

Left atrial deformation and risk of transient ischemic attack and stroke in patients with paroxysmal atrial fibrillation

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Abstract

Left atrial (LA) remodeling is closely related to the occurrence of cerebral stroke; however, the relationship between early-stage impaired deformability of the left atrium and stroke/transient ischemic attack (TIA) remains unclear. The aim of this study was to evaluate the changes in LA deformability and to assess its relationship with stroke/TIA events using speckle tracking echocardiography. A total of 365 patients with paroxysmal atrial fibrillation (non-stroke/TIA [n = 318]; stroke/TIA [n = 47]) underwent comprehensive echocardiography with speckle tracking imaging to calculate mean LA longitudinal strain and strain rate values from apical 4-chamber, 2-chamber, and 3-chamber views. The stroke/TIA group was older, had a greater proportion of males, and had lower LA strain rate during left ventricular early diastole (SRE), and the difference was statistically significant ($P < .05$). On univariate linear regression analysis, the following clinical and conventional echocardiographic parameters showed a significant linear correlation ($P < .001$) with SRE: E/A ratio; LA volume index (VI); body mass index; mean E/e'; left ventricular ejection fraction; age; and hypertension. Multiple linear regression analysis revealed a linear dependence between SRE and E/A ratio, LA VI, and body mass index. The regression equation was $y = -1.430 - 0.394X_1 + 0.012X_2 + 0.019X_3$ ($P < .001$) (y, SRE; X1, E/A ratio; X2, LA VI; X3, body mass index). In multivariate logistic regression analyses, SRE and sex ratio were independent risk factors for stroke/TIA (SRE, odds ratio 2.945 [95% confidence interval 1.092–7.943]; $P = .033$; sex, odds ratio 0.462 [95% confidence interval 0.230–0.930]; $P = .031$). Among patients with paroxysmal atrial fibrillation, SRE reflected impaired deformability of the left atrium in the early stages and was associated with the risk of stroke/TIA.

Abbreviations: AF = atrial fibrillation, CI = confidence interval, EF = ejection fraction, LA = left atrial, LV = left ventricular, SD = strain during LV diastole, SRE = strain rate during LV early diastole, SS = strain during LV systole, TIA = transient ischemic attack, TTE = transthoracic echocardiography, VI = volume index.

Keywords: echocardiography, paroxysmal atrial fibrillation (AF), speckle tracking, strain rate, stroke, transient ischemic attack (TIA)

1. Introduction

Stroke is a serious complication in patients with atrial fibrillation (AF) because AF causes an elevation in left atrial (LA) pressure. Moreover, long-term increase in the LA pressure causes progressive LA remodeling.^[1] Many studies have demonstrated a strong correlation between changes in LA function and LA remodeling.^[2] LA remodeling can lead to impaired atrial contractility, prolonging the blood flow through the left atrium and causing atrial wall fibrosis as well as mechanical and electrical conduction abnormalities. These

changes ultimately lead to LA enlargement, blood stasis, and thrombogenesis.^[3,4]

Studies have shown LA longitudinal strain is a more effective marker of LA remodeling and function compared to the conventional ultrasound echocardiography parameters such as LA volume index (VI); moreover, the former allows for a more accurate evaluation of LA reservoir, conduit, and pump function. Furthermore, it is a convenient, noninvasive examination method which shows better repeatability in the hands of experienced echocardiographic operators and, thus, may have valuable prospects for other applications.^[5,6]

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The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

The study was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Ethical Committee of Beijing Anzhen Hospital, Capital Medical University.

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The present study was designed to measure conventional LA echocardiography and LA strain and strain rate parameters in patients with paroxysmal AF, and then to analyze the differences between stroke/transient ischemic attack (TIA) patients and non-stroke/TIA patients. The objective was to explore the relationship between impaired deformability of the left atrium and stroke/TIA events and to assess its predictive value for stroke/TIA events.

2. Methods

2.1. Study population

Patients who underwent pre-procedural transthoracic echocardiography (TTE) and transesophageal echocardiography prior to radiofrequency catheter ablation for symptomatic drug-refractory paroxysmal AF at the Beijing Anzhen Hospital Atrial Fibrillation Center, Capital Medical University (Beijing, China) between January 2017 and June 2020 were enrolled. Patients with persistent or permanent AF, those with AF with rheumatic valvular disease, history of valve repair or replacement, echocardiography confirmed left ventricular (LV) ejection fraction (EF) <50%, previous AF ablation, any mitral valve disease (including mild-degree disease), were excluded. All patients provided written informed consent to participate in the present study.

