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Automatic Echocardiographic Assessment of Left Atrial Function for Prediction of Low-Voltage Areas in Non-Valvular Atrial Fibrillation

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Purpose: Left atrial low-voltage areas (LA-LVAs) identified by 3D-electroanatomical mapping are crucial for determining treatment strategies and prognosis in patients with atrial fibrillation (AF). However, convenient and accurate prediction of LA-LVAs remains challenging. This study aimed to assess the viability of utilizing automatically obtained echocardiographic parameters to predict the presence of LA-LVAs in patients with non-valvular atrial fibrillation (NVAF).

Patients and Methods: This retrospective study included 190 NVAF patients who underwent initial catheter ablation. Before ablation, echocardiographic data were obtained, left atrial volume and strain were automatically calculated using advanced software (Dynamic-HeartModel and AutoStrain). Electroanatomic mapping (EAM) was also performed. Results were compared between patients with LA-LVAs ≥5% (LVAs group) and <5% (non-LVAs group).

Results: LA-LVAs were observed in 81 patients (42.6%), with a significantly higher incidence in those with persistent AF than paroxysmal AF (55.6% vs 19.3%, P <0.001). Compared with the non-LVAs group, the LVAs group included significantly older patients, lower left ventricular ejection fraction, higher heart rate, and higher E/e' ratio (P <0.05). The LVAs group exhibited higher left atrial $volume_{max}$ index ($LAVi_{max}$) and lower left atrial reservoir strain (LASr) (P <0.001). In multivariate analysis, both $LAVi_{max}$ and LASr emerged as independent indicators of LVAs (OR 0.85; 95% CI 0.80–0.90, P<0.001) and (OR 1.15, 95% CI 1.02–1.29, P =0.021). ROC analysis demonstrated good predictive capacity for LA-LVAs, with an AUC of 0.733 (95% CI 0.650–0.794, P <0.001) for $LAVi_{max}$ and 0.839 (95% CI 0.779–0.898, P <0.001) for LASr.

Conclusion: Automatic assessment of $LAVi_{max}$ and LASr presents a promising non-invasive modality for predicting the presence of LA-LVAs and evaluating significant atrial remodeling in NVAF patients. This approach holds potential for aiding in risk stratification and treatment decision-making, ultimately improving clinical outcomes in patients.

Keywords: echocardiography, Dynamic-HeartModel, AutoStrain, non-valvular atrial fibrillation, left atrial low-voltage areas

Introduction

Atrial fibrillation (AF) is a prevalent cardiac arrhythmia, often associated with atrial structural remodeling, encompassing atrial dilation and tissue fibrosis.[1] Fibrosis in the atrium diminishes the excitable tissues responsible for the local electrogram detected during electroanatomic mapping (EAM), resulting in smaller bipolar voltages, referred to as low-voltage areas (LVAs) that can exist in either the left or right atrium.[2] In clinical practice, atrial voltage mapping is commonly employed to guide ablation strategies and predict the likelihood of AF recurrence post-catheter ablation.[3,4] Notably, larger left atrial volume (LAV) and higher LVAs burden are identified as risk factors for AF recurrence, especially in patients with persistent AF.[5]

To quantitatively identify scars and fibrosis on the atrial wall, late gadolinium enhancement magnetic resonance imaging (LGE-MRI) and EAM are currently utilized.[6] However, LGE-MRI is cost-intensive and technically challenging,

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and EAM, while informative, is invasive and performed during ablation procedures, limiting its preoperative evaluation utility. Two-dimensional speckle-tracking echocardiography (2D-STE) emerges as a non-invasive and convenient modality for detecting early functional remodeling preceding anatomical changes.[7] Studies have demonstrated its utility as an alternative marker for left atrial(LA) structural remodeling and fibrosis, showing a direct correlation between histological LA fibrosis and 2D-STE.[8] Specifically, left atrial reservoir strain (LASr) has been associated with fibrosis extent observed on LGE-MRI, suggesting its role as a surrogate marker for fibrosis in patients with persistent AF.[9] Importantly, LASr remains less influenced by the patient's rhythm during examination, whether in sinus or AF rhythm.[10] This aligns well with our goal to provide a practical imaging technique that can be applied to all patients, regardless of their AF rhythm during examination. A previous study demonstrated that a larger left atrial volume (LAV), indicative of LA remodeling, exhibited a negative correlation with LASr, this association was observed independently of left ventricular global longitudinal strain (LV-GLS).[11] However, conventional myocardial strain measurement methods are complex and observer-dependent.

Recent technological advancements introduce new echocardiographic techniques for accurate volume quantification, including Dynamic-HeartModel, an fully automated adaptive left heart chamber quantification software.[12] This technology enables rapid and simple quantification of LAV and left ventricular (LV) volume, and left ventricular ejection fraction (LV EF). Additionally, automated quantification techniques for LA strain assessment offer time-saving benefits and improved measurement accuracy and reproducibility.[13] In our study, we obtained left atrial maximum volume index ($LAVi_{max}$) using Dynamic-HeartModel and analyzed myocardial motion using AutoStrain quantification technology. Our aim was to predict the presence of left atrial low-voltage areas (LA-LVAs) through a comprehensive evaluation of LA morphology and function, providing a reference for risk assessment and personalized ablation treatment in patients with NVAF.

