


# Distinct atrial remodeling in patients with subclinical atrial fibrillation: Lessons from computed tomographic images

Sung-Hao Huang<sup>1</sup> | Chao-Feng Liao<sup>1</sup> | Zu-Yin Chen<sup>1</sup> | Tze-Fan Chao<sup>2,3</sup> |  
Shih-Ann Chen<sup>2,3,4</sup> | Hsuan-Ming Tsao<sup>1,3</sup> 

<sup>1</sup>Division of Cardiology, Department of Medicine, National Yang-Ming Chiao-Tung University Hospital, Yilan, Taiwan

<sup>2</sup>Heart Rhythm Center, Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

<sup>3</sup>School of Medicine, National Yang-Ming Chiao-Tung University, Taipei, Taiwan

<sup>4</sup>Cardiovascular Center, Taichung Veterans General Hospital, Taichung, Taiwan

## Correspondence

Hsuan-Ming Tsao, National Yang-Ming Chiao-Tung University Hospital, No. 169, Xiao-She road, Yilan, 26058, Taiwan.  
Email: hmtsao@ymuh.ym.edu.tw

## Funding information

This work is supported by a research grant from National Yang-Ming Chiao-Tung University Hospital, Taiwan (RD 2019-001)

## Abstract

**Aims:** Cardiac implanted electronic devices (CIEDs) can detect atrial high-rate episodes (AHREs) and challenge current management of subclinical atrial fibrillation (AF).

**Methods:** To characterize the anatomic and functional remodeling of cardiac structures between patients with subclinical AF (SCAF) and clinical AF. The predictors for AHREs  $\geq 6$  min were also investigated.

**Results:** We compared the atrial volume, dynamic function, and peri-atrial fat between 104 CIEDs (AHREs = 0,  $n = 12$ ; SCAF,  $n = 66$ ; CIEDs with AF,  $n = 26$ ) and 40 paroxysmal AF patients who were planning for catheter ablation (AF for ablation) using 256-slice multidetector computed tomography for the duration of the AHREs. The maximal volume of the left atrium (LA) and LA appendage (LAA) were significantly smaller; the total emptying fraction (EF) and active EF of the LA and LAA were significantly better in the patients with SCAF than in those with clinical AF. Less peri-atrial fat ( $p < 0.001$ ) and a greater LAA/ascending aorta (AA) Hounsfield unit (HU) ratio ( $p < 0.05$ ) were noted in the patients with SCAF. Significantly increased volume reduced the total EF of LA and LAA and a reduced LAA/AA HU ratio ( $0.91 \pm 0.18$  vs  $0.98 \pm 0.03$  vs  $0.97 \pm 0.05$ ,  $p < 0.05$ ) were demonstrated in patients with AHREs  $\geq 6$  min compared to those with AHREs  $< 6$  min and without AHRE. Multivariate analysis showed the reduced LAA/AA HU ratio is an independent predictor for the development of AHREs  $\geq 6$  min.

**Conclusion:** As compared to clinical AF, patients with SCAF show a more favorable LA remodeling process. Among the patients with device-detected AHREs, worse LA remodeling and a reduced LAA/AA HU ratio were associated with the occurrence of AHREs  $\geq 6$  min. These findings may provide an incremental value for understanding SCAF.

## KEYWORDS

atrial fibrillation, atrial high-rate episode, multidetector computed tomography, remodeling

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. *Pharmacology Research & Perspectives* published by John Wiley & Sons Ltd, British Pharmacological Society and American Society for Pharmacology and Experimental Therapeutics.

## 1 | INTRODUCTION

Atrial fibrillation (AF) is a substantial risk factor for the development of stroke and adverse cardiovascular events.<sup>1,2</sup> The evaluation and management of clinical AF, which is documented by electrocardiography (ECG), are relatively straightforward and well established.<sup>3</sup> As the technological advancement of cardiac implanted electronic devices (CIEDs) enables the continuous detection of atrial activities, asymptomatic atrial tachyarrhythmia has emerged as a relatively new entity and merits further consideration. These episodes are described as atrial high-rate episodes (AHREs) and are clinically asymptomatic, referred to as subclinical AF (SCAF). They are clinically distinct from ECG-documented clinical AF episodes due to the lower stroke rate, variability of detection by different devices, and lack of evidence-based approaches to treatment.<sup>4-9</sup> In addition, the pathophysiology of SCAF has yet to be clearly studied. However, atrial cardiomyopathy associated with atrial arrhythmias has been believed to predispose patients to future thromboembolic risk.<sup>10</sup> Previous studies have suggested that atrial remodeling is significantly associated with the development of AF and subsequent stroke.<sup>11,12</sup> Cardiac imaging studies also indicated that the circulation stasis of the left atrial (LA) appendage (LAA) and peri-atrial fat may have a relevant impact on AF-related stroke.<sup>13-16</sup> It is important to understand the association between atrial remodeling and the duration of AHREs. Recently, ongoing randomized control trials, including ARTESiA and NOAH-AFNET 6, have been focused on the efficacy of oral anti-coagulants in high-risk patients with device-detected AHREs lasting longer than 6 min.<sup>17,18</sup> We hypothesize that (1) the process of atrial remodeling is different between SCAF and clinical AF and (2) the characteristics of the LA substrate may be linked to the future development of AHREs  $\geq 6$  min. The aim of this study was to explore the relationship between the structural and functional remodeling of atria and AHRE duration using multidetector computed tomography (MDCT) in CIED patients with SCAF.