Patients were divided into 2 groups according to history of stroke/TIA to evaluate difference(s) in echocardiographic data, especially with respect to LA strain and strain rate, and to determine the best predictive parameters. Ischemic stroke was confirmed by sudden-onset focal neurological deficit(s) and magnetic resonance imaging or computed tomography findings. TIA was defined as sudden-onset focal neurological signs or symptoms that resolved within 24 hours.

The study was approved by the Ethics Committee of the Beijing Anzhen Hospital, Capital Medical University.

2.2. Conventional TTE

All subjects underwent comprehensive TTE study using a cardiovascular ultrasound system (Vivid 7 or Vivid E9, GE Medical Systems, Horten, Norway), equipped with a S51 phased-array sector probe (2.5–3.5 MHz). Standard M-mode, 2-dimensional, and Doppler images were acquired in the parasternal and apical views. LV EF was calculated using the biplane Simpson rule. LV diastolic function was assessed according to mean E/e' , E/A , and LA VI. Tissue Doppler imaging was performed to measure myocardial velocities. A pulsed sample volume was placed at both the septal corner and lateral wall of the mitral annulus; early diastolic (e') and late diastolic (a') myocardial velocities were recorded. The mean E/e' ratio was then calculated. All measurements were calculated and recorded as the average value of three cardiac cycles according to the American Society of Echocardiography guidelines.^[7,8]

2.3. Speckle tracking echocardiography

LA velocity vector imaging data were collected from each patient. The standard gathering sections were apical 4-chamber view, apical 2-chamber view, and apical 3-cavity view; each section was set to acquire 3 cardiac cycles, with the frame rate adjusted to >60 frames/s. The analysis was performed offline using workstation software (EchoPAC PC version 201; GE Medical Systems, Milwaukee, WI, United States). LA strain was set to 0 at the beginning of the P wave (i.e., P-triggered analysis). After manual tracing of the endocardial LA borders, an epicardial surface tracing was automatically generated by the system creating a region of interest, which was automatically determined, and speckles were traced frame by frame. The region

of interest was divided into 6 segments and the averages of the values and curves for strain and strain rate in the longitudinal direction for each segment were generated automatically. The LA roof segments in each view were excluded in this study due to the discontinuity of the LA wall at the connection of the pulmonary veins. Segments with suboptimal images were rejected by the software and excluded from analysis. By calculating the average LA strain and strain rate in the 4-chamber, 2-chamber, and 3-chamber views, the mean longitudinal LA strain and strain rate were obtained.

The LA strain versus time curves were generated; the positive peak strain during LV systole (SS) is LA SS and negative peak strain during LV diastole (SD) is LA SD; the distance between the 2 peaks is the global longitudinal strain of LA (Fig. 1). For the LA strain rate versus time curves, the positive peak in the middle during LV systole indicates LA strain rate during LV systole, the negative peak on the right side indicates LA strain rate during LV early diastole (SRE), and another negative peak on the left side indicates LA strain rate during LV late diastole (Fig. 2).

2.4. Inter- and intra-observer variability

To assess inter- and intra-observer variability, LA strain and strain rate were measured in 15 randomly selected patients. First, measurements were repeated twice by a single observer. Subsequently 2 experienced observers, who were blinded to one another's measurements and to the study time-point, obtained ventricular demand (i.e., velocity vector imaging) data from the same patients.

2.5. Statistical analysis

Continuous data are expressed as mean \pm standard deviation. Categorical data are summarized as frequencies and percentages. Continuous variables were compared using the Student *t* test (for comparisons between 2 groups) and analysis of variance (for multi-group comparisons). Categorical variables were compared using the chi-squared test. Univariate and multivariate logistic regression analyses were performed to determine risk factors for stroke/TIA in patients with paroxysmal AF. Statistical analyses were performed using SPSS version 23.0 (IBM Corporation, Armonk, NY). Two-tailed *P* values <.05 were considered indicative of statistical significance.