Materials and Methods

Study Design and Population

This single-center, retrospective study consecutively included 227 patients with NVAF who underwent transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) before catheter ablation and EAM during sinus rhythm at the First Affiliated Hospital of Guangxi Medical University between January 2022 and October 2023. The research included paroxysmal and persistent AF, were classified into two types based on the guideline.[14] The exclusion criteria are as follows: (1)atrial and/or atrial appendage thrombi; (2)valvular heart disease, prosthetic valve replacement; (3)congenital heart disease; (4)moderate or severe mitral regurgitation; and(5)acute coronary syndrome. According to inclusion and exclusion criteria, a total of 190 individuals were included. LA-LVAs are typically defined as regions in the LA with bipolar voltage <0.5 mV during sinus rhythm, often reflecting signs of diseased myocardium and progressive remodeling of LA. The correlation between LVAs and LA fibrosis has been confirmed.[15] Based on previous research findings, patients with LA-LVAs ≥5% had a higher recurrence rate of AF after ablation.[16] We divided the cohort into two groups: the LVAs group (LA-LVAs ≥5%) and the non-LVAs group (LA-LVAs <5%) (Figure 1). Retrospective analysis incorporated the clinical and echocardiographic data of the included patients.

This study complied with the Declaration of Helsinki. All patients provided written informed consent and study was approved by the Research Ethics Committee of First Affiliated Hospital of Guangxi Medical University(approval number 2022-KT-077).

Echocardiographic Imaging and Analysis

Measurement of Cardiac Chamber Volume Data and Left Ventricular Function

Routine transthoracic echocardiography was performed 1–2 days before catheter ablation. The imaging was conducted using either the Philips Epic7C or Philips CVx cardiac ultrasound scanner, along with the S5-1 broadband sector array transducer and X5-1 xMATRIX array transducer. All echocardiographic imaging was conducted by 2 experienced echocardiographers.

The left ventricular end-diastolic volume (LV EDV), left ventricular end-systolic volume (LV ESV), and left ventricular ejection fraction (LV EF) were calculated using Dynamic-HeartModel. Additionally, the maximum left atrial

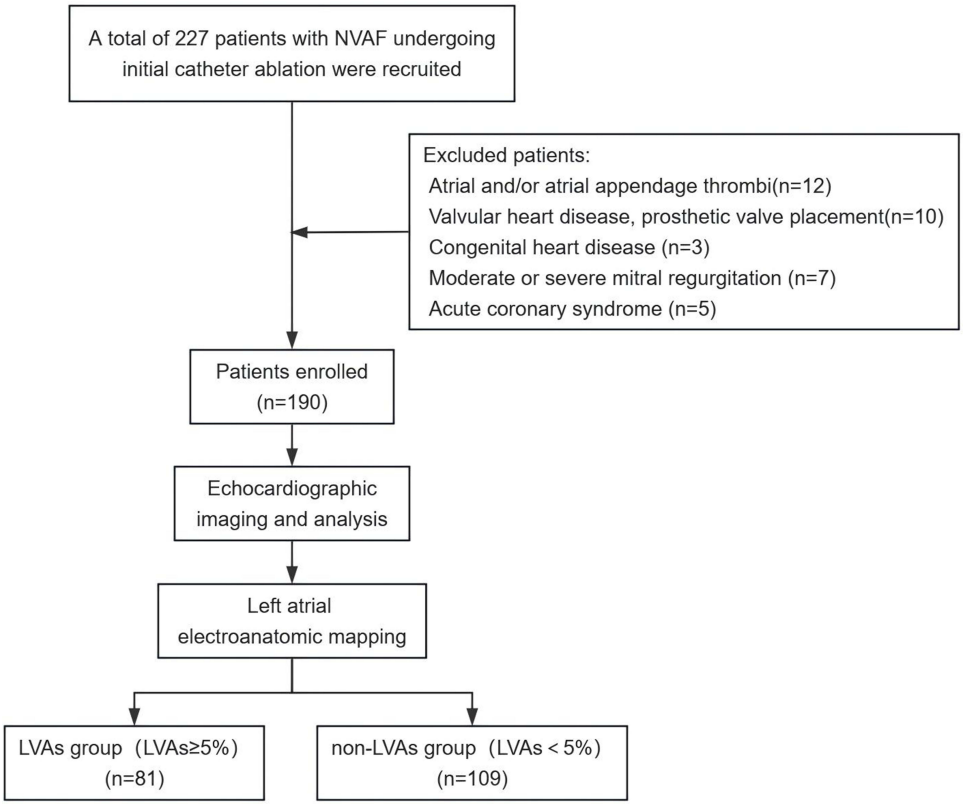

Figure 1 The flowchart of the selection of study participants.
Abbreviations: NVAF, non-valvular atrial fibrillation; LVAs, low-voltage areas.

volume (LAVmax) was also determined (Figure 2). LV EDV and LAVmax were adjusted by the body surface area(LV EDVi, $LAVi_{max}$, respectively).

LV diastolic function was assessed based on established recommendations from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[17] Trans-mitral flow was recorded using pulsed wave Doppler echocardiography from the apical four-chamber view, with the sample volume positioned at the tips of the mitral leaflets to measure the peak E wave velocity.