## 2 | METHODS

### 2.1 | Study population

We included the patients with CIEDs who received regular device follow-up and underwent heart CT angiography 3–6 months before the next follow-up visit as part of the study protocol. The CIED patients without ECG-documented AF were categorized into three groups according to the duration of AHREs with cutoff values of 6 min and 0 AHREs. CIED patients with any ECG-documented clinical AF (CIEDs with AF) during the medical visits and age-/sex-matched patients with paroxysmal AF who were prepared to receive the first catheter ablation (AF for ablation) were compared. (Figure 1) All paroxysmal AF for ablation patients underwent CT examination during sinus rhythm before ablation. The exclusion criteria were serum creatinine  $>2$  mg/dL, a history of contrast allergy, or inability to provide informed consent. This study was approved by

### What's New?

1. Device-detected atrial high-rate episodes (AHREs), referred to as subclinical atrial fibrillation (SCAF), are clinically distinct from ECG-documented AF. Cardiac computed tomography (CT) demonstrated a milder degree of atrial remodeling in SCAF that can partly explain the better outcome of AHREs compared to clinical AF.
2. In SCAF, cardiac CT showed dilatation and dynamic dysfunction of the left atrium (LA) and worsened circulation stasis of the LA appendage (LAA) that were associated with AHREs. Worse LA remodeling and a reduced LAA/AA Hounsfield unit ratio were associated with the occurrence of AHREs  $\geq 6$  min. These findings may provide an incremental value for understanding SCAF.

the Institutional Review Board of National Yang-Ming Chiao-Tung University Hospital.

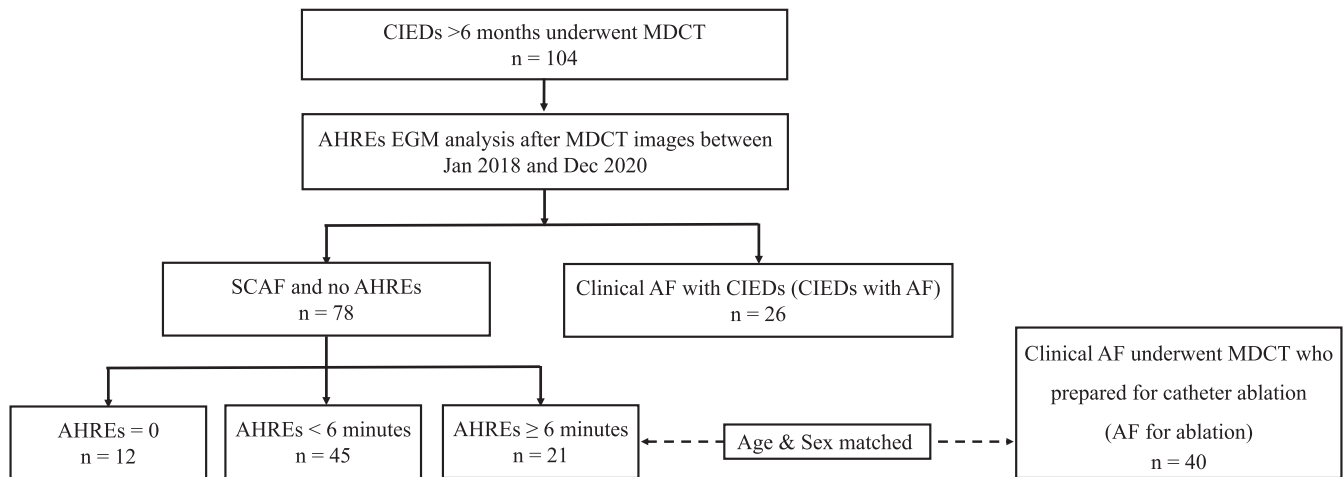
### 2.2 | CIEDs

The CIED interrogation information at every 6-month clinic visit for each patient was retrieved and analyzed. AHREs were defined as heart rate  $>175$  bpm (Medtronic, Dublin, Ireland) or  $>200$  bpm (Abbott, Minnesota, United States of America) and at least 30 s of atrial tachyarrhythmia recorded by devices during the study period. The devices were programmed with high atrial sensitivity (0.15–0.5 mV) to avoid undersensed events. If multiple AHREs were detected, the longest AHREs duration was used for analysis. The accurate confirmation of AHREs was carefully reviewed by electrophysiological experts. In addition, the total AHREs burden was counted by the automatic mode switch percentage on average based on the device's algorithm during the follow-up period. There were no AHREs more than 6 min within 4 weeks prior to CT examination in each patient in the available electrograms.

