



Left atrial enlargement and non-paroxysmal atrial fibrillation as risk factors for left atrial thrombus/spontaneous Echo contrast in patients with atrial fibrillation and low CHA₂DS₂-VASc score

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Abstract

Objective To determine the risk factors for thromboembolism in lower risk patients with non-valvular atrial fibrillation (AF) and low CHA₂DS₂-VASc scores, which remain undefined. **Methods** We retrospectively analyzed the baseline clinical characteristics, routine laboratory parameters, and echocardiographic measurements of 705 patients (71.1% male; mean age: 52.10 ± 9.64 years) with low CHA₂DS₂-VASc score (0 or 1; 1 point for female sex) out of 1346 consecutive patients with non-valvular AF who underwent transesophageal echocardiography (TEE) at Guangdong Cardiovascular Institute between January 2013 and December 2015. **Results** Patients with left atrial thrombus (LAT) or spontaneous echo contrast (SEC) on TEE (24/705, 4%) showed a higher incidence rate of vascular disease (54.2% vs. 32.9%, $P = 0.045$) and non-paroxysmal AF (79.2% vs. 29.4%, $P < 0.001$), larger left atrial diameter (43.08 ± 4.59 vs. 36.02 ± 5.53 mm, $P < 0.001$), and lower left ventricular ejection fraction (58.23 ± 8.82% vs. 64.15 ± 7.14%, $P < 0.001$) than those without. Multivariate logistic regression analysis identified left atrial diameter [odds ratio (OR) = 1.171, 95% confidence interval (CI): 1.084–1.265, $P < 0.001$] and non-paroxysmal AF (OR = 3.766, 95% CI: 1.282–11.061, $P = 0.016$) as independent risk factors for LAT/SEC. In ROC curve analysis, a left atrial diameter cutoff of 37.5 mm yielded 95.0% sensitivity and 62.7% specificity (AUC: 0.847, $P < 0.0001$, 95% CI: 0.793–0.914). **Conclusion** In patients with non-valvular AF with low CHA₂DS₂-VASc score, the presence of LAT or SEC was associated with left atrial enlargement, which had moderate predictive value, and non-paroxysmal AF.

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Keywords: Atrial fibrillation; Left atrial diameter; Left atrial spontaneous echo contrast; Left atrial thrombus

1 Introduction

Atrial fibrillation (AF), one of the most common cardiac arrhythmias, is associated with significant morbidity and mortality^[1] mainly secondary to thromboembolism.^[2] ESC guidelines recommend anticoagulation therapy in patients with AF based on the CHA₂DS₂-VASc score.^[3] However, stroke still occurs in some patients with low CHA₂DS₂-VASc score, warranting a definition of the risk factors for stroke among said “low risk” patients.

The development of thrombi within the left atrial ap-

pendage (LAA) is the underlying cause of thromboembolism,^[4,5] and left atrial thrombus (LAT) and left atrial spontaneous echo contrast (SEC) are associated with stroke in patients with AF.^[6,7] Transesophageal echocardiography (TEE) is effective for identifying LAT or SEC,^[8] however, the mechanisms and pathways underlying LAT or SEC have not been fully clarified in patients with AF and low CHA₂DS₂-VASc score.

Left atrial diameter (LAD) is a predictor of stroke/systemic embolism (SE) in AF patients,^[9-11] and was independently associated with increased risk of stroke in studies assessing the presence of LAT/SEC by TEE as endpoint.^[12,13] However, the predictive value of LAD on LAT/SEC identified by TEE has not been systematically examined in patients at low risk of stroke. In this study, we aimed to identify the clinical predictors of LAT/SEC in patients with AF and low CHA₂DS₂-VASc scores.

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2 Methods

2.1 Study population

We retrospectively assessed the clinical, laboratory, and echocardiographic data of 1347 patients with non-valvular AF who underwent TEE prior to radiofrequency catheter ablation or cardioversion in our institution between January 2013 and December 2015. There were 705 patients with a low risk of stroke (CHA₂DS₂-VASc score of 0 or 1; 1 point for female sex). All patients underwent TEE and were divided into a LAT/SEC group and a non-LAT/SEC group according to TEE findings. This study was approved by the institutional ethics committee and all patients signed a general informed consent.

2.2 Study variables and definition of terms

2.2.1 Laboratory data

Routine blood tests were performed on all patients prior to radiofrequency catheter ablation or cardioversion. Hemoglobin (HGB), red blood cell count (RBC), platelet (PLT) and white blood cell counts (WBC), and lymphocyte count (LYM) were measured by automated complete blood count.