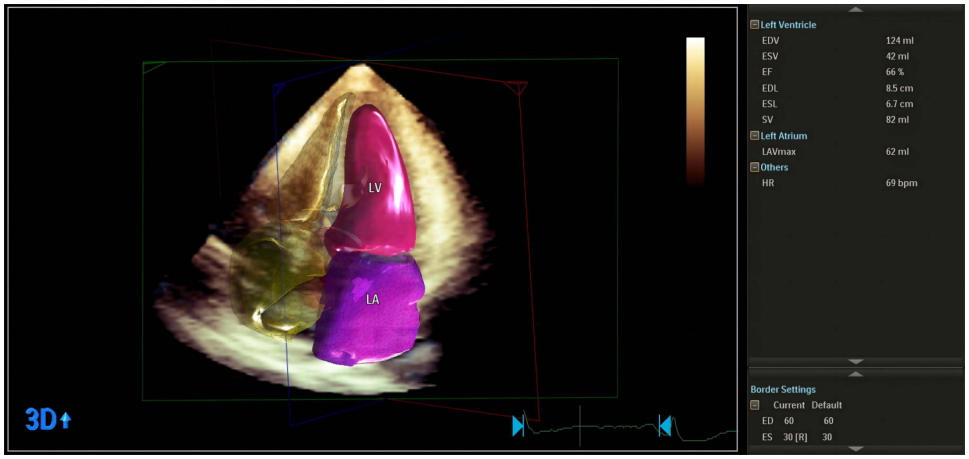

Figure 2 Representative Images of Dynamic-HeartModel.
Abbreviations: LV EDV, left ventricular end diastolic volume; LV ESV, left ventricular end systolic volume; LV EF, ejection fraction; LAVmax, maximum left atrial volume; HR, heart rate.

Tissue Doppler imaging was performed in the apical four-chamber view, with the pulsed wave Doppler sample volume placed at the septal and lateral mitral annulus. The peak annular systolic wave velocities (e' septal and e' lateral) were recorded. The mitral E/e' septal and E/e' lateral ratios were calculated from these measurements, along with their mean (E/e' ratio).

AutoStrain Analysis of LA

Online strain analysis was performed by the AutoStrain software. The LA strain application was selected for the analysis of the LA. Due to the reliable outcomes achievable with single-plane left atrial strain measurements, this study employed the apical four-chamber view for comprehensive longitudinal LA strain assessment.[7] The LA strain is measured using a minimum loop length of 2 beats from the apical four-chamber view. Advanced Automatic View Recognition technology identifies the LA, and places the LA border automatically. The software provides average strain measurements for three major LA functions throughout the cardiac cycle: reservoir (LASr), conduit (LAScd), and contractile (LASct) values.

LASr is measured as the peak positive value with LA filling in systole, prior to mitral valve opening. LAScd is measured between mitral valve opening and atrial contraction during LA passive emptying. LASct corresponds with atrial contraction in late diastole and is only observed in the sinus rhythm. During atrial fibrillation, LAScd represents the difference in LA strain values between mitral valve closure and mitral valve opening, which is a negative value. The absolute value of LAScd is equal to LASr. Therefore, we selected LASr as the research factor.[18] The reference point for deformation analysis was at end diastole (Figure 3). We chose this point as the timing of initial length for atrial strain assessment because it is easier to identify the R wave than the P wave, allowing for its generalization for all patients regardless of their basal cardiac rhythm. After the automatic strain analysis, the two observers reviewed the tracking quality for each myocardial segment. If the tracking of more than two cardiac segments in the same view was unsatisfactory, the case was considered inadequate for analysis.

The E/e' ratio to LASr was used to calculate the LA-stiffness [LA-stiffness=(E/e' ratio)/LASr].[19]

Left Atrial Electroanatomic Mapping

The administration of antiarrhythmic drugs was ceased for a minimum duration of five half-lives prior to undergoing catheter ablation. After undergoing pulmonary vein isolation (PVI), all patients with paroxysmal AF underwent LA EAM directly. In cases of persistent AF, cardioversion was performed, followed by voltage mapping after sinus rhythm restoration. Voltage mapping was performed using the ST ablation catheter (Johnson & Johnson, USA), with pressure ranging from 5 to 30g during point acquisition.

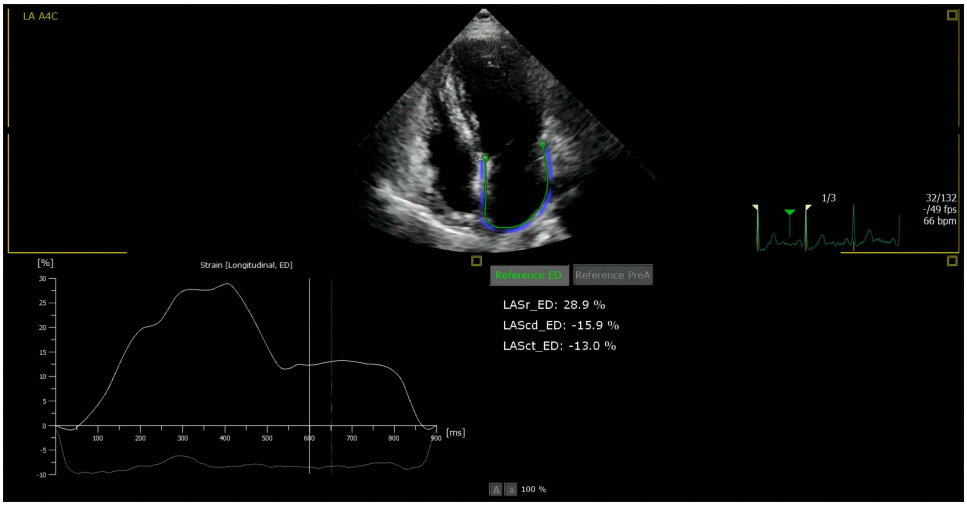

Figure 3 AutoStrain for left atrial.
Abbreviations: Reference ED, reference point at end diastole; LASr, left atrial reservoir strain; LAScd, left atrial conduit strain; LASct, left atrial contractile strain.

