



# Study on the relationship between atrial high-rate episode and left atrial strain in patients with cardiac implantable electronic device

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**Background:** Although atrial high-rate episode (AHRE) and atrial fibrillation (AF) cannot entirely be identical, recent studies suggest AHRE is linked to AF development and shares some characteristics with AF regarding thromboembolism. At present, there is still lack of predictive indicators for AHRE and diagnostic methods and clinical indicators for AHRE in patients without cardiac implantable electronic device (CIED). The aim of this study was thus to explore the relationship between AHRE and left atrial (LA) strain parameters with the goal of identifying high-risk populations of AHRE by LA strain characteristics.

**Methods:** From February 2022 to May 2023, a total of 105 CIED patients were enrolled and divided into two groups based on whether AHRE had occurred: AHRE (-) group (n=65) and AHRE (+) group (n=40). Real-time three-dimensional echocardiography (RT-3DE) technique was used to obtain the LA time-volume curve. The collected dynamic images were analyzed on the Echopac 204 workstation to obtain the parameters of LA. The four-dimensional automatic LA quantitative analysis (4D Auto LAQ) technology was used to analyze the LA strain parameters: LA reservoir longitudinal strain (LASr), LA conduit longitudinal strain (LAScd), LA contraction longitudinal strain (LASct), LA reservoir circumferential strain (LASr-c), LA conduit circumferential strain (LAScd-c), LA contraction circumferential strain (LASct-c). Correlation analysis was carried out using Binary logistic regression analysis. The area under the receiver operating characteristic (ROC) curve (AUC) was used to evaluate the diagnostic performance of LASct in AHRE.

**Results:** Body surface area (BSA) [odds ratio (OR) =8.34, 95% confidence interval (CI): 1.32–72.30, P=0.037], LASct (OR =1.20, 95% CI: 1.05–1.39, P=0.013) and LA end-systolic volume (LAESV) (OR =1.02, 95% CI: 1.00–1.04, P=0.023) were the influencing factors of AHRE. Only LASct (OR =1.18, 95% CI: 1.01–1.38, P=0.041) was found to be an independent influencing factor of AHRE. This result remained significant after adjusting for age, sex, hypertension, diabetes, and stroke history. The ROC curve showed that the cut-off for predicting AHRE was LASct =-4.125% with sensitivity of 37.5% and specificity of 87.7%.

**Conclusions:** This cross-sectional study found that decreased LASct (absolute value) is an independent

risk factor for the AHRE and has diagnostic efficacy in certain degree for the occurrence of AHRE.

**Keywords:** Atrial high-rate episode (AHRE); left atrial strain (LA strain); cardiovascular implantable electronic device; echocardiography

Submitted Aug 31, 2023. Accepted for publication Dec 04, 2023. Published online Jan 15, 2024.

doi: 10.21037/qims-23-1237

View this article at: <https://dx.doi.org/10.21037/qims-23-1237>

## Introduction

Atrial high-rate episode (AHRE) refers to the events of atrial tachyarrhythmias fulfilling the programmed or specified criteria and detected by the cardiac implantable electronic device (CIED) with atrial electrodes (1). AHRE has a high incidence in the patients with CIED (2,3). Even though AHRE and atrial fibrillation (AF) cannot entirely be identical, more and more research in recent years has discovered that AHRE is related to the development of AF and shares some characteristics with AF in terms of thromboembolism (4-6). However, there is still lack of predictive indicators for AHRE and diagnostic methods and clinical indicators for AHRE in patients without CIED.

Echocardiography is one of the most common examinations in cardiovascular diseases. It contains many parameters such as volume and strain representing various aspects of heart function. The left atrial (LA) might exhibit structural and functional defects early owing to adverse events because it contains shorter myocardial fibers, thinner walls, and a lesser compensatory ability than the left ventricle (LV). Therefore, LA parameters are more sensitive than LV parameters at detecting cardiac damage. Additionally, LA strain parameters are more sensitive than volume parameters (7-9). As a result, "LA strain"-related parameters have increasingly been attached importance and may be closely linked to the development of AHRE. Its utility for predicting AHRE is, however, not well-proven. Early identification of the high-risk populations of AHRE can provide early monitoring and intervention basis for preventing its further development into clinical AF or thromboembolism events.

Therefore, the aim of this study was to explore the relationship between AHRE and LA strain parameters with the goal of identifying high-risk populations of AHRE by LA strain characteristics. We present this article in accordance with the STROBE reporting checklist (available at <https://qims.amegroups.com/article/view/10.21037/qims-23-1237/rc>).

