Retrospective Study of 1255 Non-Anticoagulated Patients with Nonvalvular Atrial Fibrillation to Determine the Risk of Ischemic Stroke Associated with Left Atrial Spontaneous Echo Contrast on Transesophageal Echocardiography

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Background: Left atrial spontaneous echo contrast (LASEC) is associated with an increased risk of stroke in patients with nonvalvular atrial fibrillation (NVAF). Therefore, a tool that identifies the risk of LASEC in non-anticoagulated patients with NVAF may be helpful for stroke risk stratification and early stroke prevention in these patients. The aim of this retrospective study was to establish a novel risk score model to determine the risk of ischemic stroke associated with LASEC on transesophageal echocardiography (TEE).

Material/Methods: This study retrospectively and consecutively enrolled 1255 non-anticoagulated patients with NVAF who underwent TEE prior to catheter ablation or left atrial appendage occlusion. Most importantly, a novel nomogram was developed using a logistic regression model to predict the risk of LASEC.

Results: A nomogram was established for LASEC prediction which included 5 independent risk factors determined by multivariable logistic regression analysis: increased age, non-paroxysmal atrial fibrillation, previous stroke/transient ischemic attack, congestive heart failure, and left atrial enlargement. The receiver operating characteristic curve analysis showed that the area under the curve (AUC) of the novel risk score model was 0.879 (95% confidence interval: 0.849-0.909, P<0.001). Compared with the CHA2DS2-VASc score, the novel risk score model had a better predictive power (AUC: 0.879 vs 0.617, P<0.001).

Conclusions: This novel risk score model effectively predicted the presence of LASEC in non-anticoagulated patients with NVAF.

Keywords: Atrial Fibrillation • Nomograms • Thrombosis

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Background

In clinical practice, atrial fibrillation (AF) is associated with a substantial risk of morbidity and mortality [1]. One of the most serious complications of AF is thromboembolism. AF increases the risk of ischemic stroke by 5-fold [1], and 15% to 25% of ischemic strokes are associated with AF [2]. Left atrial spontaneous echo contrast (LASEC) is relatively common in patients with AF [3]. In addition, LASEC is a risk factor for left atrial thrombus (LAT) formation and an indicator of stroke events [4]. The prediction of LASEC may contribute to stroke risk stratification and early stroke prevention in patients with NVAF.

The CHA2DS2-VASc scoring system is recommended to evaluate the risk of stroke in patients with NVAF [1]. Some studies have shown that the CHA2DS2-VASc scoring system can be useful in predicting LASEC, but its predictive power may be modest [5-9]. Therefore, a new method to predict LASEC is needed. The aim of this retrospective study from a single center including 1255 non-anticoagulated patients with non-valvular atrial fibrillation (NVAF) was to establish a novel risk score model to determine the risk of ischemic stroke associated with LASEC on transesophageal echocardiography (TEE).

Material and Methods

Study Population

This retrospective cross-sectional study enrolled 1255 consecutive hospitalized patients with NVAF at Beijing Anzhen Hospital between January 2019 and July 2019. All patients underwent TEE and transthoracic echocardiography (TTE) before catheter ablation or left atrial appendage (LAA) occlusion. The exclusion criteria were valvular heart disease, a history of valvuloplasty or valve replacement, complex congenital heart disease, recent ischemic stroke, deep venous thrombosis, pulmonary embolism, active inflammatory diseases, severe liver or renal disease, biochemical parameters (C-reactive protein [CRP], uric acid, D-dimer, creatinine, fibrinogen, and homocysteine), and echocardiographic parameters (left ventricular ejection fraction [LVEF], left atrial diameter [LAD], and left ventricular end diastolic diameter). AF was diagnosed based on the patient’s medical history and a standard 12-lead electrocardiogram and/or Holter monitoring. The definition and classification of AF was based on published guidelines [1]. Non-paroxysmal AF included persistent AF and long-standing persistent AF. The CHA2DS2-VASc score (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65-74 years, sex category [female]), with a maximum value of 9 points, was calculated for each patient by the adding the points from the following risk factors: congestive heart failure, hypertension, age of 65-74 years, diabetes mellitus, vascular disease, or female sex (1 point each); and age ≥75 years or previous stroke, TIA, or thromboembolism (2 points each) [1]. Peripheral venous blood samples were collected after overnight fasting, and biochemical parameters were determined using standard laboratory methods at the central laboratory of Beijing Anzhen Hospital.

