the study by Siegl et al.,¹⁴ the group of patients in whom anticoagulation was effective was characterized by a significantly lower prevalence of heart failure than that in our population. Therefore, we suggest a more common use of TEE before cardioversion for patients with heart failure or reduced LVEF (≤40%).

It should also be emphasized that in our group normal LVEF did not exclude the possibility of LA or LA appendage thrombus—17% of the patients with a LVEF of 50% or higher had an LA thrombus present. Interestingly, the literature provides conflicting results. Khan et al.¹⁶ studied 1221 patients with paroxysmal AF who received anticoagulation and found that none of the patients with normal LVEF (defined as LVEF exceeding 50%) had LA thrombus present on TEE.

Our study has several limitations. This was a single-center retrospective analysis with a varying duration of follow-up. An additional analysis of the size and echogenicity of the thrombus would considerably improve the predictability of its persistence.¹⁷ Diagnosis of heart failure may be affected by the coexistence of AF because many symptoms are similar. In our group, the INR was measured only once—on the first day of follow-up hospitalization. This may not reflect the real effectiveness of anticoagulant therapy. Nevertheless, most patients in our study had an INR at the therapeutic range. Finally, we did not analyze patients receiving novel oral anticoagulation, which is becoming increasingly common in the population with AF¹⁸ and has been shown, in some patients, to be successful in LA thrombus resolution.^{19,20}

In conclusion, heart failure is an independent negative predictor of LA thrombus resolution in patients receiving anticoagulant therapy.

Contribution statement All authors conceived the idea for the study, contributed to the design of the research, analyzed the data, and edited and approved the final version of the manuscript. EK was involved in data collection.

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Niewydolność serca jako niezależny czynnik predykcyjny utrzymywania się skrzepliny u pacjentów z migotaniem przedsionków – badanie w oparciu o echokardiografię przezprzełykową

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SŁOWA KLUCZOWE

rozpuszczenie
skrzepliny, skrzeplina
lewego przedsionka,
skrzeplina uszka
lewego przedsionka

STRESZCZENIE

WPROWADZENIE Obecność skrzepliny w lewym przedsionku serca jest jednym z najpoważniejszych powikłań migotania przedsionków (AF).

CELE Celem badania była ocena czynników prognostycznych zanikania skrzeplin w lewym przedsionku wśród pacjentów z AF otrzymujących doustne leczenie przeciwkrzepliwe.

PACJENCI I METODY Retrospektywna analiza bazy 1877 badań TEE wykonanych w naszej klinice pomiędzy styczniem 2009 roku i czerwcem 2013 roku, pozwoliła na włączenie do badania grupy 64 pacjentów (36% kobiet, średni wiek w chwili diagnozy $64 \pm 8,8$ lat) z migotaniem przedsionków oraz zdiagnozowaną w TEE skrzepliną lewego przedsionka. Wszyscy chorzy otrzymywali doustne leczenie przeciwkrzepliwe (antagoniści witaminy K) oraz w przeciągu kilku miesięcy od chwili diagnozy mieli wykonane kontrolne badanie TEE.

WYNIKI Po średnim okresie obserwacji 88 ± 107 dni zaniknięcie skrzepliny zaobserwowano u 30 pacjentów (47%). Jednoczynnikowy model regresji Coxa wykazał, że niewydolność serca oraz obniżona frakcja wyrzutowa lewej komory wiążą się z utrzymywaniem się skrzeplin w lewym przedsionku (odpowiednio: HR 2,72; 95% CI 1,32–5,61; $p = 0,007$ i HR 0,97; 95% CI 0,94–0,99; $p = 0,04$). Międzynarodowy współczynnik znormalizowany oraz skala CHA₂DS₂-VASc nie miały wartości prognostycznej dla rozpuszczenia skrzepliny (odpowiednio: HR 0,64; 95% CI 0,37–1,1; $p = 0,1$ i HR 1,10; 95% CI 0,91–1,33; $p = 0,3$). Analiza wieloczynnikowa wskazała niewydolność serca jako jedyny niezależny czynnik prognostyczny nieskuteczności rozpuszczania skrzepliny ($p = 0,04$).

WNIOSKI Niewydolność serca jest niezależnym czynnikiem predykcyjnym utrzymywania się skrzepliny lewego przedsionka wśród pacjentów z migotaniem przedsionków otrzymujących doustne leczenie przeciwkrzepliwe.

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Praca wpłynęła: 01.01.2015.
Przyjęta do druku: 25.03.2015.
Publikacja online: 27.03.2015.
Nie zgłoszono sprzeczności
interesów.

Pol Arch Med Wewn. 2015;
125 (5): 358-362
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