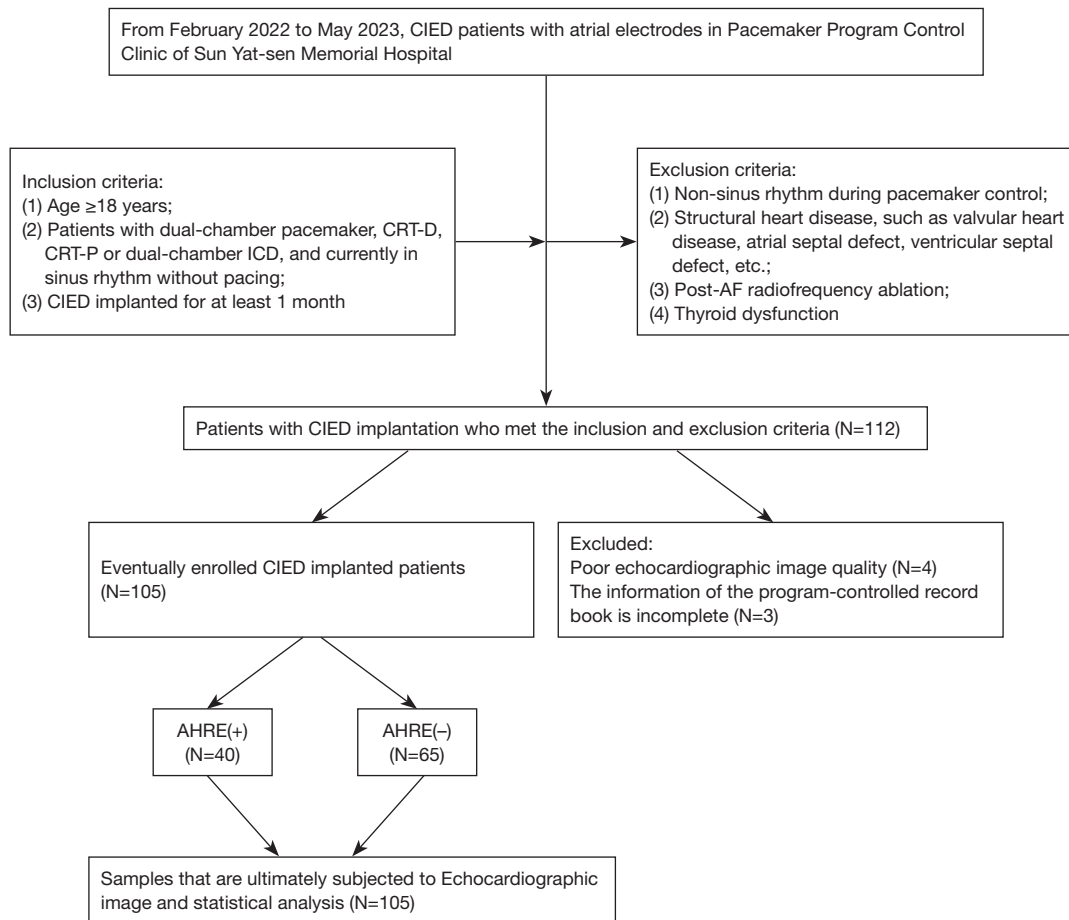
## Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and it was approved by the Institution Review Board of Sun Yat-sen Memorial Hospital. Written informed consent was obtained from all participants.

### *Patients and study protocol*

From February 2022 to May 2023, CIED patients with atrial electrodes in Pacemaker Program Control Clinic of Sun Yat-sen Memorial Hospital were included. Inclusion criteria were: (I) age  $\geq 18$  years; (II) patients with dual-chamber pacemaker, cardiac resynchronization therapy defibrillator (CRT-D), cardiac resynchronization therapy pacemaker (CRT-P) or dual-chamber implantable cardioverter defibrillator (ICD), and currently in sinus rhythm without pacing; (III) CIED implanted for at least one month. Exclusion criteria were: (I) non-sinus rhythm during pacemaker control; (II) structural heart disease, such as valvular heart disease, atrial septal defect, ventricular septal defect, etc.; (III) post-AF radiofrequency ablation; (IV) thyroid dysfunction; (V) incomplete information of the program-controlled record book; (VI) poor echocardiographic image quality.

According to the information of program-controlled record, patients were divided into AHRE (-) group and AHRE (+) group. There are subtle differences in the definition of AHRE by program-controlled devices from different CIED manufacturers. The primary CIED manufacturers in this study were Medtronic (Minnesota, USA), Boston Scientific (Massachusetts, USA), and Abbott (Chicago, USA). The definitions of AHRE were as follows: Medtronic: atrial heart rate (HR)  $>180$  beats per minute (bpm), lasting for at least five cardiac cycles; Boston Scientific: atrial HR  $>170$  bpm, lasting for at least eight cardiac cycles; Abbott: atrial HR  $>180$  bpm, lasting for at least three seconds. The significant differences in LA volume and



**Figure 1** The flowchart of the study protocol. CIED, cardiac implantable electronic device; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; ICD, implantable cardioverter defibrillator; AF, atrial fibrillation; AHRE, atrial high-rate episode; N, number.

strain parameters between the two groups of patients were compared. The correlation between various parameters and the occurrence of atrial high-frequency events, the sensitivity and specificity as AHRE prediction indicators were analyzed. The study flowchart is illustrated in *Figure 1*.

### ***Echocardiography and real-time three-dimensional echocardiography (RT-3DE) technique***

All patients underwent transthoracic echocardiography in sinus rhythm. Prior to the examination, patients were at rest for more than 20 minutes. Systolic and diastolic pressures, as well as HR, were recorded using a cuff sphygmomanometer before the examination.

The imaging was performed using the GE vivid E95 color Doppler ultrasound system (GE Healthcare, Chicago,

USA) with the M5Sc-D 2D transducer (frequency: 1.4–4.6 MHz) and the 4V transducer (frequency: 1.5–4.0 MHz). The system was equipped with the GE Echopac 204 workstation and the four-dimensional automatic LA quantitative analysis (4D Auto LAQ) offline analysis software.

The subjects were positioned in the left lateral decubitus position and connected to electrocardiography. Age, height and weight were entered to calculate body surface area (BSA). Prior blood pressure measurements were inputted before performing transthoracic echocardiography in sinus rhythm. The M5Sc-D transducer was used to acquire dynamic images (>50 frames/second) of three cardiac cycles continuously in the apical four-chamber, two-chamber, and three-chamber views. Simultaneously, the blood flow spectra of the mitral valve and aortic valve were obtained. The images obtained from this transducer were imported in

DICOM format into the GE Echopac 204 workstation for offline analysis. The following parameters were obtained: LA end-diastolic length (LALd), LA end-diastolic area (LAAd), LA end-systolic length (LALs), LA end-systolic area (LAAs), LA end-diastolic volume (LAEDV), LA end-systolic volume (LAESV), mitral ratio of peak early to late diastolic filling velocity (E/A), ratio of early diastolic transmitral flow velocity to early diastolic mitral annular velocity (E/e'), LV ejection fraction (LVEF), left ventricular end diastolic diameter (LVDd). The 4V transducer was used to acquire four-dimensional volume images of the entire left atrium in the apical four-chamber view using RT-3DE technology (>16 frames/second). Two-dimensional gain and zoom functions were adjusted for optimal visualization.