Statistical Analysis

Continuous variables were presented as mean ± SD for normally distributed data, and as median with interquartile range (IQR) for non-normally distributed data. Categorical variables were expressed as frequency (%). Non-normally distributed variables were analyzed using Spearman correlation tests. Statistical analysis of continuous variables between groups was conducted using paired Student's *t*-test for normally distributed variables or Wilcoxon rank-sum test for non-normally distributed variables, as appropriate. Categorical variables were compared using the chi-square test. Linear binary regression was employed to evaluate risk factors for dichotomous variables. Univariate analyses were initially performed, and only variables found to be statistically significant were entered into multivariate analysis. The independent association with LA-LVAs was assessed using multivariate analysis. Receiver operating characteristic (ROC) curves were generated to calculate the area under the ROC curve (AUC) values, with 95% confidence intervals (CI), and to determine the sensitivity and specificity of each variable as predictors of LA-LVAs. All analyses were conducted using R software (version 4.2.2).

Results

Clinical and Paraclinical Characteristics

In total, 190 patients undergoing initial catheter ablation were enrolled. Basic clinical data of patients were shown in Table 1.

Left Atrial Low-Voltage Areas Study

The statistical analysis compared data between the non-LVAs group and the LVAs group, revealing a higher prevalence of LA-LVAs in patients with Persistent AF and older age compared to those without. Additionally, significant differences were observed in several other clinical and echocardiographic parameters between the two groups, including heart rate

Table 1 Basic Clinical Data of Study Subjects

Variable	Value
Age (years)	60 (53, 66)
Female Gender, n(%)	53 (27.9%)
BMI ($kg/m^{2)}$	24.4 (22.6, 26.8)
BSA (m^2)	1.75 (1.63, 1.85)
SBP (mmHg)	126 ±19
DBP (mmHg)	79 (72, 88)
HR (bpm)	78 (69, 89)
Hypertension, n(%)	78 (41.1%)
Diabetes Mellitus, n(%)	24 (12.6%)
Cerebrovascular disease, n(%)	19 (10.0%)
Coronary Artery Disease, n(%)	56 (29.5%)
Lipid disorders, n(%)	41 (21.6%)
CHA_2DS_2-VASc, score(%)	
0	54 (28.4%)
1	54 (28.4%)
2	51 (26.8%)
3	19 (10.0%)
4	8 (4.2%)
5	4 (2.1%)
Smoke, n(%)	78 (41.1%)
Achole, n(%)	79 (41.6%)

Abbreviations: BMI, body mass index; BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; CHA2DS2-VASc score, score for atrial fibrillation stroke risk that includes congestive heart failure, hypertension, age above 65 or 75, diabetes, previous stroke, vascular disease history and female sex.

(HR), LV EF, $LAVi_{max}$, LASr, E/e' ratio, and LA-stiffness. These findings underscore the association between the presence of LA-LVAs and various clinical characteristics in patients with AF (Table 2). The observed differences in age, AF type, and other echocardiographic parameters between the non-LVAs and LVAs groups emphasize the potential role of LA-LVAs as a marker of atrial remodeling and disease progression. Representative LA electroanatomic maps of patients with different LASr are shown in Figure 4.

Predictors of Left Atrial Low-Voltage Areas Prevalence

Table 3 summarizes the predictors of LA-LVAs prevalence identified through univariate and multivariate analyses. Several factors demonstrated significant associations with the presence of LA-LVAs. In the univariate analysis, it was found that patients with LA-LVAs were significantly older and had a higher prevalence of persistent AF compared to those without. Additionally, patients in the LVAs group had higher HR, lower EF, higher $LAVi_{max}$, lower LASr, higher E/e', and higher LA-stiffness than the non-LVAs group. In the multivariate analysis, after adjusting for potential confounders, $LAVi_{max}$ (OR:1.15, 95% CI:1.02–1.29, P =0.021) and LASr (OR:0.85, 95% CI:0.80–0.90, P <0.001) remained independently associated with the presence of LA-LVAs. The Spearman correlation coefficient between LASr and $LAVi_{max}$ was −0.57, indicating a moderate negative correlation between the two variables (P<0.001). We also calculated the variance inflation factor (VIF) to assess multicollinearity between LASr and $LAVi_{max}$. For these variables, the VIF values were 2.36 and 1.35, respectively. These results suggest that there is no significant multicollinearity issue between LASr and $LAVi_{max}$.

ROC Curve Analysis

ROC curve analysis was conducted to identify the optimal cut-off values for related factors in predicting the presence of LA-LVAs. A comparison analysis of two ROC curves (LASr and $LAVi_{max}$) using the area under the curve (AUC). The AUC was higher for LAS (AUC 0.839, $P < 0.001$) compared to $LAVi_{max}$ (AUC 0.733, $P < 0.001$), with respective best cut-off values of 12.5% (LASr, sensitivity 86.4%, specificity 78.9%) and 23.7 ($LAVi_{max}$, sensitivity 61.7%, specificity 75.2%) (Figure 5).