TTE and TEE

TTE and TEE were performed using a General Electric Vivid E9 ultrasound system according to standard practice guidelines [10,11]. Left atrial dimension was measured in the parasternal long-axis view at the end of left ventricular systole. LVEF was calculated using the modified Simpson’s rule in the apical 2- and 4-chamber views. Left atrial enlargement (LAE) was defined as an LAD >40 mm. Left ventricular systolic dysfunction was defined as an LVEF <50%.

Prior to TEE, patients fasted for 6 h and received local pharyngeal anesthesia. TEE was performed using a Philips X7-2T transesophageal probe inserted 25 to 35 cm into the esophagus. The left atrium (LA) and LAA were inspected in different tomographic planes, from 0° to 180°, to detect the presence of LASEC. LASEC was defined as dynamic “smoke-like” echoes in the LA chamber/LAA with characteristic swirling motions that could not be eliminated by changing the gain settings [3]. All examinations were performed by experienced echocardiographers, and all TEE images were independently reviewed by 2 experienced echocardiographers who were blinded to the study protocol.

Statistical Analysis

Normally distributed continuous variables are expressed as mean±standard deviation. Non-normally distributed variables are presented as medians (interquartile ranges), and categorical variables are expressed as frequencies (percentages). Inter-group comparisons of continuous variables were performed using the t test or Mann-Whitney U test. Inter-group comparisons of categorical variables were performed using the
chi-squared or Fisher exact test. Univariate and multivariate logistic regression analyses were performed to identify independent risk factors for LASEC. Variables with a $P$ value <0.05 in univariate analysis were incorporated into the multivariable analysis. Subsequently, variables with a $P$ value <0.05 in multivariable analysis were included in the final multivariate logistic regression model. Ultimately, a nomogram was established using the regression modeling strategies package in the R programming language based on the final multivariate logistic regression model. A receiver operating characteristic (ROC) curve analysis was performed to assess the predictive ability of the nomogram model and the CHA2DS2-VASc score. Pairwise comparisons of the ROC curves were performed using the DeLong test. Statistical significance was defined as a 2-sided $P$ value <0.05. Statistical analyses were performed using SPSS software (version 23.0, IBM Corp, Armonk, NY, USA), R programming language (version 3.6.1, R Foundation), and MedCalc software (version 20.0, MedCalc Software, Belgium).

### Results

#### Characteristics of the Study Population

A total of 1255 non-anticoagulated patients with NVAF (68.5% men) with a mean age of 59.75±10.23 years were enrolled.

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**Table 1.** Baseline clinical characteristics of patients with and without left atrial spontaneous echo contrast.

