

Left Atrial Strain Helps Identifying the Cardioembolic Risk in Transient Ischemic Attacks Patients with Silent Paroxysmal Atrial Fibrillation

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Purpose: Patients with transient ischemic attacks often present asymptomatic and paroxysmal atrial fibrillation. Since atrial fibrillation initiates in the atria, we aimed to identify whether the abnormalities in left atrial structure and function could identify the cardioembolic etiology of the transient ischemic attacks in patients at sinus rhythm.

Patients and Methods: A total of 190 patients over 50 years old with sinus rhythm discharged after a transient ischemic attack were included in the study and divided into two groups according to the presence (group I) or absence (group II) of documented paroxysmal atrial fibrillation. The documentation of paroxysmal atrial fibrillation was based on the examination of medical registers. Cardiac ultrasound assessment was performed at a minimum of 14 days after the onset of the transient ischemic attack, to avoid assessment of atrial stunning.

Results: The group I patients were older, more frequent women, with a history of stroke or transient ischemic attack and a higher CHA₂DS₂-VASc score. They also presented larger left atrial volumes, lower left atrial emptying fraction, and significantly impaired left atrial deformation patterns. Multivariate logistic regression identified three variables that were independently associated with paroxysmal atrial fibrillation: age, left atrial reservoir strain, and left atrial emptying fraction ($P < 0.0001$). The cut-off levels for the variables were age > 55 years, reservoir strain $< -17\%$, and emptying fraction $< 51\%$.

Conclusion: The present study demonstrates that the LA strain is independently associated with paroxysmal atrial fibrillation in transient ischemic attack patients and might be of great help in identifying their cardioembolic etiology and preventing subsequent strokes by the initiation of anticoagulant therapy.

Keywords: transient ischemic attack, speckle tracking echocardiography, paroxysmal atrial fibrillation

Introduction

Atrial fibrillation (AF) causes significant problems to patients, medical doctors, and healthcare systems, demanding a multidisciplinary approach and management. It is the most common sustained cardiac arrhythmia in adults, with an estimated prevalence of 2–4%.¹ Hypertension, diabetes, coronary heart disease, abnormalities of lipid metabolism are classic risk factors for both AF development and for ischemic stroke.² Age is another important risk factor. When compared to those over 50, subjects under 50 have a substantially lower risk of developing AF.³ Men are more likely than women to develop atrial fibrillation (AF) at any age, but women with AF are at greater risk of having a stroke.⁴ Hematological disorders seem to be an often overlooked cause of acute stroke.⁵ Being in the coronavirus pandemic, we have to mention that AF is the most frequent arrhythmia related to COVID infection and that, when present, it is strongly related to mortality.⁶

Frequently, stroke is preceded by transient ischemic attacks (TIA's). Ischemic strokes associated with AF are frequently severe, recurrent, and leading to death or permanent disability. About 20 to 30% of ischemic strokes have an unidentified etiology and are categorized as being cryptogenic.⁷ Using modern diagnostic procedures, up to 30% of cryptogenic strokes have been detected as having a cardioembolic etiology, due to silent atrial fibrillation (AF).^{1,7}

Detecting individuals at increased risk of developing AF could improve a prompt AF detection. As soon as AF is detected, anticoagulation treatment is recommended, independent of the arrhythmia duration.¹

The risk of stroke is important in patients with asymptomatic and paroxysmal atrial fibrillation (PAF), as these patients lack the protection offered by an adequate anticoagulant treatment.^{7,8} Silent PAF has been identified as the causing mechanism in about 15% of TIA's.^{9,10} Holter-monitoring is commonly used for identifying PAF. Its efficiency is limited, as this arrhythmia is sporadic and frequently not recognized by the patients. Long term monitoring by insertable loop recorders represents a more efficient method, but is invasive and expensive and can't be achieved in all stroke patients.¹¹

Since AF initiates in the atria, we aimed to identify whether the abnormalities in LA structure and function could identify the cardioembolic etiology of the TIA's in patients at sinus rhythm, using echocardiography. Echocardiography plays a significant role in the evaluation of patients who suffered an ischemic stroke, as it is non-invasive, efficient and repeatable.¹²