Table 2 Comparison of Characteristics Between Non-LVAs Group and LVAs Group

Characteristic	Total n = 190	Non-LVAs Group n = 109	LVAs Group n = 81	*P*-Value
Age (year)	60 (53, 66)	57 (50, 66)	63 (57, 67)	0.004
Female Gender, n(%)	53 (27.9%)	28 (25.7%)	25 (30.9%)	0.431
Persistent AF, n(%)	66 (34.7%)	21 (19.3%)	45 (55.6%)	<0.001
CHA2DS2-VASc (score)	1 (0, 2)	1 (0, 2)	1 (1, 2)	0.071
BMI (kg/m^2)	24.4 (22.6, 26.8)	24.6 (22.7, 26.8)	24.2 (22.5, 26.8)	0.385
BSA (m^2)	1.75 (1.63, 1.85)	1.75 (1.65, 1.85)	1.70 (1.60, 1.85)	0.224
HR (bpm)	78 (69, 89)	76 (67, 86)	80 (73, 90)	0.034
LV EDVi (mL/m^2)	66.7 (58.6, 78.4)	65.2 (58.5, 74.4)	68.4 (59.4, 83.1)	0.196
EF (%)	65 (58, 69)	66 (61, 70)	62 (56, 68)	0.012
$LAVi_{max}$ (mL/m^2)	28.1 (21.4, 38.6)	24.0 (18.5, 32.2)	33.5 (26.5, 43.8)	<0.001
LASr (%)	12.8 (8.4, 21.8)	19.8 (13.6, 26.5)	8.6 (6.8, 11.3)	<0.001
E/e'	11.5±3.12	11.0±3.37	12.2±2.61	0.006
LA-stiffness	0.9 (0.4, 1.5)	0.6 (0.3, 0.8)	1.3 (1.0, 1.9)	<0.001
Hypertension, n(%)	78 (41.1%)	42 (38.5%)	36 (44.4%)	0.413
Diabetes Mellitus, n(%)	24 (12.6%)	15 (13.8%)	9 (11.1%)	0.587
Cerebrovascular disease, n(%)	19 (10.0%)	10 (9.2%)	9 (11.1%)	0.660
Coronary Artery Disease, n(%)	56 (29.5%)	32 (29.4%)	24 (29.6%)	0.968
Lipid disorders, n(%)	41 (21.6%)	23 (21.1%)	18 (22.2%)	0.853
Smoke, n(%)	78 (41.1%)	42 (38.5%)	36 (44.4%)	0.413
Drink, n(%)	79 (41.6%)	41 (37.6%)	38 (46.9%)	0.198

Abbreviations: LV EDVi, left ventricular end diastolic volume index; EF, ejection fraction; $LAVi_{max}$, left atrial maximum volume index; LASr, left atrial systolic peak strain; LVAs, low voltage areas; LA-stiffness, left atrial stiffness.

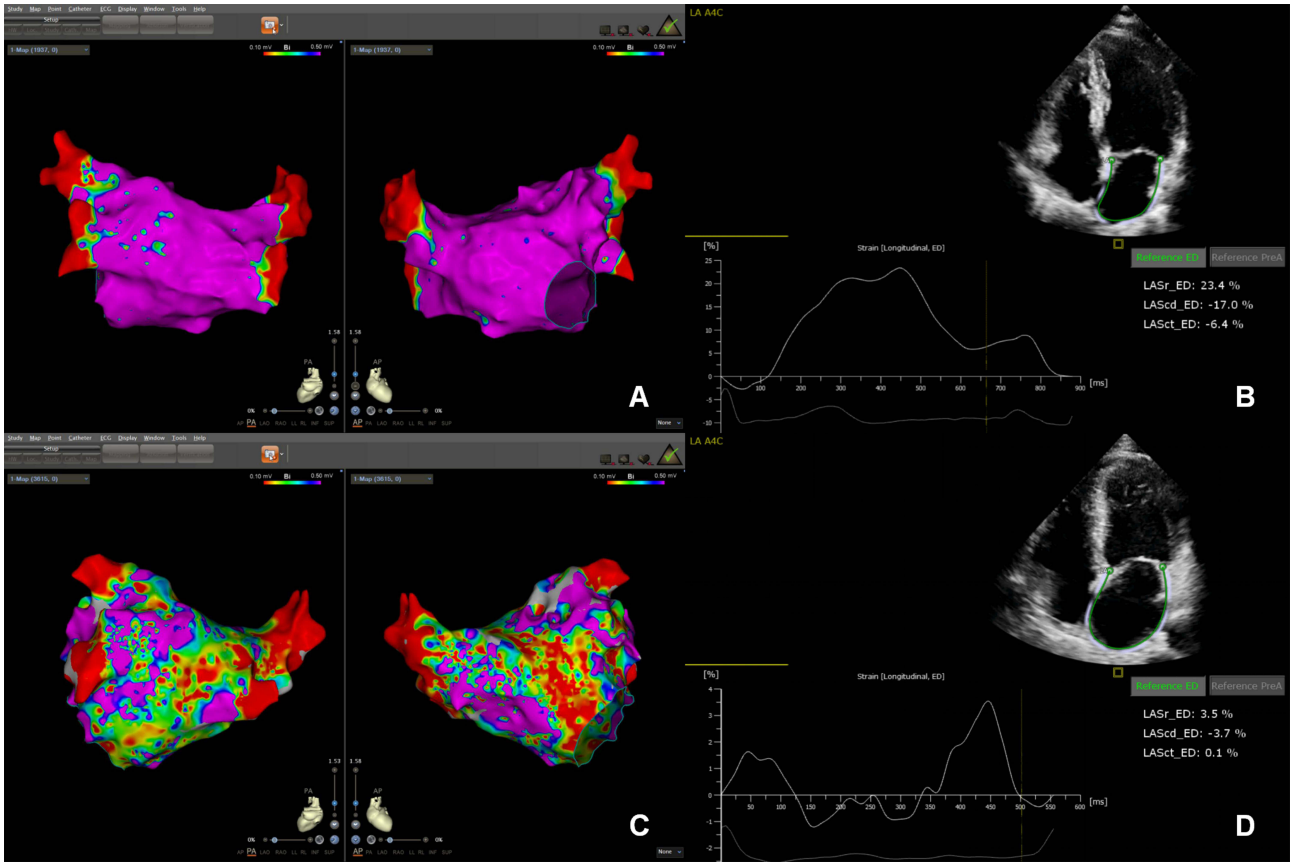

Figure 4 The left atrial electroanatomic maps of representative patients with different left atrial strain. The color gradient indicates serial changes in the electrogram amplitude from purple at >0.5mV to gray at <0.1mV. The proportion of low voltage area was 3.8% (**A**) in a 57-year-old female patient with LASr of 23.4% (**B**). The burden of low voltage area was extensive 44.1% (**C**) in a 65-year-old male patient with LASr of 3.5% (**D**).