| Variables                      | All n=1255 | LASEC (-) n=1116 | LASEC (+) n=139 | $P$ value |
|-------------------------------|------------|------------------|----------------|----------|
| Age, years                    | 59.75±10.23| 59.48±10.30      | 61.94±9.41     | 0.007    |
| Age ≥75, n (%)                | 75 (6)     | 65 (5.8)         | 10 (7.2)       | 0.567    |
| Age 65-74, n (%)              | 338 (26.9) | 293 (26.3)       | 45 (32.4)      | 0.125    |
| Female, n (%)                 | 395 (31.5) | 360 (32.3)       | 35 (25.2)      | 0.1      |
| BMI, kg/m$^2$                 | 25.65±2.94 | 25.59±2.96       | 26.17±2.68     | 0.027    |
| Hypertension, n (%)           | 664 (52.9) | 583 (52.2)       | 81 (58.3)      | 0.207    |
| Diastolic heart failure, n (%)| 216 (17.2) | 189 (16.9)       | 27 (19.4)      | 0.475    |
| Prior myocardial infarction, n (%)| 77 (6.1) | 57 (5.1) | 20 (14.4) | <0.001 |
| Vascular disease, n (%)       | 34 (2.7)   | 27 (2.4)         | 7 (5)          | 0.09     |
| Non-paroxysmal AF, n (%)      | 436 (34.7) | 315 (28.2)       | 121 (87.1)     | <0.001   |
| Ejection fraction, n (%)      | 160 (12.7) | 142 (12.7)       | 18 (12.9)      | 0.893    |
| Left atrial diameter, mm      | 38.89±4.70 | 38.37±4.56       | 40.07±3.64     | <0.001   |
| Left atrial enlargement, n (%)| 422 (33.6) | 317 (28.4)       | 105 (75.5)     | <0.001   |
| Ejection fraction, n (%)      | 62.10±5.88 | 62.52±5.42       | 58.69±7.95     | <0.001   |
| LVEF <50%, n (%)              | 47 (3.7)   | 26 (2.3)         | 21 (15.1)      | <0.001   |
| CHA2DS2-VASc Score            | 1.62±1.33 | 1.56±1.31        | 2.13±1.42      | <0.001   |
| CRP, mg/L                     | 0.89 (0.45-2.02) | 0.84 (0.43-1.92) | 1.22 (0.60-2.52) | <0.001 |
| Uric acid, μmol/L             | 356.39±90.28 | 352.23±87.76     | 389.77±102.85  | <0.001   |
| D-dimer, ng/mL                | 81 (52-125) | 79.5 (51-124.00) | 88 (61-132.50) | 0.05     |
| Creatinine, mg/dL             | 75.89±44.28 | 75.56±34.28      | 74.69±18.48    | 0.43     |
| eGFR, mL/min/1.73 m$^2$        | 91.51±17.42 | 92.02±17.56      | 87.39±15.78    | 0.003    |
| Homocysteine, μmol/L          | 14.17±7.32 | 14.01±7.30       | 15.49±7.38     | 0.025    |

LASEC – left atrial spontaneous echo contrast; BMI – body mass index; TIA – transient ischemic attack; AF – atrial fibrillation; LVEF – left ventricular ejection fraction; LVEDD – left ventricular end diastolic diameter; CRP – C-reactive protein; eGFR – estimated glomerular filtration rate.

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**Table 1.** Baseline clinical characteristics of patients with and without left atrial spontaneous echo contrast.
The mean CHA2DS2-VASc score was 1.62±1.33. LASEC was observed in 139 (11.1%) patients. The characteristics of patients with and without LASEC are shown in Table 1. There were no significant differences between the 2 groups in terms of sex, age ≥75 years, age 65-74 years, and antplatelet agent use or in frequency of hypertension, diabetes mellitus, vascular disease, or coronary artery disease. The patients with LASEC were relatively older, with higher body mass index and CHA2DS2-VASc scores than patients without LASEC. The frequency of non-paroxysmal AF, congestive heart failure, and previous stroke/TIA were significantly higher in patients with LASEC. In addition, patients with LASEC had higher levels of CRP, uric acid, and homocysteine, lower levels of eGFR, and similar levels of D-dimer, and creatinine, compared with patients without LASEC. Patients with LASEC also had significantly larger LAD, more LAE, and lower LVEF than patients without LASEC.