RT-3DE technique was used to reconstruct LA images by tracing the LA endocardial boundary to obtain the LA time-volume curve. The LA function is reflected by describing the dynamic changes of LA volume in different phases of the cardiac cycle, and the collected dynamic images were imported into the GE Echopac 204 workstation in DICOM format for offline analysis to obtain the parameters of LA. The 4D Auto LAQ technology was used to analyze the LA strain parameters: LA reservoir longitudinal strain (LASr), LA conduit longitudinal strain (LAScd), LA contraction longitudinal strain (LASct), LA reservoir circumferential strain (LASr-c), LA conduit circumferential strain (LAScd-c), LA contraction circumferential strain (LASct-c). At least three duplicate images were collected for each patient, and the average of each parameter was taken.

### Statistical analysis

The CIED patients were divided into two groups: AHRE (-) group and AHRE (+) group, in accordance with the previous program control records on whether AHRE had happened. The Kolmogorov-Smirnov (K-S) method was used to test the normality of the numerical data, and two independent samples *t*-test was used for data of normal distribution, presented as mean  $\pm$  standard deviation; Mann Whitney *U* test was used for data of non-normal distribution, presented as quartile interval; Chi-squared test was used for classification data, presented as frequency and percentage. Correlation analysis was carried out using Binary logistic regression analysis. Furthermore, the area under the receiver operating characteristic (ROC) curve (AUC) was used to evaluate the diagnostic performance of LASct in AHRE. A *P* value <0.05 (two-sided) was considered statistically significant.

## Results

### Patient characteristics

The study included 105 cases of patients with CIED implantation. There were 65 cases in the AHRE (-) group and 40 cases in the AHRE (+) group. The median duration of AHRE was 1.9 (0.2–8.9) hours. In terms of disease types: there were 67 cases of sick sinus syndrome, 20 cases of atrioventricular block, 10 cases of dilated cardiomyopathy, three cases of hypertrophic cardiomyopathy, three cases of ischemic cardiomyopathy, and two cases of ventricular tachycardia. Regarding the types of implanted CIED: there were 80 cases of dual-chamber pacemakers, six cases of CRT-D/CRT-P, and 19 cases of dual-chamber ICD. The baseline clinical characteristics of these patients are shown in *Table 1*.

Compared to the AHRE (-) group, the AHRE (+) group showed a significant increase in height (162.08 $\pm$ 7.81 *vs.* 165.38 $\pm$ 8.75, *P*=0.047) and a decrease in the time from CIED implantation to first AHRE/echocardiogram recording [22 [interquartile range (IQR), 6–64] *vs.* 12 (IQR, 1–32), *P*=0.039], indicating statistically significant differences. There were no statistically significant differences between the two groups in terms of weight, BSA, body mass index (BMI), age, gender, systolic blood pressure (SBP), diastolic blood pressure (DBP), HR, hypertension, diabetes, history of stroke, smoking, alcohol consumption, CIED type, and type of diseases (*P*>0.05) (*Table 1*).

### Echocardiographic parameters

Compared to the AHRE (-) group, the AHRE (+) group showed statistically significant differences in the following echocardiographic parameters: an decrease in LASct (absolute value) (-7.22 $\pm$ 3.16 *vs.* -5.57 $\pm$ 3.06, *P*=0.010), an increase in LAESV [51.86 (IQR, 41.45–63.40) *vs.* 61.03 (IQR, 46.16–77.52), *P*=0.023], and an increase in E/A [0.78 (IQR, 0.69–1.00) *vs.* 0.92 (IQR, 0.76–1.12), *P*=0.025]. However, there were no statistically significant differences between the two groups in terms of other echocardiographic parameters such as LAVmin, LAVmax, LAVpreA, LASr, and LAScd (*P*>0.05) (*Table 2*).

### Univariate and multivariate logistic regression analysis of AHRE

Univariate logistic regression analysis revealed that increased BSA [odds ratio (OR) =8.34, 95% confidence interval (CI): 1.32–72.3, *P*=0.037], decreased LASct

**Table 1** Baseline clinical characteristics of patients with CIED

Characteristics	AHRE (-) (N=65)	AHRE (+) (N=40)	P value
Height (cm)	162.08±7.81	165.38±8.75	0.047*
Weight (kg)	63.00 (53.00 to 67.00)	67.00 (54.50 to 74.00)	0.101
BSA (m <sup>2</sup> )	1.65 (1.49 to 1.71)	1.71 (1.51 to 1.85)	0.072
BMI (kg/m <sup>2</sup> )	23.56 (21.23 to 25.39)	23.73 (21.50 to 24.99)	0.879
Age (years)	67.00 (62.00 to 72.00)	66.00 (56.50 to 75.00)	0.890
Male	34 (52.3)	24 (60.0)	0.570
SBP(mmHg)	139.00 (125.00 to 151.00)	132.00 (120.50 to 148.00)	0.322
DBP (mmHg)	78.18±12.85	79.33±14.00	0.671
HR (bpm)	67.00 (61.00 to 74.00)	62.00 (59.50 to 72.00)	0.181
Hypertension	33 (50.8)	16 (40.0)	0.383
Diabetes mellitus	11 (16.9)	5 (12.5)	0.739
TIA/prior stroke	5 (7.7)	3 (7.5)	>0.99
Smoke			0.144
Never	38 (58.5)	30 (75.0)	
Smoking cessation >1 year	16 (24.6)	4 (10.0)	
Persistent smokers	11 (16.9)	6 (15.0)	
Alcohol			0.674
Never	49 (75.4)	33 (82.5)	
Alcohol cessation >1 year	6 (9.2)	2 (5.0)	
Persistent drinkers	10 (15.4)	5 (12.5)	
Type of CIEDs			0.617
Dual-chamber pacemaker	48 (73.8)	32 (80.0)	
CRT-D/CRT-P	5 (7.7)	1 (2.5)	
Dual-chamber ICD	12 (18.5)	7 (17.5)	
Time from CIED implantation to first AHRE/ echocardiogram recording (months)	22.00 (6.00 to 64.00)	12.00 (1.00 to 32.00)	0.039*
Type of diseases			0.872
SSS	40 (61.5)	27 (67.5)	
AVB	12 (18.5)	8 (20.0)	
Dilated cardiomyopathy	7 (10.8)	3 (7.5)	
Hypertrophic cardiomyopathy	2 (3.1)	1 (2.5)	
Ventricular tachycardia	1 (1.5)	1 (2.5)	
Ischemic cardiomyopathy	3 (4.6)	0	

Data are presented as mean ± SD, median (IQR), or number (%). \*, P<0.05. CIED, cardiac implantable electronic device; AHRE, atrial high rate episode; BSA, body surface area; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TIA, transient ischemic attack; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; ICD, implantable cardioverter defibrillators; SSS, sick sinus syndrome; AVB, atrioventricular block; SD, standard deviation; IQR, interquartile range.