Reproducibility of the Echocardiographic Parameters

A randomly selected cohort of 20 patients was analyzed to evaluate intra-observer and inter-observer variabilities in cardiac chamber volume, left ventricular function, and LASr measurements with an interval of more than one week. Excellent reproducibility was observed in both intra- and inter-observer analyses, with high intraclass correlation coefficients (ICCs) for all parameters, as shown in Table 4.

Discussion

This retrospective study aimed to explore the predictive factors of LA-LVAs in patients with NVAF. Our findings revealed that LA-LVAs (load ≥5%) were present in 42.3% of the patients. Notably, patients with LA-LVAs were older

Table 3 Predictors of LA-LVAs

Factor	Odds Ratio	95% CI	Univariate Analysis *P*-Value	Odds Ratio	95% CI	Multivariate Analysis *P*-Value
Age (years)	1.04	1.01, 1.07	0.006			
Persistent AF, n	5.24	2.74, 10.00	<0.001			
LV EDVi (mL/m^2)	1.08	1.00, 1.16	0.062			
EF (%)	0.97	0.94, 1.00	0.032			
$LAVi_{max}$ (mL/m^2)	1.24	1.14, 1.35	<0.001	1.15	1.02, 1.29	0.021
LASr(%)	0.83	0.79, 0.88	<0.001	0.85	0.80, 0.90	<0.001
E/e'	1.14	1.03, 1.25	0.009			
LA-Stiffness	2.85	1.80, 4.51	<0.001			

Abbreviations: OR, odds ratio; CI, confidence interval.

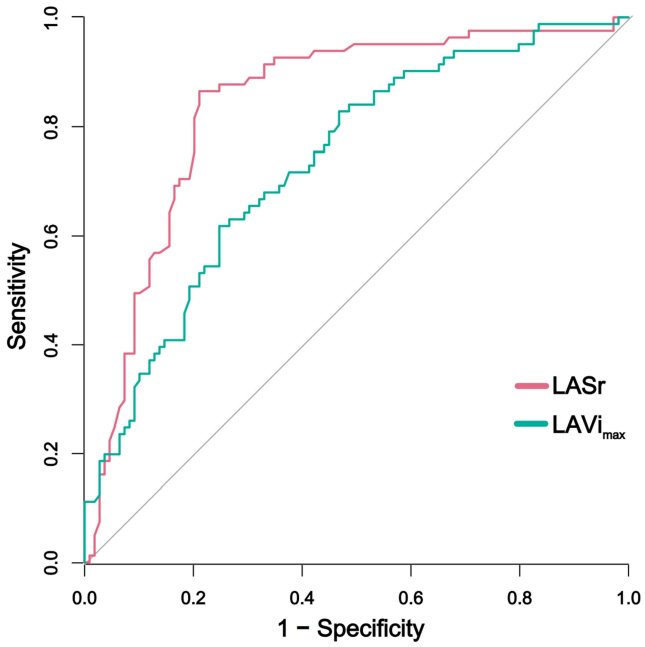

Figure 5 The ROC curve analysis of LASr and $LAVi_{max+}$. The red curve is for LARs, AUC is 0.839 (95% CI 0.779–0.898, *P*< 0.001). The green curve is for LAVi, AUC is 0.733 (95% CI 0.662–0.804, *P*< 0.001).

and had a higher incidence of persistent AF. Moreover, these patients exhibited higher HR, $LAVi_{max}$, E/e', and LA-Stiffness, along with lower LV EF and LASr compared to those without LA-LVAs. Multivariate analysis identified higher $LAVi_{max}$ and LASr as independent factors associated with the presence of LA-LVAs. The ROC curve analysis demonstrated that LASr had the highest AUC, suggesting its potential as a robust predictor for LA-LVAs. Since the study was retrospective, we conducted a post-hoc power analysis using the "pwr" package in R software to evaluate whether the sample size was appropriate. Based on our dataset of 190 samples and including 2 independent predictors in the multiple regression analysis, we assumed a medium effect size (Cohen's $f^2 = 0.15$) and a significance level (α) of 0.05. The post-hoc analysis indicated a power of 0.9986, suggesting a 99.86% probability of correctly rejecting the null hypothesis if a true effect exists. These results indicate that our study was adequately powered to detect medium-sized effects, thereby minimizing the risk of Type II errors.