2.2.2 Echocardiographic data

Transthoracic echocardiography was performed using a Vivid S5 (2-4 MHz phased array transducer; GE, Horten, Norway) system. Standard parasternal long- and short-axis views and apical 2- and 4-chamber views were obtained in all patients. LAD was measured in the parasternal long-axis view. Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson method.^[14]

TEE was performed with patients under local pharyngeal anesthesia with lidocaine spray and using a 5 MHz biplane phased array transducer (Vivid S5, GE, Horten, Norway). The left atrium and LAA were imaged in different tomographic planes to detect the presence of LAT or SEC. SEC was classified according to previously described criteria.^[15] SEC was defined as minimal echogenicity located in the LAA or in the main cavity of the left atrium (LA). LAT was defined as a dense swirling pattern in the LAA that is less intense in the main LA cavity, may fluctuate in intensity but is constantly detectable throughout the cardiac cycle, or intense echo density and a very slow swirling pattern in the LAA with similar intensity in the main LA cavity.

2.2.3 Medical history

The CHA₂DS₂-VASc score, which is widely used to assess the risk of stroke in patients with non-valvular AF,^[16,17] was calculated for each patient. The CHA₂DS₂-VASc score

includes congestive heart failure (CHF) (1 point), hypertension (1 point), age 65–74 years (1 point), age 75 years (2 points), diabetes mellitus (DM) (1 point), previous stroke, transient ischemic attack, or thromboembolism (2 points), vascular disease (1 point), and female gender (1 point). CHF was defined as signs/symptoms of heart failure or objective evidence of reduced LVEF. Hypertension (HTN) was defined as a resting blood pressure > 140/90 mmHg on at least two occasions or current antihypertensive treatment. DM was defined as fasting glucose > 125 mg/dL (7 mmol/L) or treatment with an oral hypoglycemic agent and/or insulin. Vascular disease was defined as previous myocardial infarction, peripheral artery disease, or aortic plaque. CHF, HTN, DM and vascular disease were defined according to ESC guidelines for the management of AF.^[18] Paroxysmal AF was defined as self-terminating AF, whereas non-paroxysmal AF was defined as AF episodes lasting over 7 days (AF present at least twice during 24-h Holter monitoring demonstrated AF persistence for 24 h).

2.3 Statistical analysis

Continuous variables are expressed as mean \pm SD and compared using the Student's *t*-test. Categorical variables are expressed as number and percentage values and compared using the chi-square test. Receiver-operating characteristic (ROC) analyses were used to detect the cutoff value of LAD for predicting LAT/SEC in patients with non-valvular AF. Multiple logistic regression analysis was performed to identify the independent predictors of LAT/SEC. One-sided *P* value < 0.05 was considered significant. All statistical analysis was carried out using SPSS 19.0 for Windows (SPSS Inc., Chicago, IL, USA).

3 Results

3.1 Baseline characteristics

A total of 705 patients with non-valvular AF (71.1% male; mean age: 52.10 \pm 9.64 years) were included in the study, of which 24 showed LAT/SEC on TEE examination. Patients with LAT/SEC had a higher incidence of vascular disease than those without (54.2% vs. 32.9%, *P* = 0.045), whereas age, sex, HGB, PLT, WBC, RBC, LYM, HTN, HF, DM, and anticoagulation did not differ significantly between the two groups (Table 1). LAD was larger (43.08 \pm 4.59 vs. 36.02 \pm 5.53 mm, *P* < 0.001; Figure 1), LVEF was lower (58.23% \pm 8.82% vs. 64.15% \pm 7.14%, *P* < 0.001), and non-paroxysmal AF (79.2% vs. 29.4%, *P* < 0.001; Figure 2) was present more often in patients with LAT/SEC than in those without.

Table 1. Baseline characteristics of patients with or without LAT/SEC by transesophageal echocardiography examination.

	Non-LAT/SEC group (n = 681)	LAT/SEC group (n = 24)	P
Clinical characteristics			
Men	483 (70.9%)	17 (70.8%)	1.000
Age, yrs	52.01 ± 9.65	54.58 ± 9.38	0.199
CHF	7 (1.0%)	1 (4.2%)	0.243
Hypertension	83 (12.2%)	1 (4.2%)	0.343
Diabetes mellitus	8 (1.1%)	0	1.000
Vascular disease	224 (32.9%)	13 (54.2%)	0.045
Anticoagulation	84 (11.9%)	4 (16.7%)	0.528
CHA ₂ DS ₂ -VASc Score	0.80 ± 0.69	1.0 ± 0.66	0.154
Non-paroxysmal AF	207 (29.4%)	19 (79.2%)	< 0.001
Laboratory examinations			
HGB, g/L	141.41 ± 13.98	144.42 ± 14.21	0.123
PLT, 10 ⁹ /L	201.49 ± 46.57	205.81 ± 46.61	0.259
WBC, 10 ⁹ /L	6.38 ± 1.44	6.88 ± 1.39	0.102
RBC, 10 ⁹ /L	4.78 ± 0.58	4.68 ± 0.42	0.436
LYM, 10 ⁹ /L	2.26 ± 0.64	2.42 ± 0.53	0.215
Echocardiogram parameters			
LAD, mm	36.02 ± 5.53	43.08 ± 4.59	< 0.001
LVEF, %	64.15 ± 7.14	58.23 ± 8.82	0.006