**Table 2** The comparison of echocardiographic parameters between the AHRE (-) group and the AHRE (+) group

Characteristics	AHRE (-) (N=65)	AHRE (+) (N=40)	P value
LAVmin (mL)	25.75 (22.50 to 31.75)	29.25 (21.00 to 36.88)	0.373
LAVmax (mL)	45.75 (40.75 to 54.00)	51.12 (39.34 to 61.25)	0.297
LAVpreA (mL)	37.50 (32.75 to 44.75)	40.25 (30.75 to 49.66)	0.484
LAVImax (mL/m <sup>2</sup> )	27.67 (25.00 to 33.25)	30.50 (23.50 to 35.50)	0.555
LAEV (mL)	20.00 (16.75 to 23.33)	19.38 (16.00 to 26.25)	0.649
LAEF (%)	42.50 (36.50 to 48.00)	43.21 (33.88 to 49.25)	0.995
LASr (%)	15.07±5.05	14.67±5.97	0.714
LAScd (%)	-7.00 (-9.75 to -5.00)	-8.38 (-12.00 to -5.88)	0.079
LASct (%)	-7.22±3.16	-5.57±3.06	0.010*
LASr-c (%)	17.50 (13.50 to 23.00)	19.25 (14.25 to 25.75)	0.364
LAScd-c (%)	-7.47±4.45	-9.20±5.61	0.083
LASct-c (%)	-10.25 (-14.00 to -7.50)	-11.00 (-14.75 to -5.58)	0.817
LALd (cm)	4.52±0.75	4.46±0.70	0.664
LAAd (cm <sup>2</sup> )	10.98 (9.62 to 13.28)	11.96 (9.55 to 14.34)	0.303
LALs (cm)	5.02±0.73	5.04±0.70	0.849
LAAs (cm <sup>2</sup> )	15.85 (14.02 to 19.80)	17.12 (15.05 to 21.45)	0.101
LAEDV (mL)	28.40 (22.27 to 34.06)	29.24 (24.83 to 42.38)	0.241
LAESV (mL)	51.86 (41.45 to 63.40)	61.03 (46.16 to 77.52)	0.023*
E/A	0.78 (0.69 to 1.00)	0.92 (0.76 to 1.12)	0.025*
E/e'	10.40 (8.00 to 14.17)	9.35 (7.59 to 11.90)	0.268
LVEF (%)	66.00 (62.00 to 70.00)	66.00 (61.50 to 69.50)	0.771
LVDd (cm)	49.00 (44.00 to 52.00)	47.50 (46.00 to 53.50)	0.606

Data are presented as mean ± SD, or median (IQR). \*, P<0.05. AHRE, atrial high rate episode; LAVmin, LA minimal volume; LAVmax, LA maximal volume; LAVpreA, LA pre-systolic volume; LAVImax, LA maximum volume index; LAEV, LA end-diastolic volume; LAEF, LA ejection fraction; LASr, LA reservoir longitudinal strain; LAScd, LA conduit longitudinal strain; LASct, LA contraction longitudinal strain; LASr-c, LA reservoir circumferential strain; LAScd-c, LA conduit circumferential strain; LASct-c, LA contraction circumferential strain; LALd, LA end-diastolic length; LAAd, LA end-diastolic area; LALs, LA end-systolic length; LAAs, LA end-systolic area; LAEDV, LA end-diastolic volume; LAESV, LA end-diastolic volume; E/A, mitral ratio of peak early to late diastolic filling velocity; E/e', ratio of early diastolic transmitral flow velocity to early diastolic mitral annular velocity; LVEF, LV ejection fraction; LVDd, left ventricular end diastolic diameter; SD, standard deviation; IQR, interquartile range; LA, left atrial.

(absolute value) (OR =1.2, 95% CI: 1.05–1.39, P=0.013), and increased LAESV (OR =1.02, 95% CI: 1.00–1.04, P=0.023) were risk factors for AHRE (Table 3). Multivariate logistic regression analysis including these parameters found that only LASct (OR =1.18, 95% CI: 1.01–1.38, P=0.041) was an independent influencing factor for AHRE (Table 4). After adjusting for age, gender, hypertension, diabetes, and history of stroke, decreased LASct (absolute

value) (OR =1.22, 95% CI: 1.06–1.42, P=0.010) remained an independent risk factor for AHRE (Table 5) (Figure 2).

#### ROC curves of LASct

The ability of LASct to predict AHRE was evaluated using the AUC, which was 0.631 (95% CI: 0.519–0.742, P=0.025). The optimal threshold for LASct to predict AHRE was

**Table 3** Univariate logistic regression analysis of AHRE

Characteristics	OR	95% CI	P value
Height (cm)	1.05	1.00–1.11	0.051
Weight (kg)	1.03	1.00–1.06	0.059
BSA(m <sup>2</sup> )	8.34	1.32–72.3	0.037*
BMI (kg/m <sup>2</sup> )	1.05	0.97–1.16	0.212
Age (years)	0.98	0.95–1.02	0.393
Male	0.73	0.33–1.62	0.442
SBP (mmHg)	0.99	0.97–1.01	0.461
DBP (mmHg)	1.01	0.98–1.04	0.667
HR(bpm)	0.98	0.94–1.02	0.404
Hypertension	0.65	0.29–1.43	0.284
Diabetes mellitus	0.70	0.21–2.11	0.542
TIA/prior stroke	0.97	0.19–4.20	0.971
Smoke			
Never	–	–	
Smoking cessation >1 year	0.32	0.08–0.97	0.059
Persistent smokers	0.69	0.22–2.04	0.512
Alcohol			
Never	–	–	
Alcohol cessation >1 year	0.49	0.07–2.30	0.406
Persistent drinkers	0.74	0.21–2.29	0.615
Type of CIED			
Dual-chamber pacemaker	–	–	
CRT-D/CRT-P	0.30	0.02–1.97	0.282
Dual-chamber ICD	0.88	0.30–2.42	0.800
Time from CIED implantation to first AHRE/echocardiogram recording (months)	0.99	0.98–1.00	0.059
LAVmin (mL)	1.01	0.98–1.04	0.503
LAVmax (mL)	1.01	0.99–1.03	0.345
LAVpreA (mL)	1.00	0.98–1.03	0.715
LAVImax (mL/m <sup>2</sup> )	1.01	0.97–1.05	0.629
LAEV (mL)	1.04	0.97–1.12	0.235
LAEF (%)	0.99	0.95–1.03	0.728
LASr (%)	0.99	0.92–1.06	0.711
LAScd (%)	0.92	0.84–1.01	0.079
LASct (%)	1.20	1.05–1.39	0.013*
LASr-c (%)	1.01	0.96–1.06	0.649