3. Results

3.1. Study population

A total of 385 patients were enrolled in our research. Among them, LA strain was confirmed in 365 patients (222 [61%] male; mean [\pm standard deviation] age, 58.9 ± 10.5 years) using high-quality speckle tracking imaging. Forty-seven patients had a history of ischemic stroke or TIA while 318 patients had no such history (Fig. 3).

Basic clinical and echocardiographic data of all patients according to history of stroke or TIA are summarized in Table 1. There were significant differences between the 2 groups with respect to age, sex, and SRE ($P < .05$). Compared with the non-stroke/TIA group, the stroke/TIA group was significantly older, had a greater proportion of males, and had lower SRE. There were no significant between-group differences with respect to other clinical descriptive and conventional 2-dimensional echocardiographic parameters.

Intra-observer variability for LA SS, SD, global longitudinal strain, strain rate during LV systole, SRE, and strain rate during LV late diastole was 9.6%, 9.7%, 8.5%, 8.8%, 9.0%, and 9.1%, respectively. The corresponding values for the inter-observer variability were 8.7%, 9.1%, 8.5%, 8.0%, 7.9%, and 8.4%, respectively.

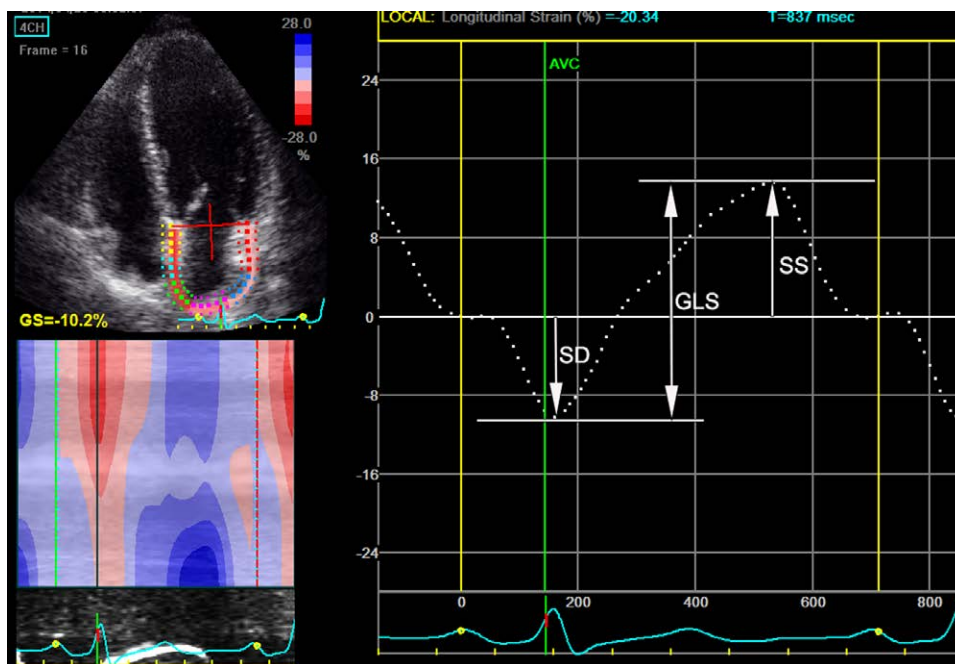


Figure 1. A normal left atrial strain curve in a complete cardiac cycle. LA = left atrial, SS = strain during left ventricular systole; SD = strain during left ventricular diastole, GLS = global longitudinal strain of LA. (LA strain was set to zero at the beginning of the P wave).