Data are presented as n (%) or mean ± SD. CHF: chronic heart failure; HGB: hemoglobin; LAD: left atrial diameter; LAT/SEC: left atrium thrombus or left atrial spontaneous echo contrast; LVEF: left ventricular ejection fraction; LYM: lymphocyte count; PLT: platelet; RBC: red blood cell counts; WBC: white blood cell counts.

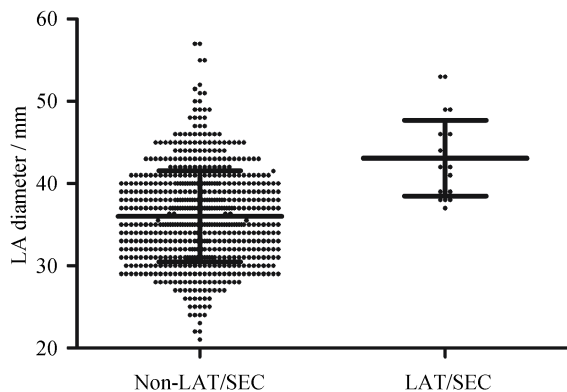


Figure 1. The left atrial diameter was larger in patients with than without left atrial thrombus/spontaneous echo contrast (LAT/SEC: 44.10 ± 5.53 vs. 36.21 ± 5.52 mm, respectively, P < 0.001). LAT: left atrial thrombus; SEC: spontaneous echo contrast.

3.2 Predictive value of LAD and non-paroxysmal AF on LAT/SEC in patients with non-valvular atrial fibrillation with low CHA₂DS₂-VASc score

Multivariate logistic regression analysis showed that LAD [odds ratio (OR) = 1.171, 95% CI: 1.084–1.265, P < 0.001] and non-paroxysmal AF (OR = 3.766, 95% CI: 1.282–11.061, P = 0.016) were independent predictors of LAT/SEC in patients with non-valvular AF with low CHA₂DS₂-VASc score (Table 2).

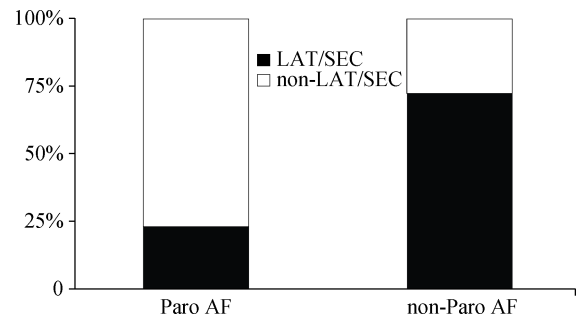


Figure 2. The proportion of patients with non-paroxysmal AF was higher among patients with than without left atrial thrombus/spontaneous echo contrast (LAT/SEC: 79.2% vs. 29.4%, respectively, P < 0.001). AF: atrial fibrillation; LAT: left atrial thrombus; SEC: spontaneous echo contrast.

Table 2. Multivariate logistic regression analysis for left atrial thrombus or left atrial spontaneous echo contrast in patients with non-valvular atrial fibrillation with low CHA₂DS₂-VASc score.

Variables	Odds ratio	95% confidence interval	P-value
LAD	1.171	1.084–1.265	< 0.001
Non-paroxysmal AF	3.766	1.282–11.061	0.016
Vascular disease	1.327	0.437–4.031	0.053
CHF	3.705	0.368–37.328	0.267

LAD: left atrial diameter; CHF: chronic heart failure.

ROC curve analysis was used to determine the best cut-off value of LAD for predicting LAT/SEC. LAD > 37.5 mm predicted LAT/SEC with 95.0% sensitivity and 62.7% specificity [area under the curve (AUC) = 0.847, $P < 0.001$, 95% CI: 0.793–0.914] (Figure 3).