It is known that LA size is a valuable predictor of PAF in the general population, as well in patients with several disorders.^{13,14} Atrial enlargement is not specific for valvular and non-valvular AF, as it also occurs in left ventricular diastolic dysfunction and arterial hypertension. Additionally, it was reported that PAF may occur in patients with normal LA dimensions.¹⁵⁻¹⁷ Recent researches have proven the superiority of LA function versus LA size as a predictor of PAF,¹⁸ especially when studying deformation abnormalities by means of two-dimensional speckle-tracking echocardiography (2D-STE).^{19,20}

In the present study, we aimed to assess whether LA two dimensional-speckle tracking echocardiography (2D-STE) could offer useful parameters to identify the cardioembolic etiology of TIA's in patients with silent PAF.

Patients and Methods

Subject Selection

This is a retrospective cohort study that included all patients with transient ischemic attack aged ≥ 50 years old discharged consecutively from November 2017 to November 2021 from the Department of Neurology of the Timisoara County Hospital with a final diagnosis of TIA, and submitted for LA 2D-STE.

Exclusion criteria were: previous history of AF, the presence of AF within 24 hours after the TIA or at the time of cardiologic examination, moderate or severe valvular stenosis and/or regurgitation, mechanical heart valves, congenital heart disease, severe systolic dysfunction (left ventricular ejection fraction $<40\%$), ventricular akinesia, permanent cardiac pacemaker, as well as inadequate echocardiography imaging.

The diagnosis of TIA was established in the presence of briskly evolving clinical signs of cerebral disorder (documented by neurological examination), lasting up to 24 h, and with no sign of infarction on brain-imaging.²¹

PAF was defined as an AF detected by a 12 leads standard resting electrocardiogram (ECG) or by a 24- hours Holter ECG monitoring, with a minimum duration of 30 seconds, and a spontaneously or interventional termination within 7 days of onset.¹

Data Extraction

PAF was documented by review of the medical records when at least one episode was reported at any time in the patient's history, during hospitalization for the TIA or during the post-hospital cardiologic examination. The clinical baseline data and the medical history of the TIA patients were obtained by review of the medical records.

The CHA2DS2-VASc risk score was assessed for every patient by giving 1 point for each of the following parameters: age between 65 and 74 years, a history of hypertension, diabetes mellitus, heart failure or atherosclerotic vascular disease, and female gender, and 2 points for a history of ischemic stroke/TIA or an age ≥ 75 years.²²

Echocardiographic Evaluation

All patients were evaluated by a 2-D transthoracic echocardiography during hospitalization for the TIA, using a Vivid 5S General Electric echocardiography device. LA 2D-STE was performed after a minimum of 14 days following the onset of the TIA, to avoid atrial stunning after a possible PAF.^{23,24} A single investigator with substantial echocardiography experience that was blinded to all other information performed all the echocardiographic evaluations, according to the common approach for the patients with TIA in the echocardiography laboratory.

Conventional Echocardiography

All patients were examined in a left lateral decubitus posture, using parasternal long and short axis, apical 4-, 3-, and 2-chambers visualizations. ECG trace was registered throughout the assessment. All recordings were performed at end-expiration, with a 3-cardiac cycle registration. The systolic left ventricular function was assessed by measuring left ventricular ejection fraction (LVEF) using Simpson's biplane method. The diastolic LV function was assessed by means of transmitral pulsed Doppler and tissue Doppler imaging. The ratio between the peak early diastolic inflow and the peak late diastolic inflow (E/A), respectively the septal E/E' ratio were calculated.²⁴ Left atrial indexed volume (LAVI) to body surface area was calculated in the apical view, using the biplane area length method. The total left atrial emptying fraction (LAEF) was calculated using the formula: $(LAEDV - LAESV) / LAEDV \times 100$.

2D-Speckle Tracking Echocardiography

Global peak longitudinal strain (GLS) of the LV was calculated from the three peak longitudinal strain curves of the apical 4-, 2-, and 3-chamber views using appropriate frame rates.