Table 3 (continued)

Table 3 (continued)

Characteristics	OR	95% CI	P value
LAScd-c (%)	0.93	0.86–1.01	0.086
LASct-c (%)	1.03	0.96–1.11	0.382
LALd (cm)	0.88	0.50–1.53	0.661
LAAAd (cm <sup>2</sup> )	1.05	0.95–1.15	0.353
LALs (cm)	1.06	0.60–1.85	0.847
LAAs (cm <sup>2</sup> )	1.06	0.98–1.16	0.165
LAEDV (mL)	1.02	0.99–1.04	0.171
LAESV (mL)	1.02	1.00–1.04	0.023*
E/A	3.04	0.81–13.4	0.114
E/e'	0.96	0.87–1.02	0.245
LVEF (%)	0.99	0.95–1.03	0.656
LVDd (cm)	0.99	0.93–1.05	0.674

\*, P<0.05. AHRE, atrial high rate episode; OR, odds ratio; CI, confidence interval; BSA, body surface area; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TIA, transient ischemic attack; CIED, cardiac implantable electronic device; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; ICD, implantable cardioverter defibrillators; LAVmin, LA minimal volume; LAVmax, LA maximal volume; LAVpreA, LA pre-systolic volume; LAVImax, LA maximum volume index; LAEV, LA end-diastolic volume; LAEF, LA ejection fraction; LASr, LA reservoir longitudinal strain; LAScd, LA conduit longitudinal strain; LASct, LA contraction longitudinal strain; LASr-c, LA reservoir circumferential strain; LAScd-c, LA conduit circumferential strain; LASct-c, LA contraction circumferential strain; LALd, LA end-diastolic Length; LAAAd, LA end-diastolic Area; LALs, LA end-systolic length; LAAs, LA end-systolic area; LAEDV, LA end-diastolic volume; LAESV, LA end-diastolic volume; E/A, mitral ratio of peak early to late diastolic filling velocity; E/e', ratio of early diastolic transmitral flow velocity to early diastolic mitral annular velocity; LVEF, LV ejection fraction; LVDd, left ventricular end diastolic diameter; LA, left atrial.

-4.125%, with a sensitivity of 37.5% and specificity of 87.7% (Figure 3). The incidence of AHRE in patients with LASct  $\geq$  -4.125% was 65.2%, significantly higher than the incidence in patients with LASct < -4.125% (30.5%) (P=0.002) (Figure 4).

#### Intra- and interobserver variability

Echocardiograms of 30 patients were randomly selected to assess the reproducibility by the same observers and by another experienced observers two weeks later. The first observer blindly analyzed the same echocardiograms for the second time. Another observer who was blinded to patients' clinical data and the other's results, performed independent measurements of the echocardiographic data. Intra- and interobserver variability was calculated using intraclass correlation coefficients (ICCs). The ICC values ranged from 0.779 to 0.978 (Table 6), indicating good intra- and interobserver repeatability.

#### Discussion

Many chronic cardiovascular diseases, such as heart failure, hypertension, hypertrophic cardiomyopathy, ischemic cardiomyopathy, can lead to anatomical and functional remodeling of the left atrium, thereby increasing the risk of various adverse atrial events. Compared to anatomical remodeling, functional remodeling is considered an earlier and more sensitive indicator of disease progression (7-11). Therefore, early detection of these atrial abnormalities can not only assist in the early screening of atrial adverse events but also provide information for further risk stratification and decision-making. In recent years, the gradually recognized "LA strain", which reflects LA function, may be one of the indicators associated with AHRE. It has been widely studied in cardiovascular diseases such as AF, hypertension, and heart failure (9,12,13). However, the correlation between LA strain and the occurrence of AHRE and whether it can serve as a predictive factor for AHRE have not been fully confirmed.



**Table 4** Multivariate logistic regression analysis of AHRE

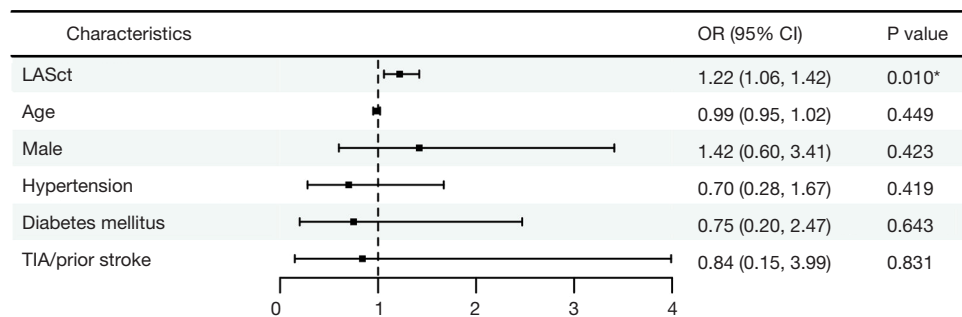
Characteristics	OR	95% CI	P value
BSA (m <sup>2</sup> )	6.50	0.84–50.28	0.073
LASct (%)	1.18	1.01–1.38	0.041*
LAESV (mL)	1.01	0.99–1.03	0.439

\*, P<0.05. AHRE, atrial high rate episode; OR, odds ratio; CI, confidence interval; BSA, body surface area; LASct, LA contraction longitudinal strain; LAESV, LA end-diastolic volume; LA, left atrial.

