Left Atrial Strain as Evaluated by Two-Dimensional Speckle Tracking Predicts Left Atrial Appendage Dysfunction in Chinese Patients with Atrial Fibrillation

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Left atrial appendage (LAA) dysfunction identified by transesophageal echocardiography (TEE) is a powerful predictor of stroke in patients with atrial fibrillation (AF). The aim of our study is to assess if there is a correlation between the left atrial (LA) functional parameter and LAA dysfunction in the AF patients. This cross-sectional study included a total of 249 Chinese AF patients who did not have cardiac valvular diseases and were undergoing cardiac ablation. TEE was performed in all the patients who were categorized into two groups according to their left atrial appendage (LAA) function. A total of 120 of the 249 AF patients had LAA dysfunction. Univariate and multivariate logistic regression was conducted to assess the independent factors that correlated with the LAA dysfunction. Different predictive models for the LAA dysfunction were compared with the receiver operating characteristic (ROC) curve. The final ROC curve on the development and validation datasets was drawn based on the calculation of each area under the curves (AUC). Univariate and multivariate analysis showed that the peak left atrial strain (PLAS) was the most significant factor that correlated with the LAA dysfunction. PLAS did not show inferiority amongst all the models and revealed strong discrimination ability on both the development and validation datasets with AUC 0.818 and 0.817. Our study showed that a decrease in PLAS is independently associated with LAA dysfunction in the AF patients.

1. Introduction

AF is the most frequent type of arrhythmia, having a global prevalence of 1% to 2%. AF is a public health challenge associated with high comorbidity and an increased mortality risk [1–4]. For example, AF increases the risk of stroke by five times and is observed in ~33.3% of all ischemic stroke patients [5, 6]. In patients presenting with nonvalvular AF, over 90% of the thrombi originate in the LAA. Anatomical remodeling, atrial fibrosis, and a decline in the contractility of the LA myocardium are factors associated with left atrial thrombus/spontaneous echocardiographic contrast (LAT/SEC), as well as reductions in LAA flow velocities by TEE, which has been found to predispose patients to stroke [7]. Conventionally, TTE has been used to observe anatomical changes of LA following remodeling in the AF patients [8]; however, it has been increasingly replaced with two-dimensional (2D) speckle tracking echocardiography in order to evaluate LA function [9–11]. Most studies that report the association between LA and LAA function [12–15] were carried out on occidental populations. Compared to Western countries, stroke incidence in China is universally higher and the number of cases undergoing AF ablation procedures has been rapidly increasing. Moreover, stroke,
which is associated with AF, is the second leading cause of death in China [16]. Here, we aim to provide a noninvasive imaging modality to evaluate the LAA function in Chinese patients.

2. Methods

A retrospective and cross-sectional study was conducted at the Guangdong Provincial People’s Hospital. This study has been approved by the institutional review board of the hospital. A total of 700 patients diagnosed with AF at the Guangdong Provincial People’s Hospital from July 2014 to December 2017 (Figure 1) were included in this study. Patients exhibiting the following criteria were excluded from this study: pregnancy (n = 105), moderate to severe valvular dysfunction (n = 212), dilated/hypertrophic cardiomyopathy (n = 50), failed TEE (n = 20), and cases containing unqualified images (n = 64), either through failure to capture the total LA geometry (mostly incomplete contours of the LA roof) or image quality precluding speckle tracking. The patients were informed of research objectives and protocols, and they provided consent to participate in the study. Clinical information was collected at the time of their first hospital visit, including demographic data, current medications, and past medical history (PMH). The CHA2DS2-VASC score was calculated for each patient, and they underwent evaluation with TTE or/and TEE before proceeding to AF management.