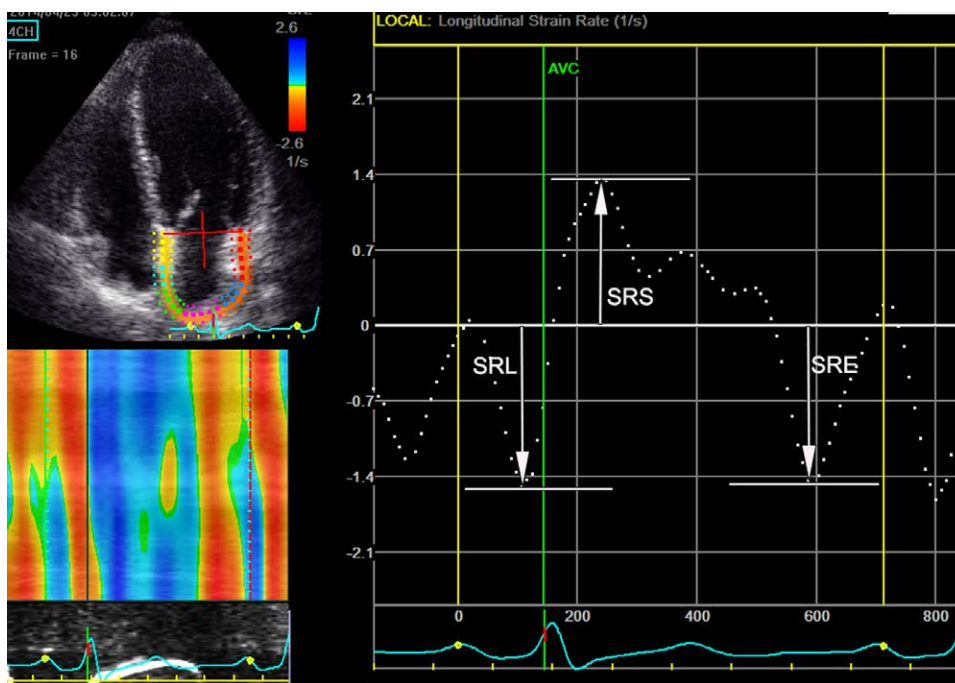


Figure 2. A normal left atrial strain rate curve in a complete cardiac cycle. LA = left atrial, SRS = strain rate during LV systole, SRE = strain rate during left ventricular early diastole; SRL = strain rate during left ventricular late diastole. (LA strain was set to zero at the beginning of the P wave).

3.2. Association of LA strain rate with clinical features, cardiac structure deformability, and function change

Univariate linear regression analysis was performed for SRE and all risk factors listed in Table 1. Each of the following clinical and conventional echocardiographic parameters showed a significant linear correlation with SRE ($P < .001$): E/A ratio; LA VI; body mass index; mean E/e' ; LVEF; age; and hypertension. After parameter optimization, multiple linear regression analysis revealed a linear dependence between SRE and multiple parameters including E/A ratio, LA VI, and body mass index. The regression equation was

$$y = -3.487 - 0.83X1 + 0.024X2 + 0.05X3 + 0.064X4 + 0.028X5 \text{ (y, SRE; X1, E/A ratio; X2, LA VI; X3, body mass index; X4, mean } E/e'; \text{ X5, age). The results of the regression analysis are summarized in Table 2.}$$

3.3. Predictive value of conventional ultrasound and strain parameters for stroke events

LA VI, mean LA systolic strain, and mean LA SRE were highly sensitive predictors of stroke/TIA events, while LV end-diastolic

diameter and mean E/e' demonstrated good specificity. Overall, however, the area under the curves were not good indicators in this study (Table 3). This was likely attributable to the relatively small sample size of the stroke group and, although the inclusion criteria were strictly adhered to, there was a high likelihood of bias.

3.4. Value of various parameters as risk factors for stroke/TIA

A summary of the logistic regression analyses for clinical and echocardiographic parameters associated with stroke/TIA is

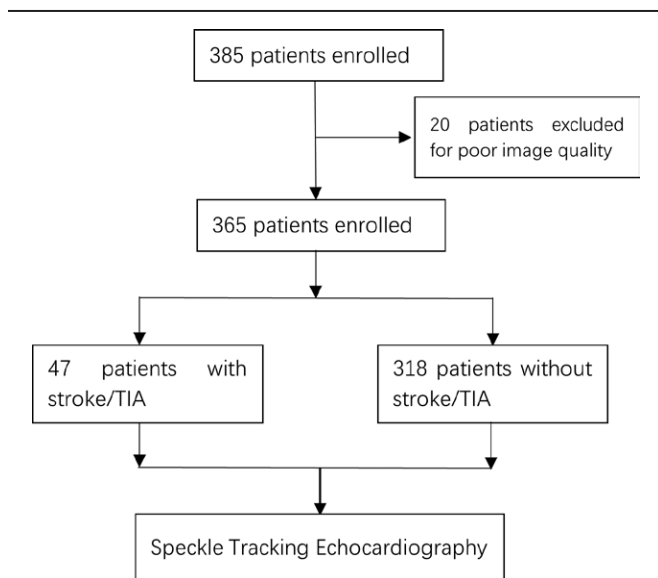


Figure 3. Flowchart of the study.