**Table 5** Multivariate logistic regression analysis of AHRE after adjustment

Characteristics	OR	95% CI	P value
LASct (%)	1.22	1.06–1.42	0.010*
Age (years)	0.99	0.95–1.02	0.449
Male, n (%)	1.42	0.60–3.41	0.423
Hypertension, n (%)	0.70	0.28–1.67	0.419
Diabetes mellitus, n (%)	0.75	0.20–2.47	0.643
TIA/prior stroke, n (%)	0.84	0.15–3.99	0.831

\*, P<0.05. AHRE, atrial high rate episode; OR, odds ratio; CI, confidence interval; LASct, LA contraction longitudinal strain; TIA, transient ischemic attack; LA, left atrial.

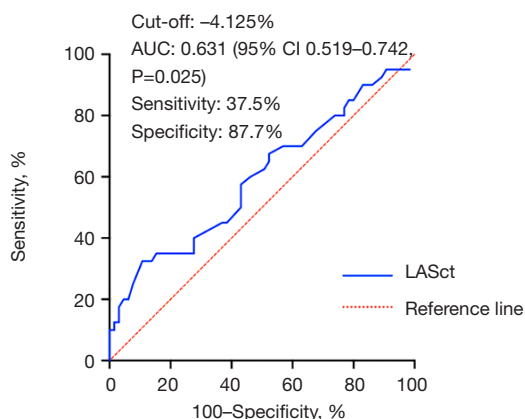


**Figure 2** Forest plot of multivariate logistic regression. \*, P<0.05. OR, odds ratio; CI, confidence interval; LASct, LA contraction longitudinal strain; TIA, transient ischemic attack; LA, left atrial.

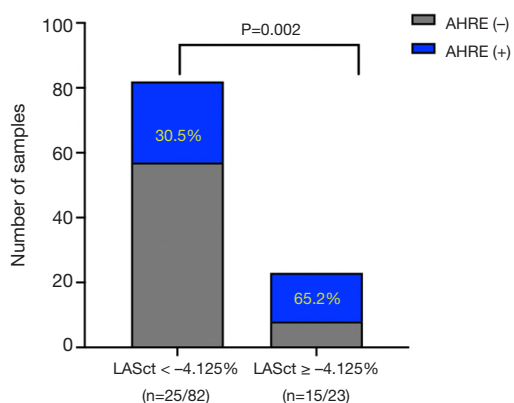
### The association between LA strain and AHRE

In this study, a comparison between the AHRE (-) group and the AHRE (+) group revealed significant differences in height, time from CIED implantation to the first AHRE/echocardiogram recording, LASct, LAESV, and E/A. In the univariate logistic regression analysis, it was found that increased BSA, decreased LASct (absolute value), and increased LAESV were risk factors for AHRE. Further multivariate logistic regression analysis showed that only decreased LASct (absolute value) was an independent risk

factor for AHRE. This result remained significant even after adjusting for age, gender, hypertension, diabetes, and history of stroke. The probability of AHRE occurrence increased with decreased LASct (absolute value) (OR =1.22, 95% CI: 1.06–1.42, P=0.010). According to the ROC curve, the AUC suggests that LASct can predict AHRE, with LASct  $\geq$ -4.125% identified as the optimal threshold. LASct reflects the longitudinal strain during LA systole, representing the auxiliary pump function of the LA and its ability to actively pump blood into the LV during late diastole. This ability depends on the contractile force and the initial length of



**Figure 3** ROC curves of LASct for predicting AHRE. AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic; LASct, LA contraction longitudinal strain; AHRE, atrial high rate episode; LA, left atrial.



**Figure 4** The incidence of AHRE when using LASct -4.125% as the threshold. AHRE, atrial high rate episode; LASct, LA contraction longitudinal strain; LA, left atrial.

the atrial myocardium. Compared to parameters such as LA volume and LAEF, LA strain has a lower dependence on load, particularly in terms of longitudinal strain, making it a robust indicator of LA myocardial function that closely reflects LA contractile force and is closely associated with fibrosis of the LA myocardial wall (14). Chen *et al.* (7) conducted an analysis of samples from a high-risk group and a low-risk group for thromboembolic events (TE). They found significant differences in LASr, LASct, LASr-c, LAScd-c, and LASct-c between the two groups, while there was no statistically significant difference in the volume at the onset of LA contraction and LAEF

between the two groups. Morris *et al.* (8) found that in patients with altered LV diastolic function and elevated LV filling pressure, the incidence of abnormal LA strain was significantly higher than the incidence of abnormal LA Volume Index (LAVI) (62.4% *vs.* 33.6%,  $P < 0.01$ ). Furthermore, among patients with normal LAVI, there was a high rate of LV diastolic function alteration (80%) and abnormal LA strain (29.4%). Our study found a significant difference in LASct between the AHRE (-) and AHRE (+) groups, with no significant difference observed in LAEF between the two groups. Additionally, decreased LASct (absolute value) was identified as an independent risk factor for AHRE.

In the population with AHRE, changes in LA strain occur earlier than alterations in LA systolic function and geometric structure. LA strain is associated with myocardial cell function and may further contribute to the remodeling of LA geometry.