AF and atrial remodeling are intricately linked, with structural changes in the atrium characterized by enlargement and fibrosis.[20] Atrial fibrosis is increasingly acknowledged as a pivotal element of vulnerable substrates, exerting a substantial influence on the emergence of LA conduction abnormalities. These abnormalities contribute to the progression from paroxysmal to persistent AF and sustain the disease continuum. Among various cardiac imaging modalities, LGE-CMR and 3D-EAM systems can quantify atrial fibrosis.[21] However, LGE-MRI is not considered the gold standard for detecting abnormal LA substrate due to limitations such as time consumption, limited reproducibility, and poor accuracy. Bipolar voltage mapping, a well-established method, has long been used to identify arrhythmogenic

Table 4 Intra- and Inter-Observer Analyses

Variable	Intraclass Correlation Coefficients (95% CI)	
	Intra-Observer	Inter-Observer
LV EDVi (mL/m^2)	0.98 (0.96, 0.99)	0.98 (0.97, 0.99)
EF (%)	0.97 (0.94, 0.99)	0.95 (0.93, 0.98)
$LAVi_{max}$(mL/m^2)	0.95 (0.91, 0.98)	0.94 (0.88, 0.98)
LASr(%)	0.97 (0.94, 0.99)	0.96 (0.92, 0.98)
E/e'	0.98 (0.95, 0.99)	0.96 (0.91, 0.99)

atrial substrate in patients with persistent AF. Recent expert consensus has emphasized the clinical applicability and superiority of the 3D-EAM system in defining atrial substrates associated with AF development.[22] EAM identifies low-voltage tissue regions, which serve as substrates for tachyarrhythmias, providing valuable insights into the underlying pathology.[23] LA-LVAs reflect endocardial scar as well as structural defects and remodeling in the atrium.[24] A meta-analysis has demonstrated a higher freedom from arrhythmia in persistent AF patients who underwent LA-LVAs ablation versus conventional ablation approaches without substrate modification.[25] Furthermore, A study conducted by Moustafa et al found that LVAs guided substrate modification significantly reduced the recurrence of all atrial arrhythmias at 1-year compared with non-LVA approaches in patients with persistent and longstanding persistent AF populations, without an increase in adverse events.[26] According to electrophysiological and imaging data, decreased voltage and fibrotic LA tissue are independent predictors of surgical outcomes. Accurate and reliable measurement of LA fibrosis has the potential to enhance clinical decision-making for clinicians.[27]

Currently, there are numerous studies exploring the assessment and prediction of LA fibrosis in patients with AF. Ammar-Busch et al investigated markers of LA-LVAs in 70 patients with non-paroxysmal AF. After adjusting for several clinical factors, they found that age, female gender, and LA surface area remained associated with LA-LVAs detected by EAM during AF rhythm.[28] Thus, age and LA volume were associated with the presence of LA-LVAs regardless of AF type, corroborating our findings. Huo et al characterized LA-LVAs in 104 AF patients. The results revealed that LA-LVAs occurred in 18.8% of paroxysmal AF patients and 54.3% of persistent AF patients, with persistent AF patients exhibiting lower bipolar voltages and a larger area than paroxysmal AF patients.[29] In two studies, Seewoster et al demonstrated that persistent AF was independently correlated with LA-LVAs.[30,31] However, in a study of 104 AF patients, Nery et al found that persistent AF did not independently predict LA-LVAs after adjusting for other risk factors.[32] Therefore, whether the type of AF represents an independent risk factor for LA-LVAs remains a subject of debate, necessitating further validation from large-scale clinical studies. Masuda et al found that the incidence of LA-LVAs gradually increased with the elevation of E/e' in 215 patients with atrial fibrillation, and high E/e' was an independent predictor of LA-LVAs in these patients.[33] A higher E/e' indicates increased left ventricular filling pressures and diastolic dysfunction. Diastolic dysfunction and elevated LV filling pressures can lead to increased LA pressure and LA remodeling, including structural changes such as fibrosis and scarring. These mechanisms could explain our research results. One study investigated the relationship between the extent of LA-LVAs and LA function in 22 AF patients. Their findings revealed that structural parameters (ie, LA volume) and functional parameters (ie, LA emptying fraction and LA strain) of the LA exhibited significant correlations with the extent of LA-LVAs.[34] Dynamic-HeartModel is an advanced, fully automated adaptive left heart chamber quantification software, developed to rapidly and accurately quantify LA and LV volumes, as well as LV EF. In light of the current study's results, the Dynamic-HeartModel requires minimal manual intervention compared to other traditional methods (such as 2D and Simpson's biplane), but exhibits the highest speed among all 3D methods currently in use. It can serve as an appropriate modality for NVAF patients, accurately measuring LA size.[12]

Recent prospective studies with long-term follow-up have demonstrated that LA strain is a robust and independent predictive factor for future AF occurrence across various cohorts.[35] A notable advantage of LA strain is its ability to provide comprehensive information with a single measurement, surpassing other composite indices used for assessing diastolic function. This capability makes LA strain an invaluable clinical tool.[13] Kishima et al found in their study of 92 AF patients that the LA strain was independently associated with the LA-LVAs and had high predictive value.[19] Laish-Farkash et al, in their examination of 42 AF patients using 2D-STE, observed a negative correlation between LA strain rate and LVAs, which served as an independent predictor of LA-LVAs.[8] Our study focused on evaluating LASr, which is an essential index for analyzing chamber function, providing highly repeatable measurements of LA impairment through non-Doppler, angle-independent assessment. The mechanism underlying the association between impaired LA strain and AF development remains incompletely understood. One potential explanation involves the presence of atrial myopathy. Inflammation and endothelial dysfunction associated with aging, hypertension, diabetes, and heart failure may trigger a repair process and remodeling within the LA tissue, resulting in collagen deposition.[36] This could serve as a substrate for electrical conduction abnormalities and consequent AF development. Notably, histologic analyses have indeed revealed more significant fibrosis in patients with reduced LA strain compared to those with normal LA strain.[37] LASr is less affected by the patient's rhythm during examination, whether sinus or AF, aligning with our objective to

offer a practical imaging technique suitable for all patients. We utilized an automated quantification technique for evaluating LASr, known as AutoStrain, which offers advantages such as time efficiency, enhanced accuracy, and improved reproducibility of measurements. AutoStrain allows for easy acquisition with a simple click, eliminating the need for manual tracing. Its accurate endocardial tracking significantly reduces human intervention during measurements, ensuring precise results. LA fibrosis leads to decreased LA compliance, decreased strain and increased stiffness, resulting in elevated LA pressure. Therefore, E/e', LA-stiffness, LA volume, LA strain can all predict low LA-LVAs in AF patients, findings that could support our results. The superiority of LA strain variables over LA volume may be attributed to their higher sensitivity in detecting the effects of LA fibrosis and more accurate estimation of LA loading pressure, both crucial determinants of AF development.[38]