### Table 2. Predictors of left atrial spontaneous echo contrast on univariate logistic analysis.

| Variables                        | OR    | 95% CI       | P value |
|----------------------------------|-------|--------------|---------|
| Age                              | 1.025 | 1.007-1.044  | <0.001  |
| Congestive heart failure         | 9.354 | 5.926-14.763 | <0.001  |
| Previous stroke/TIA              | 3.123 | 1.813-5.377  | <0.001  |
| Hypertension                     | 1.277 | 0.893-1.823  | 0.18    |
| Diabetes mellitus                | 1.182 | 0.755-1.851  | 0.464   |
| Non-paroxysmal AF                | 17.094| 10.244-28.523| <0.001  |
| Vascular disease                 | 2.139 | 0.914-5.008  | 0.08    |
| CHA2DS2-VASc score               | 1.305 | 1.152-1.479  | <0.001  |
| Left atrial enlargement          | 7.784 | 5.176-11.706 | <0.001  |
| LVEF                             | 0.914 | 0.891-0.938  | <0.001  |
| LVEF ≤50                         | 7.461 | 4.072-13.671 | <0.001  |
| CRP                              | 1.071 | 1.033-1.111  | <0.001  |
| Uric acid                        | 1.004 | 1.002-1.006  | <0.001  |
| Homocysteine                     | 1.023 | 1.003-1.044  | 0.026   |
| eGFR                             | 0.984 | 0.973-0.994  | 0.002   |

LASEC – left atrial spontaneous echo contrast; OR – odds ratio; CI – confidence interval; TIA – transient ischemic attack; AF – atrial fibrillation; LVEF – left ventricular ejection fraction; CRP – C-reactive protein; eGFR – estimated glomerular filtration rate.

### Table 3. Independent predictors of left atrial spontaneous echo contrast on multivariate logistic analysis.

| Variables                        | OR    | 95% CI       | P value |
|----------------------------------|-------|--------------|---------|
| Age                              | 1.042 | 1.013-1.071  | 0.004   |
| Non-paroxysmal AF                | 10.010| 5.768-17.370 | <0.001  |
| Congestive heart failure         | 6.100 | 2.929-12.704 | <0.001  |
| Left atrial enlargement          | 3.360 | 2.111-5.377  | <0.001  |
| LVEF ≤50                         | 1.873 | 0.728-4.816  | 0.193   |
| CRP                              | 1.040 | 0.994-1.089  | 0.86    |
| Uric acid                        | 1.001 | 0.999-1.004  | 0.253   |
| eGFR                             | 1.003 | 0.988-1.018  | 0.711   |
| Homocysteine                     | 1.003 | 0.974-1.033  | 0.847   |

LASEC – left atrial spontaneous echo contrast; OR – odds ratio; CI – confidence interval; AF – atrial fibrillation; TIA – transient ischemic attack; LVEF – left ventricular ejection fraction; CRP – C-reactive protein; eGFR – estimated glomerular filtration rate.
Independent Predictors of LASEC

The results of the univariate and multivariate logistic regression analyses are presented in Tables 2 and 3. Increased age, congestive heart failure, previous stroke/TIA, non-paroxysmal AF, LAE, LVEF <50%, and higher levels of CRP, uric acid, homocysteine, and eGFR were associated with the risk of LASEC. Furthermore, the independent predictors for LASEC were increased age, non-paroxysmal AF, previous stroke/TIA, congestive heart failure, and LAE. These variables were included in the final multivariate logistic regression model (Table 4).

Construction of the New Risk Score Model

Using the independent predictors identified in the multivariable logistic regression analysis, a nomogram was generated to predict LASEC, and a weighted score ranging from 0 to 100 was assigned to each of the variables (Figure 1). To use the nomogram, each variable was located on the corresponding variable axis, and the number of points for each variable was determined by drawing a vertical line upward to the “Points” axis. Then, the total points were calculated by adding the number of points for all the variables. The sum numbers were located on the “Total Points” axis, and a vertical line was drawn down to the “Risk” axis to determine the risk of LASEC. AF – atrial fibrillation; TIA – transient ischemic attack.