presented in Table 4. Univariate logistic regression analyses revealed that stroke/TIA was associated with older age ($P < .05$), female sex ($P < .05$), and greater LA SRE (absolute value was near 0; $P < .001$). Multivariate logistic regression analyses revealed that LA SRE and sex ratio were independent risk factors for stroke/TIA (SRE, odds ratio 2.945 [95% confidence interval 1.092–7.943]; $P = .033$; sex, odds ratio 0.462 [95% confidence interval 0.230–0.930]; $P = .031$).

4. Discussion

In this study, we analyzed changes in LA strain and strain rate in patients with paroxysmal AF using a speckle tracking technique and explored its utility in predicting the risk of stroke/TIA. Our main findings include the following: changes in LA SRE occurred earlier in patients with paroxysmal AF complicated with stroke/TIA events; LA SRE and clinical and conventional ultrasound echocardiography parameters were significantly related; and LA SRE was an independent risk factor for stroke among patients with paroxysmal AF.

4.1. LA reservoir, conduit, and pump function, and LA deformability

LA function in the entire cardiac cycle is divided into 3 phases: storing of blood in the LV systolic phase; most blood in the left atrium flows into the LV in the early diastolic phase; and LA contraction pumps the remaining blood into the LV in the late LV diastolic phase.^[5,9] Accordingly, 3 different peaks in the LA strain rate curve were recorded: 1 positive in the LV systolic phase and 2 negative in the LV early and late diastolic phases, respectively, corresponding to LA reservoir, conduit, and pump function.^[10,11] It has been established that, with regard to strain, strain rate can theoretically reflect damage to LA deformability at an early stage due to a combination of time change, which

Table 1

Clinical and echocardiographic characteristics of patients with paroxysmal AF.

Variable	Overall (n = 365)	Non stroke/TIA (n = 318)	Stroke/TIA (n = 47)	P
Clinical characteristics				
Age (yr)	58.95 ± 10.52	58.46 ± 10.55	62.32 ± 9.73	.02
Female sex	143 (39%)	131 (41%)	12 (26%)	.04
Body mass index (kg/m ²)	25.32 ± 3.77	25.41 ± 3.79	24.71 ± 3.64	.24
Body surface area (m ²)	1.78 ± 0.19	1.78 ± 0.19	1.77 ± 0.16	.67
Diabetes mellitus	59 (16%)	49 (15%)	10 (21%)	.31
Hypertension	200 (55%)	171 (54%)	29 (62%)	.31
Hyperlipemia (%)	64 (18%)	53 (17%)	11 (23%)	.26
Coronary heart disease (%)	51 (14%)	44 (14%)	7 (15%)	.85
Smoking (%)	88 (24%)	77 (24%)	11 (23%)	.90
Drinking (%)	66 (18%)	57 (18%)	9 (19%)	.84
Family history of atrial fibrillation (%)	18 (5%)	14 (4%)	4 (9%)	.39
Conventional 2-dimensional echocardiography				
LV end-diastolic diameter (mm)	48.47 ± 3.72	48.50 ± 3.66	48.28 ± 4.16	0.71
LV ejection fraction (%)	65.60 ± 4.99	65.53 ± 4.93	66.04 ± 5.40	0.52
Mean E/e'	9.93 ± 3.42	9.82 ± 3.26	10.63 ± 4.32	0.13
E/A ratio	1.07 ± 0.41	1.08 ± 0.42	1.00 ± 0.35	0.25
LA volume index (mL/m ²)	35.67 ± 12.31	35.44 ± 12.52	37.24 ± 10.72	0.35
Speckle tracking				
Mean LA systolic strain (%)	10.87 ± 4.26	10.96 ± 4.35	10.31 ± 3.53	0.33
Mean LA diastolic strain (%)	-10.67 ± 3.12	-10.72 ± 3.16	-10.38 ± 2.85	0.49
Global longitudinal strain (%)	21.55 ± 5.57	21.68 ± 5.70	20.69 ± 4.59	0.26
Mean LA SRS	1.03 ± 0.27	1.04 ± 0.27	0.98 ± 0.24	0.13
Mean LA SRE	-0.93 ± 0.37	-0.95 ± 0.39	-0.83 ± 0.30	0.04
Mean LA SRL	-1.31 ± 0.51	-1.33 ± 0.53	-1.20 ± 0.37	0.11

AF = atrial fibrillation, LA = left atrial, LV = left ventricular, SRE = strain rate during left ventricular early diastole, SRL = strain rate during left ventricular late diastole, SRS = strain rate during left ventricular systole, TIA = transient ischemic attack.