Left atrial reservoir (RV), conduit (CD), and booster pump (BP) strains (S) were assessed using 2D-STE on images obtained in the apical 4-chamber view. The images were analyzed offline using the General Electric Echo PAC software version 201. ECG was referenced to the peak of the R wave, and the region of interest was adjusted to the thickness of the LA wall. LARVS was calculated as the peak positive longitudinal strain during ventricular systole, while the negative strains during early and late diastole assessed the CD and BP atrial functions (Figure 1).

To define the intra- and inter-observer variability, the 2D-STE measurements were repeated for 10 randomly selected patients at one month distance by the same observer on the same echocardiographic images. The intra-class correlation coefficient and the mean absolute difference between the repeated measures were calculated.²⁴

Statistical Analysis

Normally distributed continuous variables are shown mean \pm SD, while categorical variables are presented as number (percentage). Continuous variables were compared using an unpaired 2-tailed *t*-test, and categorical variables were compared using the χ^2 or Fisher exact test, as suitable Logistic regression analysis was performed to evaluate the risk prediction of PAF in TIA patients after adjusting for baseline characteristics and echocardiographic parameters. Receiver-operating characteristic (ROC) curves were utilized to determine the optimal sensitivity and specificity of the analyzed parameters. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards models. The threshold for statistical significance was established at a P-value of <0.05 using the MedCalc Statistical Software version 20.15 (MedCalc Software Ltd, Ostend, Belgium) for Windows.

Ethics

The Ethics Committee of the Victor Babes University of Medicine and Pharmacy in Timisoara gave its approval for the research to be conducted (Nr. 47/2017). In accordance with the Helsinki Declaration's principles of informed consent, all patients provided written informed consent prior to participating in the study.

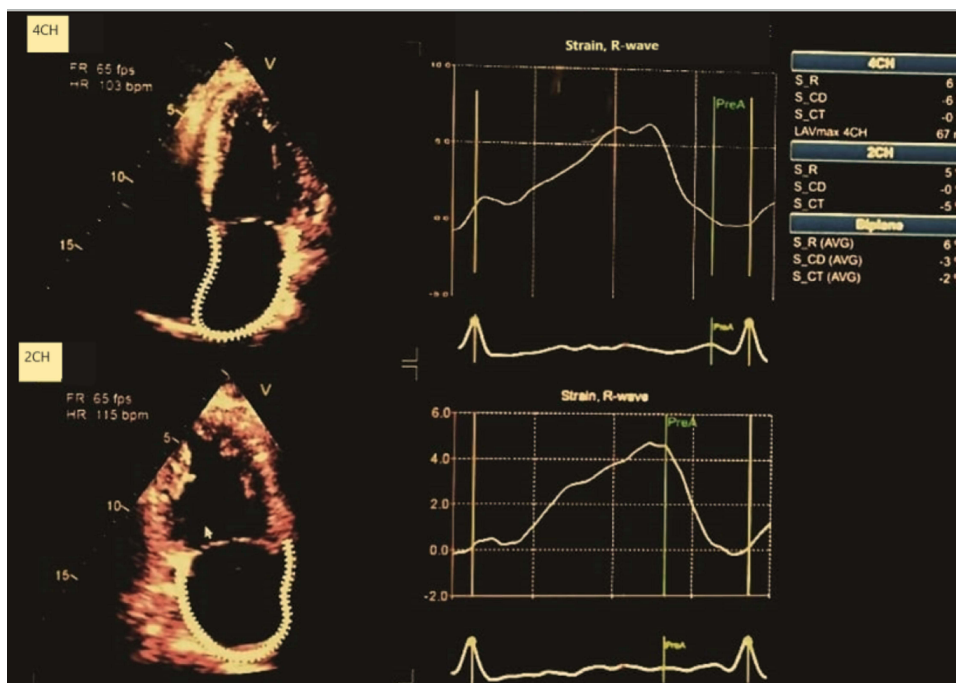


Figure 1 Strain curves from left atrial speckle-tracking, in apical four-chamber and two-chamber.