Predictive Performance of the New Risk Score Model

To assess the ability of the new risk score model and the CHA2DS2-VASc score to predict LASEC, ROC curve analysis was performed. The area under the curve (AUC) of the new risk score model was 0.879 (95% confidence interval [CI] 0.849-0.909, \( P < 0.001 \)), with a sensitivity of 85.61% and specificity of 80.47. Thus, the new risk score demonstrated good predictive power for occurrence of LASEC. In contrast, the CHA2DS2-VASc score showed a relatively low predictive power (AUC 0.617, sensitivity 61.1, specificity 55.2, 95% CI 0.568-0.666, \( P < 0.001 \)). Pairwise comparison of the ROC curves showed that the new risk score of points for all the variables. To locate the sum numbers on the “Total Points” axis, a vertical line was drawn down to the “Risk” axis to determine the risk of LASEC. AF – atrial fibrillation; TIA – transient ischemic attack.

Table 4. Multivariate analysis for the construction of the new scoring model.

| Variables              | OR     | 95% CI       | \( P \) value |
|------------------------|--------|--------------|--------------|
| Age                    | 1.039  | 1.016-1.063  | 0.001        |
| Non-paroxysmal AF      | 10.186 | 5.897-17.594 | <0.001       |
| Previous stroke/TIA    | 2.367  | 1.230-4.554  | 0.01         |
| Congestive heart failure| 4.640  | 2.761-7.798  | <0.001       |
| Left atrial enlargement| 3.464  | 2.196-5.462  | <0.001       |

Figure 1. Nomogram for assessing the risk of left atrial spontaneous echo contrast (LASEC) in patients with nonvalvular atrial fibrillation (NVAF). To use the nomogram, each variable was located on the corresponding variable axis, the number of points for each variable was determined by drawing a vertical line upward to the “Points” axis. Then, the total points were calculated by adding the number of points for all the variables. The sum numbers were located on the “Total Points” axis, and a vertical line was drawn down to the “Risk” axis to determine the risk of LASEC. AF – atrial fibrillation; TIA – transient ischemic attack. (R programming language, version 3.6.1, R Foundation) (Adobe Illustrator, version 2020, Adobe Inc.).

Independent Predictors of LASEC

The results of the univariate and multivariate logistic regression analyses are presented in Tables 2 and 3. Increased age, congestive heart failure, previous stroke/TIA, non-paroxysmal AF, LAE, LVEF <50%, and higher levels of CRP, uric acid, homocysteine, and eGFR were associated with the risk of LASEC. Furthermore, the independent predictors for LASEC were increased age, non-paroxysmal AF, previous stroke/TIA, congestive heart failure, and LAE. These variables were included in the final multivariate logistic regression model (Table 4).
The main findings of our study were as follows: (1) The prevalence of LASEC was 11.1% in the non-anticoagulated patients with NVAF who underwent TEE before catheter ablation or LAA occlusion. (2) In the multivariate logistic analysis, increased age, non-paroxysmal AF, previous stroke/TIA, congestive heart failure, and LAE were independent predictors of LASEC. (3) The predictive value of the CHA2DS2-VASc score for LASEC was relatively low, and the new risk score model, composed of variables from the multivariate logistic analysis, showed a much better ability to predict LASEC.

AF is associated with an increased risk of stroke events, and the evaluation of stroke risk is critical for the management of patients with AF [12]. LASEC is a common phenomenon in patients with NVAF, and several studies have shown that its presence is related to LAT formation and stroke events [4,13-15]. Prediction of LASEC may provide additional information for stroke risk stratification in patients with NVAF.