Table 2
Univariate and multivariate linear regression for LA SRE in paroxysmal AF.

Factor	Univariate			Multivariate		
	R	R ²	P	B	β	P
E/A ratio	0.403	0.163	<.001	-0.830	-0.342	<.001
LA volume index	0.382	0.143	<.001	0.024	0.297	<.001
Body mass index	0.186	0.035	<.001	0.050	0.188	<.001
Mean E/e'	0.398	0.158	<.001	0.064	0.220	<.001
LV ejection fraction	0.197	0.039	.003	-	-	-
LVEDD	0.109	0.012	.037	-	-	-
Age	0.532	0.283	<.001	0.028	0.291	<.001

AF = atrial fibrillation, LA SRE = left atrial strain rate during left ventricular early diastole, LV = left ventricular, LVEDD = left ventricular end-diastolic diameter.

Table 3
Diagnostic value of conventional ultrasonic parameters and strain parameters.

Parameter	Cut off value	AUC (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)	P value
Conventional 2D echo					
LV end-diastolic diameter (mm)	<42.50	0.5054 (0.4126–0.5981)	12.77 (4.832%–25.74%)	93.71 (90.45%–96.12%)	.9057
LV ejection fraction (%)	>67.50	0.5277 (0.4330–0.6224)	40.43 (26.37%–55.73%)	62.26 (56.69%–67.61%)	.5398
Mean E/e'	>14.95	0.5340 (0.4453–0.6227)	14.89 (6.204%–28.31%)	93.08 (89.71%–95.61%)	.4514
E/A ratio	<1.050	0.5426 (0.4606–0.6246)	61.70 (46.38%–75.49%)	49.06 (43.44%–54.69%)	.3455
LA volume index (mL/m ²)	>27.95	0.5544 (0.4741–0.6347)	85.11 (71.69%–93.80%)	30.82 (25.79%–36.21%)	.2286
Speckle tracking					
Mean LA systolic strain(%)	<14.31	0.5268 (0.4432–0.6104)	89.36 (76.90%–96.45%)	21.38 (17.01%–26.30%)	.5526
Mean LA diastolic strain (%)	>-11.27	0.5417 (0.4561–0.6274)	68.09 (52.88%–80.91%)	44.97 (39.41%–50.62%)	.3558
Global longitudinal strain (%)	<23.28	0.5495 (0.4673–0.6317)	78.72 (64.34%–89.30%)	34.59 (29.37%–40.10%)	.2731
Mean LA SRS	<1.025	0.5872 (0.5045–0.6700)	72.34 (57.36%–84.38%)	47.17 (41.58%–52.82%)	.05349
Mean LA SRE	>-1.085	0.5910 (0.5109–0.6712)	87.23 (74.26%–95.17%)	30.50 (25.49%–35.89%)	.04395
Mean LA SRL	>-1.305	0.5841 (0.4994–0.6687)	68.09 (52.88%–80.91%)	48.43 (42.81%–54.07%)	.06280

AUC = area under the curve, CI = confidence interval, LA = left atrial, LV = left ventricular, SRE = strain rate during LV early diastole, SRL = strain rate during LV late diastole, SRS = strain rate during LV systole.

Table 4
Results of univariate and multivariate logistic regression for analyzing risk factors of stroke/TIA.

	Univariate			Multivariate		
	B	OR	95% CI	B	OR	95% CI
LA SRS	-1.004	0.366	0.101–1.334	-	-	-
LA SRE	0.988	2.687	1.018–7.090*	1.080	2.945	1.092–7.943*
LA SRL	0.650	1.916	0.908–4.041	-	-	-
GLS	-0.033	0.967	0.913–1.025	-	-	-
Age	0.038	1.038	1.006–1.072*	-	-	-
Sex	-0.715	0.489	0.245–0.978*	-0.771	0.462	0.230–0.930*
Mean E/e'	0.062	1.063	0.981–1.153	-	-	-
LA VI	0.012	1.012	0.987–1.037	-	-	-

CI = confidence interval, GLS = global longitudinal strain, LA = left atrial, SRE = strain rate during left ventricular early diastole, SRL = strain rate during left ventricular late diastole, SRS = strain rate during left ventricular systole, VI = volume index, OR = odds ratio, TIA = transient ischemic attack.