Results

A total of 232 patients were registered in the present analysis. Seven patients were eliminated because of unacceptable quality of conventional echocardiographic images and 25 because AF was documented during the out-of-hospital cardiologic examination. Furthermore 10 patients had inadequate image quality for 2D-STE.

At last, 190 TIA patients were enrolled in the study. They were divided into two groups, according to presence (group I) or absence (group II) of documented episodes of PAF. Demographics, clinical characteristics and echocardiographic data are shown in Tables 1 and 2.

PAF was detected in 33% of patients that had suffered a TIA. The patients with detected PAF were older (mean age 67.5 vs 60 years, $P < 0.0001$), more frequent women (48% vs 32%, $P = 0.04$) and had more often a history of TIA or stroke (65% vs 23%, $P < 0.0001$). Significant differences were noted among the two groups regarding the LA functional parameters. The patients with documented episodes of PAF had larger LA indexed volume ($P < 0.001$), poorer LA total emptying fraction ($P < 0.0001$), and impaired LA deformation patterns (Table 2, Figure 2). In contrast, other echocardiographic measures of LV systolic and diastolic function, as well as LV GLS, were not notably different between the groups (Table 2).

The univariate analysis of the clinical and echocardiographic features presented in Tables 1 and 2 found that age, female gender, LAVI, LAEF and LA strains were significantly associated with the risk of PAF (Table 3). The CHA2D2S-VASc risk score, although significantly higher in group I ($P < 0.001$), was not significantly associated with PAF in the TIA patients at logistic regression analysis.

Multivariate logistic regression (forward method) included the variables associated with PAF identified by univariate analysis and found that three of them were independently associated with PAF in patients with TIA's: age, LAEF and LARVS (Table 3).

The ROC curves analyses of these independent variables associated with PAF indicated appropriate sensitivities and specificities: age (AUC=0.922, sensitivity: 72.92, specificity 90.1, $P < 0.0001$), LARVS (AUC=0.915, sensitivity: 100.0, specificity 64.8, $P < 0.0001$), and LAEF (AUC=0.717; sensitivity: 72.9; specificity 90.1; $P < 0.0001$). The comparison of the ROC curves showed significant differences between the areas under the ROC curves (AUC) for age and LARVS versus LAEF (0.198, $P < 0.0001$), as shown in Figure 3. The cut-off levels of the variables associated with PAF were as follows: LARVS $< -17\%$, LAEF $< 51\%$, and age > 55 years.

Table 1 Baseline Demographics of the Patients with Transient Ischemic Attacks

	With PAF n=48	Without PAF n=142	P value	All Patients
Age (y)	67.5 ± 6.9	60.0 ± 7.4	<0.0001	64±7
Male sex (n, %)	25 (52)	97 (68)	0.04	122 (64)
Systolic BP (mmHg)	134.2 ± 25.9	131.9 ± 22.0	0.55	132.5±23.7
Diastolic BP (mmHg)	74.7 ± 14.4	72.5 ± 14.2	0.83	73.9±14.3
Heart rate (beats/min)	91 ± 24	88 ± 20	0.39	89±22
Body mass index (kg/m ²)	26.5 ± 5.3	25.5 ± 4.7	0.21	25.9±5.1
Obesity (n, %)	5 (10)	10 (7)	0.50	15 (8)
Smoker (n, %)	10 (20)	20 (14)	0.32	30 (16)
Hypertension (n, %)	38 (80)	96 (65)	0.07	134 (70)
Diabetes mellitus (n, %)	12 (24)	20 (14)	0.10	32 (17)
Thyroid disease (n, %)	4 (8.3)	15 (10.6)	0.54	19 (10)
Dyslipidemia (n, %)	19 (40)	45 (32)	0.31	64 (34)
Ischemic heart disease (n, %)	15 (23)	23 (16)	0.20	38 (20)
Heart failure (n, %)	17 (35)	3 (26)	0.23	20 (10)
PAD (n, %)	4 (0.83)	10 (0.70)	0.92	14 (7)
COPD (n, %)	10 (21%)	21 (15)	0.41	31 (17)
End stage renal disease (n, %)	1 (0.02)	6 (0.04)	0.94	7 (3)
Previous stroke or TIA (n, %)	31 (65%)	33 (23%)	<0.0001	44 (23)
CHA2DS2-VASc score (mean ± 1 SD)	5.7±1.5	4.6±1.9	<0.001	4.9±1.7
0–1	8 (17)	44 (31)		52 (28)
≥2	40 (83)	98 (69)	0.04	138 (72)

Note: Statistically significant values are shown in bold (P<0.05).