Our results are consistent with those of previous studies that suggest non-paroxysmal AF is associated with an increased risk of LASEC [18-20]. During AF, rapid and disorganized contraction of the LA and LAA results in blood stasis, contributing to LASEC and LAT formation [21,22]. Because of the higher AF burden, patients with non-paroxysmal AF are more likely to develop LASEC and LAT [23]. AF induces atrial fibrosis [24,25]. Compared with paroxysmal AF, non-paroxysmal AF shows a higher degree of atrial fibrosis [26]. Increased atrial fibrosis can cause LASEC and LAT formation [27]. Abnormal blood constituents are another important factor for thrombogenesis in patients with AF. There are different degrees of coagulation factor abnormality in paroxysmal and non-paroxysmal AF, which may explain the difference in incidence of LASEC [28].

Previous studies have shown that LAE is associated with LAT/LASEC and consequent thromboembolic events [5,29,30]. The exact mechanisms of this association are not fully understood, but several hypotheses have been proposed. First, LAE induces changes in LA hemodynamics, promoting blood stasis, which
may predispose patients to LASEC and LAT formation [31,32]. Second, LAE is associated with AF burden [33], which was previously found to be associated with an increased risk of thrombus formation [34].

The CHA2DS2-VASc score is a validated tool for predicting the risk of stroke events in patients with NVAF [35,36]. However, previous studies have shown that the predictive power of the CHA2DS2-VASc score for the presence of LASEC in patients with NVAF is modest [5-9]. In our analysis, patients with LASEC had significantly higher CHA2DS2-VASc scores than did patients without LASEC. Nevertheless, consistent with previous studies, we showed that the CHA2DS2-VASc score had a relatively low predictive power for LASEC [5-9]. There are several possible explanations for this result. First, LASEC is a risk factor for cardioembolic stroke [37]. However, most components of the CHA2DS2-VASc score are risk factors for atherosclerosis, which may not be applicable to the prediction of LASEC. Secondly, the causes of LASEC vary [5,19,38]. The CHA2DS2-VASc score might not include all risk factors associated with LASEC formation, such as AF type or biochemical and echocardiographic parameters.

Based on the final multivariate logistic model, we successfully established a new risk score model that included variables for increased age, non-paroxysmal AF, previous stroke/TIA, congestive heart failure, and LAE. The AUC of the new scoring model was 0.879, and in a pairwise comparison of ROC curves, the AUC of the new scoring model was significantly higher than that of the CHA2DS2-VASc score (0.879 vs 0.617, P<0.001). This indicates that the new scoring model had a very good ability to predict LASEC in patients with NVAF, which was better than that of the CHA2DS2-VASc score. Using the new scoring model to predict the presence of LASEC may help clinicians to stratify the stroke risk in non-anticoagulated patients with NVAF and facilitate the decision-making process on treatment strategy. Moreover, the new risk scoring model is composed of simple and easily obtained clinical variables, making it convenient to use in clinical practice.

**Limitations**

The present study had several limitations. First, this was a single-center study, and the sample size was relatively small, which may have underpowered the results. In the future, multicenter studies with larger sample sizes are needed. Second, this was a retrospective, cross-sectional study, and the potential causal relationship could not be determined. Third, most of the study population was eligible for AF catheter ablation, creating a selection bias in our study; our study’s population might not represent the general population with NVAF. In addition, these patients had relatively low CHA2DS2-VASc scores and were not on anticoagulation, which would affect the correlation between the assumed predictive score model and the CHA2DS2-VASc score model. Fourth, we did not establish a validation group to verify the accuracy of the risk score model, and future external validations in a different cohort are needed.

**Conclusions**

In conclusion, our study demonstrated that increased age, non-paroxysmal AF, previous stroke/TIA, congestive heart failure, and LAE were independent predictors of LASEC. The new risk score model combining the above predictors could precisely predict the presence of LASEC in non-anticoagulated patients with NVAF, which may help us to optimize the stroke risk stratification and early stroke prevention in these patients. Further prospective, multicenter studies with larger populations are needed to confirm the predictive value of our new scoring model for LASEC and subsequent thromboembolic events.

**Declaration of Figures’ Authenticity**

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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