**The association between LA strain, AF, and AHRE**

Studies have shown a negative correlation between LA wall fibrosis and LA strain and strain rate, and the assessment of LA functional remodeling using echocardiography may aid in predicting AF (15,16). In a large prospective cohort study called CCHS5 (17), Hauser *et al.* found that in the general population, the peak atrial longitudinal strain (PALS) [hazard ratio (HR) 1.05, 95% CI: 1.03–1.07,  $P < 0.001$  per 1% decrease] obtained through two-dimensional speckle-tracking echocardiography (2D-STE) and peak atrial contraction strain (PACS) [HR 1.08, 95% CI: 1.05–1.12,  $P < 0.001$  per 1% decrease] were independent predictors of AF. These findings remained consistent in subjects with normal LA size and normal left ventricular systolic function, further demonstrating that changes in LA strain function occur earlier than alterations in LA geometry and systolic function. In a continuous five-year follow-up study of 2,461 patients with heart failure and sinus rhythm, Park *et al.* (18) found that patients with decreased PALS (PALS <18%) had a higher incidence of new-onset AF compared to the control group (18.2% *vs.* 12.7%;  $P < 0.001$ ). Additionally, for every 1% increase in PALS, the risk of new-onset AF decreased by 3% (HR 0.97, 95% CI: 0.95–0.98,  $P < 0.001$ ). Recently, Romano *et al.* (19) confirmed the improvement of LA strain and AF burden in patients with severe mitral regurgitation following transcatheter edge-to-edge repair. Furthermore, a good correlation was observed between PAF burden and LA reservoir strain (R\_s), with R\_s

**Table 6** Interobserver and intraobserver variability

Characteristics	Intraobserver variability			Interobserver variability		
	ICC	95% CI	P value	ICC	95% CI	P value
LAVmin (mL)	0.964	0.921–0.981	<0.001	0.978	0.929–0.998	<0.001
LAVmax (mL)	0.954	0.912–0.979	<0.001	0.976	0.927–0.997	<0.001
LAVpreA (mL)	0.912	0.867–0.932	<0.001	0.934	0.901–0.944	<0.001
LAVImax (mL/m <sup>2</sup> )	0.924	0.892–0.946	<0.001	0.958	0.921–0.977	<0.001
LAEV (mL)	0.899	0.858–0.922	<0.001	0.921	0.891–0.939	<0.001
LAEF (%)	0.911	0.887–0.934	<0.001	0.934	0.901–0.953	<0.001
LASr (%)	0.798	0.773–0.828	<0.001	0.779	0.749–0.811	<0.001
LAScd (%)	0.872	0.839–0.899	<0.001	0.853	0.811–0.876	<0.001
LASct (%)	0.869	0.833–0.896	<0.001	0.812	0.780–0.829	<0.001
LASr-c (%)	0.835	0.801–0.856	<0.001	0.892	0.859–0.921	<0.001
LAScd-c (%)	0.815	0.798–0.832	<0.001	0.889	0.851–0.919	<0.001
LASct-c (%)	0.851	0.821–0.872	<0.001	0.801	0.776–0.824	<0.001
LALd (cm)	0.915	0.873–0.932	<0.001	0.901	0.859–0.928	<0.001
LAAAd (cm <sup>2</sup> )	0.898	0.845–0.921	<0.001	0.901	0.853–0.929	<0.001
LALs (cm)	0.876	0.847–0.902	<0.001	0.828	0.789–0.841	<0.001
LAAs (cm <sup>2</sup> )	0.912	0.870–0.932	<0.001	0.951	0.917–0.978	<0.001
LAEDV (mL)	0.894	0.847–0.922	<0.001	0.877	0.835–0.899	<0.001
LAESV (mL)	0.841	0.811–0.872	<0.001	0.832	0.799–0.857	<0.001
E/A	0.867	0.823–0.899	<0.001	0.879	0.827–0.913	<0.001
E/e'	0.837	0.798–0.857	<0.001	0.854	0.801–0.878	<0.001
LVEF (%)	0.913	0.865–0.938	<0.001	0.899	0.864–0.923	<0.001
LVDd (cm)	0.921	0.889–0.946	<0.001	0.908	0.867–0.932	<0.001

ICC, interclass correlation coefficient; CI, confidence interval; LAVmin, LA minimal volume; LAVmax, LA maximal volume; LAVpreA, LA pre-systolic volume; LAVImax, LA maximum volume index; LAEV, LA end-diastolic volume; LAEF, LA ejection fraction; LASr, LA reservoir longitudinal strain; LAScd, LA conduit longitudinal strain; LASct, LA contraction longitudinal strain; LASr-c, LA reservoir circumferential strain; LAScd-c, LA conduit circumferential strain; LASct-c, LA contraction circumferential strain; LALd, LA end-diastolic Length; LAAAd, LA end-diastolic area; LALs, LA end-systolic length; LAAs, LA end-systolic area; LAEDV, LA end-diastolic volume; LAESV, LA end-diastolic volume; E/A, mitral ratio of peak early to late diastolic filling velocity; E/e', ratio of early diastolic transmitral flow velocity to early diastolic mitral annular velocity; LVEF, LV ejection fraction; LVDd, left ventricular end diastolic diameter; LA, left atrial.

serving as a significant predictor of AF burden. Moreover, LA strain has important implications in predicting the risk of ischemic stroke in AF populations (20) and predicting the success and postoperative recurrence of AF radiofrequency ablation (21–23).

Although the association between LA strain and AHRE has not been fully established, the findings of our study regarding the use of LA strain to predict AHRE are

consistent with previous literature reporting the use of LA strain to predict AF. Specifically, the results indicate that as strain capacity decreases, the risk of AHRE or AF increases.

Unlike the difficulty in capturing most cases of AF, CIED can provide long-term continuous monitoring for the occurrence of AHRE, even capturing and recording AHRE episodes that last only a few seconds. Previous studies

have found that approximately 13% to 16% of patients with CIED who are detected with AHRE would develop AF within an average follow-up period of 2.5 years (5,24). Witt *et al.* (25) conducted a prospective study involving 394 patients with no history of AF who received CIED. Within the first 6 months of follow-up, they found that 79 patients (20%) experienced at least one early AHRE with duration longer than 6 minutes. Among these 79 patients, clinical AF occurred in a median of 2.4 years (IQR, 1.3–4.4 years) after implantation. The annual incidence rate of clinical AF in patients with early AHRE was 9.6%, compared to 4.1% in patients without AHRE (HR 2.35; 95% CI: 1.47–3.74;  $P < 0.001$ ). This result remained consistent after adjusting for age, gender, SBP, BMI, and baseline use of beta-blockers and amiodarone (HR 2.24; 95% CI: 1.39–3.64;  $P = 0.001$ ). In another study involving 923 CIED-implanted patients, 86 patients experienced AHRE, and among them, 33 (38%) developed AF during an average follow-up period of 21 months (range, 10–34 months) (26). When comparing patients with and without AHRE, the AF incidence rate in the AHRE group was 21.1 per 100 person-years, while the control group had a rate of 5.2 per 100 person-years (HR 5.6, 95% CI: 2.3–13.4,  $P < 0.001$ ). Taken together, these findings suggest that AHRE is considered a precursor to AF to some extent (27). In other words, it is of significant importance to identify individuals at high risk for AHRE in order to closely monitor and intervene early in this population, preventing the progression to AF, which plays a crucial role in the prevention, early detection, early treatment, and improvement of outcomes related to AF.