In this study, although the prevalence of coronary artery disease (CAD) did not differ significantly between the two groups, both demonstrated a similarly high proportion, approaching 30%. It is well known that coronary artery perfusion is crucial for LA function, as these arteries ensure that the LA receives adequate blood supply to maintain normal function. Evidence indicates that ischemia at the microcirculatory level not only affects atrial tissue excitability but also leads to atrial fibrosis and remodeling, thereby further promoting the development of AF.[39] CAD may be present before the onset of AF or may exacerbate the clinical complexity of the disease, with the location of lesions and the extent of vascular damage possibly being closely related to prognosis.[40,41] Studies have confirmed that coronary revascularization, multi-vessel stenosis, and LA diameter are important predictors of AF recurrence after RFCA in patients with obstructive CAD.[42] Additionally, AF-induced LA dysfunction has been shown to play a significant role in the prognosis of patients with ischemic cardiomyopathy (ICM) and is becoming a therapeutic target for both pharmacological and non-pharmacological interventions.[43] Thus, a bidirectional relationship exists between CAD and AF, with multiple shared risk factors. Recent studies have illuminated important connections between AF, cardiac function, and cardiovascular outcomes. Güzel et al identified increased LAV as a predictor of AF development in heart failure patients with mildly reduced ejection fraction (HFmrEF), with LAV also serving as a determinant of morbidity and mortality in this group.[44] Complementing this, Kılıç et al reported that AF patients under a rhythm control strategy experienced lower rates of ischemic cerebrovascular events compared to those without such management, underscoring the potential benefits of this approach in AF treatment.[45] Furthermore, correlation studies have demonstrated a negative relationship between LAS and mean thrombolysis in myocardial infarction(TIMI) frame count, suggesting that as coronary blood flow velocity decreases, overall LA function may further decline.[46] Subtle global and segmental alterations in myocardial contraction secondary to ischemic insult can be reflected in LAS imaging results.[47] However, we categorized the cases into two groups based on the presence or absence of a CAD history, and no significant difference in LASr was observed between the two groups. This may be due to the lack of coronary angiography or CT angiography results for all CAD patients, which prevented us from performing detailed subgroup analysis based on the extent of coronary artery lesions. As a result, assessing the potential impact of CAD on LASr was challenging, representing a limitation of our study. In future research, we plan to increase the sample size and obtain more detailed data on the degree of coronary artery stenosis in order to further investigate the impact of CAD on LA function.

In summary, the study confirmed the potential of automatic echocardiography parameters, especially LASr and $LAVi_{max}$, as predictors of LA-LVAs in patients with NVAF. The significant associations observed between LASr, $LAVi_{max}$, and LA-LVAs suggest that changes in LA function assessed by echocardiography may reflect underlying structural remodeling processes leading to LVAs development. These findings align with previous research demonstrating the prognostic value of LA volume and strain in AF patients. The automated software, Dynamic-HeartModel and AutoStrain, provided accurate and reliable measurements of LA function parameters in our study, facilitating the integration of echocardiographic assessment into routine clinical practice. Furthermore, our study underscores the importance of LA-LVAs as markers of atrial substrate remodeling in NVAF patients. The identification of LA-LVAs during catheter ablation procedures is associated with increased arrhythmia recurrence rates and poorer clinical outcomes (see Supplementary Table 1).[3,26,31,48–72] The ability to non-invasively predict the presence of LA-LVAs using echocardiography may aid in risk stratification and treatment decision-making for patients undergoing catheter ablation for NVAF.

Despite these promising findings, several limitations should be acknowledged. Firstly, our study was conducted at a single center with a relatively small sample size, which may limit the generalizability of our results. Larger-scale multicenter cohort studies are needed in the future to validate our findings and assess the external validity of our predictive model. Second, studies have shown that, compared with systolic blood pressure (SBP), diastolic blood pressure (DBP) is more strongly associated with left atrial reservoir/conduit strain and LV-GLS.[73,74] Although there was no significant difference in the proportion of hypertension between the two groups, we did not conduct 24-hour ambulatory blood pressure monitoring for each patient and did not include left ventricular diastolic pressure as a factor affecting LASr. Future research should be more comprehensive to address these aspects. Third, the retrospective nature of our analysis, along with the higher proportion of patients with persistent AF and male individuals undergoing catheter ablation may introduce selection bias and confounding factors that were not accounted for in our analysis. Furthermore, there was a lack of MRI volume and strain measurements for comparison.

Conclusion

In this retrospective analysis, $LAVi_{max}$ and LASr, obtained through the automatic echocardiographic assessment, were independently associated with the presence of LA-LVAs identified during EAM. These findings have important clinical implications for risk stratification and treatment planning in AF patients undergoing catheter ablation. Further research is warranted to confirm our results and elucidate the underlying mechanisms linking LA function to atrial substrate remodeling in AF.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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