Abbreviations: TIA, transient ischemic attack; PAF, paroxysmal atrial fibrillation; BP, blood pressure; COPD, chronic obstructive pulmonary disease.

Discussion

The findings from our research prove the value of echocardiography for detection of atrial disorder in the background of TIA's. We performed a combined evaluation of LA size and function by conventional and 2D-STE. Moreover, echocardiographic cut-off points were calculated for the variables independently associated with PAF in TIA patients.

LA enlargement implies adverse LA structural remodelling, which is associated with electrical instability and thrombus formation.^{25,26} But AF was also diagnosed in patients with normal LA size,¹⁷ and explained by LA functional remodelling. This is demonstrated by a decreased myocardial deformation and is more sensitive in detecting subclinical atrial dysfunction.^{27,28} Atrial remodelling implies morphologic changes in the atrial tissue with the development of interstitial fibrosis.^{29,30} The degree of atrial fibrosis can be rated using cardiac imaging methods,³¹ and is inversely correlated with the value of the strain calculated by echocardiography.³² In this respect, retrospective studies achieved in patients with cryptogenic strokes have shown that STE improved the detection accuracy of AF.³³

These findings have been confirmed in the present study, that increased the challenge by enrolling TIA patients with and without documented episodes of PAF. Logistic multivariable regression analysis demonstrated that age, LARVS and

Table 2 Echocardiography

	With PAF n=48	Without PAF n=142	P value	All Patients
LVEDV (mL)	97.4±21.2	103.5±19.9	0.07	99.2±20.4
LVESD (mL)	46 ± 11	49.3±12.6	0.10	47.3±10.6
LVMI (g/m ²)	145 ± 43	137 ± 36	0.20	141 ± 40
LVEF (%)	58 ± 7	62 ± 14	0.05	60.5±9.4
Mitral E/A-ratio	1.3 ± 0.5	1.2 ± 0.4	0.16	1.2±0.6
EDT	148 ± 53	154 ± 45	0.45	151 ± 48
Septal E/E'	13.8 ± 5.2	13.1 ± 3.8	0.32	11.3 ± 3.8
TAPSE (cm)	2.4 ± 0.47	2.4 ± 0.50	1	2.4±0.49
GLS (%)	-14.4 ± 3.1	-15.2 ± 3.2	0.13	-14.7±3.2
LAVI (mL/m ²)	50.5 ± 14.0	43.5 ± 10.3	<0.001	47 ± 20
LAEF (%)	47.9 ± 4.9	59.7 ± 5.9	<0.0001	56.3±7.3
LA strain (%)	14.89 ± 1.21	16.83 ± 2.54	<0.0001	16.24 ± 2.14
LA RV strain (%)	20.2±4.5	23.8±3.6	<0.0001	21.9±5.1
LA CD strain (%)	12.1±2.6	13.4±2.8	0.001	12.1 ±3.1
LA BP strain (%)	10.2±3.2	12.3±3.4	<0.001	10.9 ±3.8

Note: Statistically significant values are shown in bold (P<0.05).

Abbreviations: LVEDV, left ventricular end diastolic volumes; LVESV, left ventricular end systolic volumes; LVEF, left ventricular ejection fraction; E, peak transmitral early diastolic inflow; A, peak transmitral late diastolic inflow; EDT, E/E' TAPSE, tricuspid annular plane systolic excursion; GLS global longitudinal strain; LA, left atrium; LAVI, indexed left atrial volume; LAEF, left atrial total emptying fraction; RV, reservoir; CD, conduit; BP, booster pump.