2.1. Transthoracic Echocardiography. A two-dimension gray scale echocardiography was used to obtain standard view images, parasternal long-axis view, apical four-chamber view, and apical two-chamber views, where the frame rate was set between 65 and 75 frames per second. In addition, foreshortening of the left atrium was avoided [17]. Briefly, echocardiographic parameters were averaged from a total of five cardiac cycles [12], all of which contained clear image quality. TTE was measured using a Vivid E9 ultrasound instrument (GE Healthcare, Wauwatosa, WI, USA), containing a sector transducer (2.5–3.75MHz). A total LA geometry (mostly incomplete contours of the LA roof) or image quality precluding speckle tracking. The patients were informed of research objectives and protocols, and they provided consent to participate in the study. Clinical information was collected at the time of their first hospital visit, including demographic data, current medications, and past medical history (PMH). The CHA2DS2-VASC score was calculated for each patient, and they underwent evaluation with TTE or/and TEE before proceeding to AF management.

2.2. Transesophageal Echocardiography. During TEE examination (Figure 2), images were acquired using a transesophageal probe (2.9–7.0MHz). Briefly, LAAeV was measured using a pulsed wave Doppler, where the sample volume was placed 1 cm distal from the mouth of the appendage. The maximum emptying velocity was calculated from an average of five well-defined emptying waves [18]. The LAT was defined as a fixed or mobile echogenic mass that clearly differed from the LA or LAA tissue. SEC was defined when dynamic, “smoke-like” echoes were seen within the atria and could not be eliminated by altering the gain settings [19, 20]. According to TEE findings, (1) the LAAeV < 40 cm/s and (2) LAT/SEC was found regardless of LAAeV; if either one is positive, the condition of LAA dysfunction was met [7].

2.3. Speckle Tracking Imaging. Cine loops were used to determine speckle tracking analysis (Figure 2) At least 5 consecutive beats from the three standard apical views were collected for analyses. Average PLAS was measured at the end of the reservoir phase with the tracking location marker placed at the end of the QRS wave calculated from 5 beats in patients with AF rhythm [21]. The LA endocardial border was manually traced in both the four- and two-chamber views with the regions of interest (ROI) encompassing the endocardial border of the mitral annulus, carefully excluding pulmonary veins and the LA appendage orifices. The thickness of the ROI was adjusted to the thinnest part to adapt to the atria. The data were analyzed using EchoPAC software (version 201) by two independent echocardiologists, who were blinded to clinical as well as other identifiers revealing patient characteristics.

2.4. Statistical Analysis. Data were analyzed using R (http://www.R-project.org) and Empower Stats software (http://www.empower.stats.com, X&Y solutions, Inc., Boston, MA, USA). Continuous variables were analyzed using the t-test (normal distribution) or Kruskal–Wallis rank sum test (nonnormal distribution), and categorical variables were analyzed using the χ² test. Variables associated with LAAeV were evaluated by univariate logistics regression analysis, and those with a p value <0.1 were further analyzed using the multivariable logistics regression model to test for independence. The receiver operating characteristic (ROC) curve was used to evaluate the prognostic predictive value of PLAS in LAA dysfunction. Two-sided p values with p <0.05 are considered statistically significant.

Reproducibility of the PLAS measurement was assessed in 20 randomly selected subjects. The inter- and intraobserver correlation coefficients were 0.8 and 0.9, respectively, which are consistent with those of previous work [22].
700 AF patients with TTE or/and TEE assessments from July 2014 to December 2017

Exclusion criteria:
- Pregnancy (n = 105);
- Moderate to severe valvular dysfunction (n = 212);
- Dilated/ Hypertrophic cardiomyopathy (n = 50);
- Failed TEE (n = 20);

313 AF patients with TTE and TEE assessments

Imaging sieving criteria:
- Unqualified images (n = 40);
- Unclear ECG (n = 24);

Final 249 AF patients were analysed

Figure 1: Flow chart of the study screening and selection process for patients used in the study.