Our study found that compared to the AHRE (-) group, LASct was significantly decreased (absolute value) in the AHRE (+) group, and the decreased in LASct was an independent risk factor for AHRE. Therefore, LASct may serve as an indicator for identifying high-risk individuals for AHRE, which has important clinical implications for the screening and detection of AHRE.

### **LA function assessment techniques**

The currently used conventional two-dimensional echocardiography in clinical practice can relatively intuitively display the anatomical structure of the heart. The diameters of the LA and LV measured in the apical four-chamber or two-chamber views can provide an initial assessment of the size of the cardiac chambers. The biplane Simpson's method or biplane area-length

method can measure the volume changes of the left atrium during one cardiac cycle, and the calculated parameters such as LA active and passive emptying fractions can objectively evaluate LA function. However, measuring the LA in the apical view is inaccurate because the apical view optimally displays the LV, causing the LA to appear shortened in this view. This necessitates repeated measurements in the four-chamber and two-chamber views to obtain relatively accurate measurements of various parameters of the LA on two-dimensional echocardiography. In contrast, three-dimensional (3D) ultrasound imaging technology captures consecutive two-dimensional images of the heart from different planes and angles. These images are then reconstructed into a 3D representation of the actual shape of the heart using computer technology, without relying on geometric assumptions. This allows for a comprehensive volumetric visualization of the heart's actual shape, enabling a more accurate assessment of chamber volumes and function. On the other hand, STE technology treats myocardial tissue as uniformly distributed stable speckles. It tracks the trajectory of myocardial motion by identifying these speckles. Compared to traditional ultrasound techniques, STE provides a better reflection of regional myocardial function. It is not influenced by the angle between the ultrasound beam direction and the direction of wall motion, making it angle-independent and more suitable for analyzing LA strain (28). However, 2D-STE is still limited to the two-dimensional plane, while myocardial motion occurs in 3D space. This can lead to the phenomenon of "off-plane tracking". To address this limitation, the subsequent development and application of 3D-STE technology has emerged. This technique tracks myocardial acoustic speckles in 3D space and analyzes volumetric images, thereby avoiding the issue of "off-plane tracking". 3D-STE allows for a more accurate assessment of myocardial motion and strain capabilities (29,30).

The four-dimensional ultrasound imaging technique was used in this study, also known as RT-3DE, is based on 3D ultrasound images with the addition of the time dimension parameter. This enables the real-time visualization of the 3D structure of the heart, unaffected by its morphology. RT-3DE provides precise and detailed ultrasound images with enhanced detail and depth, offering higher accuracy and stronger diagnostic capabilities. It can better identify early changes in the LA associated with various cardiovascular diseases (31,32). However, RT-3DE has limited clinical application due to its high

image quality requirements, susceptibility to patient arrhythmias, and the need for specialized analysis software. Therefore, this study only included patients with sinus rhythm and used the 4D Auto LAQ technique for analysis of these real-time 3D images on the Echopac 204 workstation. Unlike 3D-STE, which utilizes software designed specifically for LV analysis to calculate LA strain parameters, 4D Auto LAQ is a technique specifically designed for the LA. It dynamically tracks the size and deformation of the LA throughout the cardiac cycle and automatically identifies the endocardial border, thereby improving the repeatability and accuracy of LA volume and strain measurements. It is expected to have broad applications in clinical practice in the future (33,34).

### Expectation

Although the relationship between LA strain and AHRE has not been fully elucidated, a limited number of studies have indicated that a decreased LA strain capacity is associated with an increased risk of AHRE/AF. As AHRE is considered a precursor to AF, the early identification of individuals at high risk for AHRE is crucial for preventing the progression to AF.

In our study, the measurement and analysis of LA parameters in AHRE (-) group and AHRE (+) group, revealed that LASct is an independent predictor of AHRE, with an optimal predictive threshold of LASct  $\geq -4.125\%$ . This finding not only serves as a sensitive indicator of early functional changes in the LA myocardium in AHRE patients but also contributes to better prediction of individual risk for AHRE. This, in turn, provides an early monitoring and intervention basis for preventing further development of high-risk individuals into clinical AF.

A recent study has indicated potential harm in the use of anticoagulants in patients with AHRE (35). However, it is important to note that the study populations have been predominantly European. Further research is needed among East Asian populations.

### Study limitations

This study is a single-center study and further research is needed in larger populations or multiple centers. In addition, due to the relatively limited sample size, stratified analysis of AHRE duration was not performed, and it is recommended to expand the sample size in future studies to allow for more detailed analysis.

### Conclusions

Patients with CIED implantation who experienced AHRE showed increased LAESV and E/A, as well as decreased LASct (absolute value). The decrease in LASct (absolute value) was identified as an independent risk factor for AHRE occurrence and had predictive value for AHRE development.

### Acknowledgments

*Funding:* This research was supported by National Natural Science Foundation of China (No. 81870294).

### Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://qims.amegroups.com/article/view/10.21037/qims-23-1237/rc>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://qims.amegroups.com/article/view/10.21037/qims-23-1237/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and it was approved by the Institution Review Board of Sun Yat-sen Memorial Hospital. Written informed consent was obtained from all participants.

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**Cite this article as:** Wang P, Huang B, Fang C, Wang P, Tan C, Zheng Y, Wu G, Zheng S, Zhou S. Study on the relationship between atrial high-rate episode and left atrial strain in patients with cardiac implantable electronic device. *Quant Imaging Med Surg* 2024;14(2):1844-1859. doi: 10.21037/qims-23-1237