4 Discussion

This is the largest study analyzing TEE findings in patients with AF with low CHA₂DS₂-VASc score. The data indicated that LAD and non-paroxysmal AF were associated with the presence of LAT/SEC in this patient population.

4.1 Risk factors of stroke

In recent years, an increase in morbidity has brought AF to the forefront. AF is an independent risk factor for stroke, and the medical history-based CHA₂DS₂-VASc score is used to predict the risk of stroke and the requirement for anticoagulation therapy. However, the need for anticoagulation therapy in low-risk patients (CHA₂DS₂-VASc score 0 or 1) remains controversial. LAT or SEC is associated with increased thromboembolic risk.^[19] Although TEE is effective for identifying LAT or SEC in patients with AF, it is not used routinely to assess stroke risk in patients with AF because of limitations in its implementation, including its invasiveness. Therefore, it is clinically relevant to define easily detectable and accurate stroke risk factors in low-risk patients.

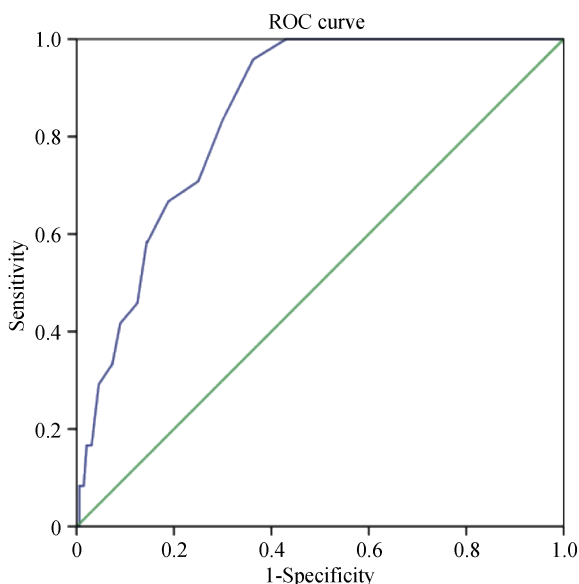


Figure 3. ROC curve analysis determined the best cutoff value of LAD for predicting LAT or left atrial SEC. AUC: area under the curve; LAD: left atrial diameter; LAT: left atrial thrombus; ROC: receiver-operating characteristic; SEC: spontaneous echo contrast.

4.2 Left atrial diameter and LAT/SEC

A relationship between LAD and increased risk of stroke in AF patients was first proposed in the 1980s. In the early 1990s, LAD was reported to be associated with stroke risk; however, these studies did not analyze patients at low risk of stroke. In a recent small sample size study, Lee, *et al.*^[20] demonstrated that LAD is associated with stroke history in patients with low CHA₂DS₂-VASc score. However, the role of LAD as an independent predictor of stroke in patients at low risk of stroke remains controversial, and are no data from large-scale studies. To the best of our knowledge, this study is one of the largest providing TEE data on the association between LAD and the incidence of LAT/SEC in AF patients at low risk of stroke. The study results suggested that LAD was independently associated with an increased risk of stroke and that LAD > 37.5 mm had moderate predictive value for LAT/SEC.

4.3 Non-paroxysmal AF and LAT/SEC

Previous cohort studies failed to show a difference in outcome between patients with paroxysmal AF and those with persistent AF. However, the GISSI-AF analysis, which included 1234 patients, showed that antithrombotic rates vary significantly between patients with paroxysmal AF and those with persistent AF (76% vs. 96%, $P < 0.0001$). A study by Boriani, *et al.*^[21] reported that the inclusion of AF burden refines the risk stratification for stroke, and this was evident even considering that anticoagulation is more commonly prescribed in patients with the highest AF burden. The ROCKET-AF trial^[22] also demonstrated that persistent AF is associated with a higher risk of death and stroke than paroxysmal AF. Even less data are available on the relationship between stroke and AF episodes in patients with low CHA₂DS₂-VASc score. The present TEE based study of patients with non-valvular AF with low CHA₂DS₂-VASc score showed that approximately 80% of patients with LAT/SEC had non-paroxysmal AF, which was identified as an independent predictor.

This study has several limitations including those inherent to its retrospective, single-center design. Although height and weight may affect LAD, we did not analyze these parameters. For patients on oral warfarin, we did not calculate the time in therapeutic range (TTR); however, because anticoagulation was sparsely used in the groups compared, there was likely a small if any effect of TTR on the results presented.

In conclusion, LAD and non-paroxysmal AF were independently associated with the presence of LAT/SEC in patients with non-valvular AF with low CHA₂DS₂-VASc score.

LAD > 37.5 mm predicted LAT/SEC with 95.0% sensitivity and 62.7% specificity.

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