3. Results

3.1. Patient Characteristics. The basic characteristics of patients used in this study are depicted by a flow diagram (Figure 1). On the basis of inclusion and exclusion criteria, a total of 249 patients undergoing both TEE and TTE were included in the study. The mean age of the patients was 59.7 years (ranging from 49.7 to 69.7 years), and the majority of the patients were male (72.7%). Following TEE measurement, it was observed that LAA dysfunction was present in 120 patients, with an incidence rate of 48.2%, where 118 patients exhibited LAAeV < 40 cm/s. Out of the 120 identified patients with the LAA dysfunction, 43 had LAT/SEC and 41 showed a LAAeV < 40 cm/s measurement. The basic characteristics of patients with and without LAA dysfunction are presented in Table 1. Patients with LAA dysfunction were older (61.4 ± 9.7 vs. 58.1 ± 12.0, p = 0.021) and had a higher heart rate (83.6 ± 24.2 vs. 76.7 ± 22.9, p = 0.006) compared to controls. The number of patients presenting both LAA dysfunction and AF rhythm (OR 3.99, 95% CI: 2.36, 6.76, p < 0.0001) were statistically significant.

3.2. Univariate and Multiple Logistic Regression Analysis of LAA Dysfunction. Univariate analysis showed that 18 variables, including age (OR 1.03, 95% CI: 1.00, 1.05, p = 0.0224), heart rhythm (OR 3.99, 95% CI: 2.36, 6.76, p < 0.0001), heart rate (OR 1.01, 95% CI: 1.00, 1.02, p = 0.0243), CHA2DS2-VASc score (OR 1.22, 95% CI: 1.04, 1.42, p = 0.0141), LAD (OR 1.20, 95% CI: 1.13, 1.27, p < 0.0001), LA longitudinal diameter (OR 1.16, 95% CI: 1.11, 1.23, p < 0.0001), LA transverse diameter (OR 1.17, 95% CI: 1.11, 1.23, p < 0.0001), LAVmax (OR 1.06, 95% CI: 1.04, 1.08, p < 0.0001), LAVmin (OR 1.09, 95% CI: 1.07, 1.12, p < 0.0001), LAEF (OR 0.92, 95% CI: 0.89, 0.94, p < 0.0001), E/e’ (OR 1.09, 95% CI: 1.02, 1.16, p = 0.0127), LVDd (OR 1.18, 95% CI: 1.10, 1.25, p < 0.0001), LVSD (OR 1.17, 95% CI: 1.10, 1.25, p < 0.0001), LVDV (OR 1.03, 95% CI: 1.02, 1.05, p < 0.0001), LVSV (OR 1.05, 95% CI: 1.03, 1.08, p < 0.0001), Simpson-LVEF (OR 0.95, 95% CI: 0.92, 0.98, p = 0.0043), and PLAS (OR 0.89, 95% CI: 0.86, 0.92, p < 0.0001) were associated with LAA dysfunction (Table 2). These identified variables were then further analyzed using multiple logistic regression, and PLAS (OR 0.90, 95% CI: 0.85, 0.95, p < 0.0005) was the only parameter significantly associated with LAA dysfunction after adjusting for sex, PMH of ablation, International Normalized Ratio (INR), AF, and isovolumic relaxation time (IVRT) (Table 2). The multivariate regression analysis showed that LAA dysfunction was consistently related to the tertials of the PLAS (Table 3). There was a linear relationship between PLAS and LAA dysfunction (Figure 3).