LAEF were independently associated with PAF. We found the following cut-off values predictive for PAF in TIA's patients: LARVS < -17%, LAEF <51%, and age >55 years. These values are confirmed by another study that analysed LA strain predictive power of AF in cryptogenic ischemic strokes.³⁴

The strong association between reduced LA strains and AF has also been reported in other settings, such as predicting recurrence of AF after catheter ablation.³⁵ Pagola reported the presence of silent AF in 86% of cryptogenic stroke patients with normal LA size and decreased LA strain.¹⁸ Bayes de Luna described a frequently under-recognized clinical condition characterized by advanced interatrial block, that is strongly associated with atrial fibrillation and that was identified as a risk factor for non-lacunar cardioembolic ischemic stroke and vascular dementia.³⁶

Vera et al³⁷ elaborated an interesting decryptoring score to predict AF in cryptogenic strokes that includes clinical, laboratory, and left atrial strain parameters (age > 75 years, hypertension, troponin T > 40 ng/L, NT pro-BNP > 200 pg/mL, LA reservoir strain < 25.3%, and LA conduct strain<10.4%). The rate of AF detection was 0% among patients with a score of 10 and 80% among patients with a score of >35. This score, however, requires more validation before being utilized in clinical practice.

Compared to other stroke studies,^{18,37,38} we selected younger patients, as the risk of non-valvular AF increases substantially in patients over 50 years. We found that TIA patients with detected PAF presented notable LA functional impairment, indicated by larger LAVI (P<0.001), poorer LAEF (P<0.0001), and reduced LA strains (P<0.001).

Our results support the importance of regular atrial function evaluation in patients with TIA's of undetermined origin. Atrial reduced contractility determines an abnormal stasis of blood within the atrium, with thrombus formation and risk of cerebral embolization. The progression from paroxysmal to persistent atrial fibrillation supports the concept of atrial cardiomyopathy as a cause of stroke.^{39,40} Although many researches assess stroke risk in AF patients, TIA is rarely

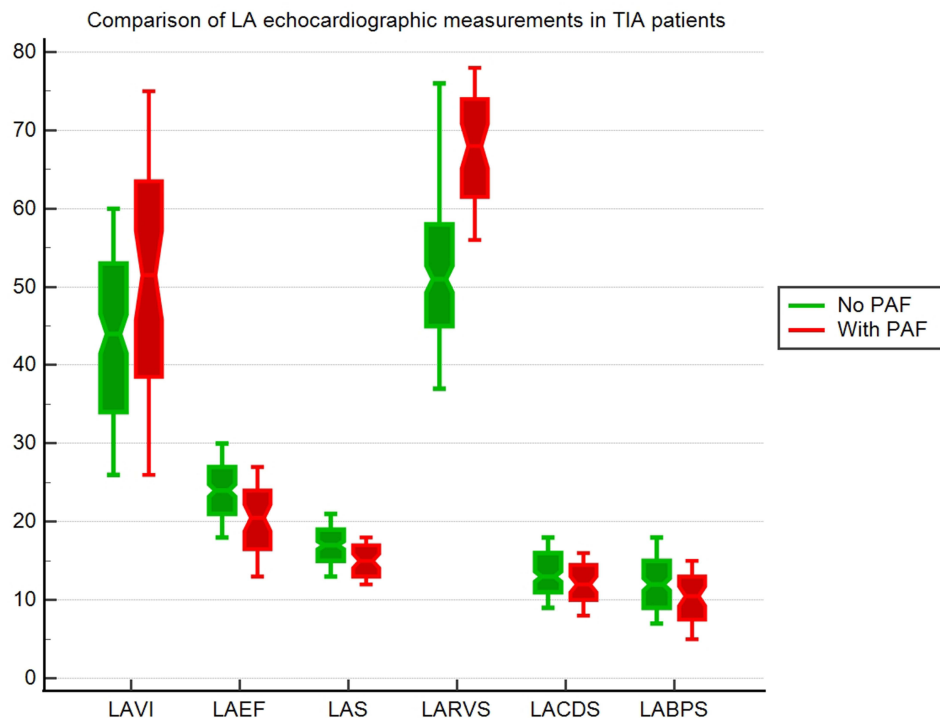


Figure 2 Comparison of left atrial echocardiographic measurements in transient ischemic attack patients.