* $P < .05$, the difference is statistically significant.

has a higher diagnostic value. The L_0 of the left atrium in the longitudinal axis should be determined first when analyzing LA strain rate; similar to LV strain and strain rate analysis, we believe that the left atrium is in the L_0 state at the beginning of LA contraction, when electrocardiogram shows the P-wave phase.^[12]

Compared with the non-stroke group, LA VI was greater in the stroke/TIA group, although the difference was not statistically significant. However, there were significant differences between the 2 groups with respect to LA SRE ($P < .05$), which indicated that there were no obvious morphological changes in the LA. Furthermore, LA deformability decreased in the early stages and LA longitudinal strain was not significantly altered.

4.2. Association between LA SRE and conventional clinical echocardiographic parameters

Previous studies have demonstrated a significant correlation between LA strain and conventional clinical echocardiographic parameters.^[3,13,14] Our results are consistent with this, as LA SRE demonstrated a significant linear correlation with age, body mass index, hypertension, LVEF, mean E/e', LA VI, and E/A ratio ($P < .001$), with an especially strong correlation with age. LA SRE not only reflected LA remodeling, but more importantly, reflected early impairment of LA deformability. As such, LA SRE is a potential marker of changes in LA function in the early stages.^[15–19]

4.3. LA deformability parameters and risk factors for stroke/TIA

LA remodeling parameters, such as LA VI, have been confirmed to be risk factors for cardiovascular events including stroke, myocardial infarction, atrial thrombosis, and recurrence of AF.^[20] Increased LA pressure and volume load would lead to the gradual fibrosis of the LA wall, leading to LA reservoir and conduit dysfunction. However, before enlargement of the left atrium, the LA deformability capacity is likely to be compromised. Thus, an ideal ultrasound parameter for accurate evaluation of LA deformability would be valuable and could facilitate earlier prediction of the above-mentioned cardiovascular events.

Previous studies have demonstrated the feasibility of use of 2-dimensional echocardiographic speckle tracking technology for evaluating LA remodeling and deformability.^[3,6,21–24] Small-sample studies have identified LA longitudinal strain as a risk factor for stroke/TIA among patients with AF.^[5] In our study, LA longitudinal strain rate showed changes at an early stage compared to LA strain and was found to be an early marker of damage to LA deformability.

Indeed, in this study, LA SRE was an independent risk factor ($P < .05$) for stroke in patients with paroxysmal AF according to multivariate logistic regression analysis—more specifically, the smaller the absolute value of SRE, the greater was the risk of stroke/TIA. However, for a more definitive characterization of the relationship between the index and stroke/TIA, studies with longer-term follow-up combined with clinical and conventional echocardiographic parameters are needed.^[25]

4.4. Clinical applications

Changes in LA strain rate reflect the capacity of LA deformability, which precedes LA remodeling,^[26,27] and is more accurate than LA strain. Therefore, it is a more suitable parameter for screening of patients at an early stage. Due to its noninvasiveness and easy operation, the speckle tracking technique is becoming increasingly popular, and we anticipate that it will prove to be a reliable parameter in subsequent studies.

4.5. Limitations

Some limitations of this study should be acknowledged while interpreting the results. First, this was a cross-sectional study, and patients were not followed up to evaluate the effectiveness of the risk factors. Second, we only included patients with paroxysmal AF. Future studies should also include patients with non-AF with or without stroke/TIA, and then compare changes in LA strain rate. Third, all patients in this study had preserved LV EF.

5. Conclusions

LA SRE reflected changes in the LA deformability in the early stages. It was an independent risk factor for stroke/TIA among patients with paroxysmal AF. Further prospective studies, including more controls and longer-term follow-up, are required to evaluate the clinical utility of changes in LA strain rate.

Author contributions

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Writing – original draft: Jian Chen.

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