3.3. Sensitivity Analysis. The ROC curve for the predictive models of LAA dysfunction are presented in Figure 3. Model 1 includes the CHA2DS2-VASc score only, while Model 2 includes both the CHA2DS2-VASc score and LAEF. Model 3 includes all the three factors, viz., CHA2DS2-VASc score, LAEF, and PLAS, while Model 4 includes PLAS only. Different models performances were compared, and it was observed that PLAS of Model 4 demonstrated similar accuracy and discriminability with Model 3, including CHA2DS2-VASc score, LAEF, and PLAS. For analyses, all subjects were categorized into two equal groups, viz., development and validation groups (Figure 4). The AUC for the development group was 0.818 (95% CI: 0.744, 0.818), yielding a sensitivity of 63.33% with a specificity of 91.18% at the optimal cutoff value (PLAS = 0.2044). In the validation set, the AUC was 0.817 (95% CI: 0.741, 0.894), along with a sensitivity of 78.33% and a specificity of 78.33% at the corresponding threshold.
Multivariate logistic regression analysis showed that a velocity and/or thrombus on TEE examination in AF patients to investigate the association between the reduced peak LA longitudinal strain, assessed by STE, and the presence of LAA reduced emptying velocity and/or thrombus on TEE examination in AF patients. Multivariate logistic regression analysis showed that a decrease in PLAS was an independent predictor of LAA dysfunction. By comparing the different models, it was observed that PLAS alone showed strong discriminability. These results indicate that in real life settings, PLAS can alternatively be used to rule out the possibility of LAA dysfunction. By comparing the different models, it was observed that PLAS alone showed strong discriminability. These results indicate that in real life settings, PLAS can alternatively be used to rule out the possibility of LAA dysfunction. By comparing the different models, it was observed that PLAS alone showed strong discriminability. These results indicate that in real life settings, PLAS can alternatively be used to rule out the possibility of LAA dysfunction. By comparing the different models, it was observed that PLAS alone showed strong discriminability. These results indicate that in real life settings, PLAS can alternatively be used to rule out the possibility of LAA dysfunction. By comparing the different models, it was observed that PLAS alone showed strong discriminability. These results indicate that in real life settings, PLAS can alternatively be used to rule out the possibility of LAA dysfunction. By comparing the different models, it was observed that PLAS alone showed strong discriminability. These results indicate that in real life settings, PLAS can alternatively be used to rule out the possibility of LAA dysfunction. By comparing the different models, it was observed that PLAS alone showed strong discriminability. These results indicate that in real life settings, PLAS can alternatively be used to rule out the possibility of LAA dysfunction. By comparing the different models, it was observed that PLAS alone showed strong discriminability. These results indicate that in real life settings, PLAS can alternatively be used to rule out the possibility of LAA dysfunction. By comparing the different models, it was observed that PLAS alone showed strong discriminability. These results indicate that in real life settings, PLAS can alternatively be used to rule out the possibility of LAA dysfunction. By comparing the different models, it was observed that PLAS alone showed strong discriminability. These results indicate that in real life settings, PLAS can alternatively be used to rule out the possibility of LAA dysfunction.

CHA2DS2-VASc scores, including risk factors of age, hypertension, heart failure, and diabetes mellitus, are...
clinically measurable indicators promoting atrial remodeling and are widely used to predict the risk of stroke in patients with AF. In our study, we did not find the CHA2DS2-VASc score to be significantly associated with LAA dysfunction, and this score was not an ideal platform to predict risks associated with stroke using the LAT value as a comparator. This inconsistency was also observed in previous studies [23, 24]. It is clear that the scoring system includes an assessment of the risks of early stroke, including those that cause vascular wall injury and hypercoagulable
status [25, 26]. However, the scoring system did not analyze the effect of AF itself on cardiac remodeling which is a continuous present risk factor for stroke. Other possible variations include AF duration, structural cardiac abnormalities, race, anticoagulation adequacy, and other cardiovascular risk factors that might be associated with the observed effects. Yet, these indicators are relatively difficult to define. Consequently, recent efforts are focused on studies to reframe the assessment of the risk of stroke based on cardiac structure and function [27, 28].

AF has been associated with electromechanical remodeling of the LA. LAA plays a role in maintaining LA pressure as an actively contracting structure [29]. As result of the intravascular volume status and remodeling in AF, LAA has become the primary location for the formation of thrombus [30, 31]. In the current study, we observed LAA as the site of thrombi in all patients. TEE is considered as the gold standard for the assessment of the LA function [32]. However, as it is a semi-invasive procedure not tolerated by all patients, it remains controversial as to whether it is rational to use it as a measurement tool for the serial resolution of LAT or SEC in patients with a history of LAT or SEC [33].