Abbreviations: LA, left atrium; PAF, paroxysmal atrial fibrillation; LAVI, indexed left atrial volume; LAEF, left atrial total emptying fraction; LAS, left atrial global strain; LARVS, left atrial reservoir strain; LACDS, left atrial conduit strain; LABPS, left atrial booster pump strain.

included. We believe that the inclusion of TIA is valuable, because of the common pathogenic mechanism, and the high risk of subsequent stroke.

An improvement of stroke risk assessment is demanded, and echocardiography provides additional high-risk features.

Our study has several limitations. It was done in a single neurology centre with a relatively small number of patients. It needs validation of the results by studies in a greater population. Because of the limited duration of PAF, and the lack of a long-term ECG monitoring for AF detection, many episodes might have been unrecognized. No investigations were

Table 3 Factors Associated with Paroxysmal Atrial Fibrillation in Patients with Transient Ischemic Attacks

Parameter	Univariable OR (95% CI)	P	Multivariable OR (95% CI)	P
Age	1.25 (1.17–1.34)	<0.0001	0.64 (0.45–0.88)	<0.01
Female gender	2.15 (1.10–4.20)	0.02		
LAVI	1.05 (1.02–1.08)	<0.001		
LAEF	0.67 (0.59–0.76)	<0.0001	0.49 (0.32–0.74)	<0.001
LAS	0.70 (0.60–0.83)	<0.0001		
LARVS	0.79 (0.72–0.87)	<0.0001	1.55 (1.23–1.94)	<0.001
LACDS	0.84 (0.74–0.95)	<0.01		
LABPS	0.83 (0.74–0.92)	<0.001		

Note: Statistically significant values are shown in bold (P<0.05).

Abbreviations: OR, odds ratio; LAVI, indexed left atrial volume; LAEF, left atrial total emptying fraction; LAS, left atrial global strain; LA, left atrium; RV, reservoir; CD, conduit; BP, booster pump.

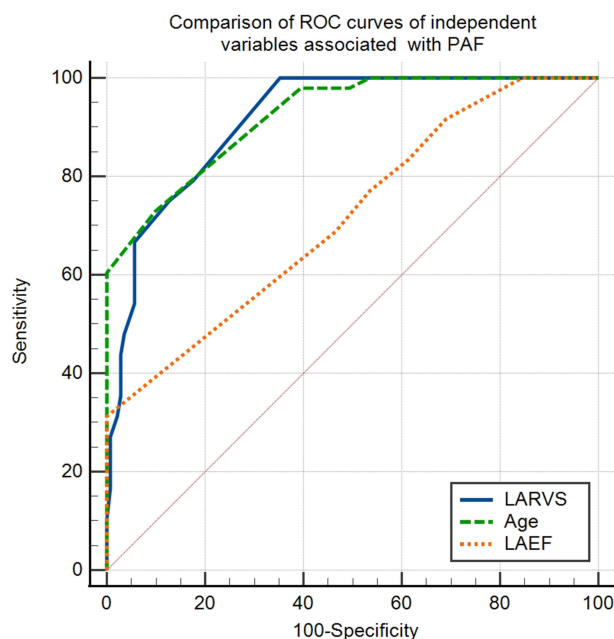


Figure 3 Comparison of receiver-operating characteristic curves of the independent variables associated with paroxysmal atrial fibrillation.

Abbreviations: ROC, receiver-operating characteristic; PAF, paroxysmal atrial fibrillation; LAEF, left atrial total emptying fraction; LARVS, left atrial reservoir strain.

done to assess an atherosclerotic origin of the TIA's. Furthermore, longitudinal studies able to accurately predict the development of AF should provide additional information.

Conclusion

The current study shows that LA strain is an independently and strongly associated with PAF in TIA patients, implying a cardioembolic etiology that could be prevented by initiating anticoagulant medication. More information is expected from longitudinal studies that aim to predict the occurrence of AF.

Our findings have considerable clinical implications because, until now, LA 2D-STE was not included in the usual evaluation of TIA patients, but it may be the ideal next step in this regard.

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Disclosure

The authors report no conflicts of interest in this work.

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