Direct assessments of LA function by TTE have also been proposed. Conventional 2D TTE has a low sensitivity of only 3–19% for the detection of thrombi in LA and especially in LAA [34]. Studies, such as those performed by Tamura et al. as well as Uretsky et al. [36], were carried out to resolve the problem. These studies found that TTE-measured LAA tip Doppler tissue velocity was an independent predictor of LA thrombus formation and may be a useful indicator for risk stratification of AF. Nevertheless, LAA is generally difficult to be clearly and totally visualized on TTE, especially in patients with small LAA.

Kuppahally et al. [13] showed that the LA strain inversely correlates with LA fibrosis in AF patients, suggesting that fibrosis decreases with LA compliance. Replacement of healthy atrial tissue with fibrotic tissue in AF leads to a reduction in the atrial contractile function and blood stasis, which results in the process of thrombus formation [37–39]. Our study observed that an impaired PLAS independently correlates with decreased LAA function. It was also found to be the strongest independent predictor of LAA dysfunction multivariate analysis. Other conventional TTE parameters were found to be significant in univariate analysis but no longer maintained their significance in multivariate analysis. The associations between LA strain and TEE changes were also described in a previous study performed by Meng-Ruo Zhu et al. [40]. The difference here is that we defined LAA dysfunction as both decreased LAAeV and presence of LAT/SEC considering patient PMH may reduce the incidence of LAT/SEC. Therefore, we had a higher LA strain threshold for predicting LAA dysfunction compared to the one used in other studies [40]. Furthermore the diagnostic performance of PLAS to detect LAA dysfunction is strong. The addition of the CHA2DS2-VASc score and LAEF to PLAS offered no further discrimination in the detection of LAA dysfunction.
that offered by PLAS alone, which suggests that in real-world practice, when an AF patient cannot undergo TEE, the PLAS can alternatively be used to rule out the possibility of thrombus and to determine the subsequent needs for other imaging assessments.

Our study has few limitations including the fact that it is composed of a small sample size with infrequent LAT events, which impaired our ability to analyze many covariates within a single regression model. Thus, we meticulously chose the covariates to be analyzed in the logistic regression models. It is still possible that some weakly associated parameters may have been missed. Secondly, the PLAS was calculated using EchoPAC software (version 201). Vendor differences should be considered when using different machines. Finally, we used the current software for LV analysis to study the LA pattern strain because a dedicated software for LA analysis has not yet been released.

Thus, it can be concluded that a decrease in PLAS is significantly associated with LAA dysfunction in patients with nonvalvular AF, providing a parameter to identify patients with nonvalvular AF at high risk of stroke.

**Abbreviations**

AF: Atrial fibrillation  
IVRT: Isovolumic relaxation time  
LA: Left atria  
LAA: Left atrial appendage  
LAAeV: Left atrial appendage emptying velocity  
LAD: Left atrial dimension  
LAEF: Left atrial emptying fraction  
LAT: Left atrial thrombi  
LAVmax: Left atrial maximum volume  
LAVmin: Left atrial minimum volume  
LVDD: Left ventricular end-diastolic dimension  
LVDV: Left ventricular end-diastolic volume  
LVEF: Left ventricular ejection fraction  
LVsd: Left ventricular end-systolic dimension  
LVSV: Left ventricular end-systolic volume  
SEC: Spontaneous echocardiographic contrast  
STE: Speckle tracking echocardiography  
TEE: Transesophageal echocardiography  
TTE: Transthoracic echocardiography  
PLAS: Peak left atrial strain.

**Data Availability**

The data used to support the findings of this study are available from the corresponding author upon request. The data are not publicly available due to the potential revealing of information compromising patient identity.

**Conflicts of Interest**

The authors declare no conflicts of interest.

**Authors’ Contributions**

Yu Wang, Mingqi Li, and Lishan Zhong contributed equally to this work.

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