### 2.3 | Computed tomographic studies

The heart was evaluated with a second-generation dual-source CT scanner (Somatom Definition Flash; Siemens, Erlangen, Germany) by prospective ECG gating. All prospective ECG-triggered studies were at 70% of the R-R interval (truly from 0% to 90%). Images were reconstructed with a slice thickness of 3 mm and a reconstruction increment of 3 mm using a soft-tissue convolution kernel (I26f medium smooth).

All CT images were analyzed offline with software developed by the Department of Biomedical Engineering, Chung Yuan Christian University, Taiwan. The details were described previously.<sup>16</sup> In brief,



**FIGURE 1** Inclusion of patients with cardiac implanted electronic devices (CIEDs) and subclinical atrial fibrillation (SCAF). \*AHREs, atrial high-rate episodes; EGM, electrogram; MDCT, multidetector computed tomography

axial images at atrial end-diastole were used to obtain the volumes of epicardial adipose tissue (EAT) surrounding the LA using threshold attenuation values of  $-50$  to  $-200$  Hounsfield unit (HU). The axial images were then reconstructed at multiple phases covering the cardiac cycle in increments of 10% of the R-R interval. 10 serial images of LA and LAA were identified visually. The endocardial border was traced for each slice and, if necessary, manually adjusted to ensure accurate tracing. A modified Simpson method was used to calculate the volume of the chambers at the 10 phases. The emptying fraction (EF) is defined as the total EF (maximal volume - minimal volume/maximal volume), the active EF (volume at P-wave beginning - minimal volume/volume at P-wave beginning), and the passive EF (maximal volume at P-wave beginning/maximal volume). The circulation stasis of the LAA was evaluated based on the HU ratio of the LAA to the ascending aorta (LAA/AA) at the end-diastolic phase of the LAA, which was fully opacified by the contrast media. For quantitative analyses, a  $1\text{-cm}^2$  region of interest was sampled within the LAA to show the lowest HU values and inside the filling defect if it existed. At the same level, another  $1\text{-cm}^2$  region was selected in the contrast-enhanced lumen of the AA. The measurements were performed independently by 2 investigators in a blinded fashion.

## 2.4 | Statistical analysis

Continuous variables with a normal distribution are presented as the mean  $\pm$  standard deviation, and categorical variables are presented as absolute values and percentages. Fisher's exact test was used for the analysis of categorical data. Student's t test or the Mann-Whitney U test was used for the analysis of continuous data. Multivariate logistic regression was performed to identify the independent predictors of AHREs  $\geq 6$  min. All variables with a  $p < 0.1$ , excluding those with significant correlations with other variables were used to create the multivariable logistic regression model. A value of  $p < 0.05$  was considered statistically significant. The data were

analyzed using SPSS version 22 for Windows (IBM Corp., Armonk, N.Y., USA). Bland-Altman plots with 95% limits of agreement and the intraclass correlation coefficient were applied to evaluate the reproducibility of intra- and interobserver measurements.

## 3 | RESULTS

### 3.1 | Patient characteristics

We analyzed the demographic, laboratory, and MDCT data that were collected from 104 patients who received CIEDs between January 2018 and December 2020. An analysis of SCAF patients revealed that the clinical variables were similar among patients with AHREs = 0, AHREs  $< 6$  min, and AHREs  $\geq 6$  min (Table 1). Forty AF for ablation patients and 26 CIEDs with AF patients were included for comparison. None of the tachy-brady arrhythmia syndrome was included in the analysis of the SCAF group according to enrollment criterion. On the contrary, 61.5% of CIEDs with AF patients ( $n = 16$ ) received device implantation that was indicated by tachy-brady arrhythmia syndrome. A total of 87.5% of AF for ablation patients were refractory to one of the antiarrhythmic drugs, including amiodarone (75%) or propafenone (12.5%). The age, sex, comorbidities, and  $\text{CHA}_2\text{DS}_2\text{-VASc}$  score were similar between the three groups (Table 2).

### 3.2 | Comparison between AHREs = 0, $< 6$ min and AHREs $\geq 6$ min in SCAF

#### 3.2.1 | Left atrium size, and function and the association with AHREs $\geq 6$ min (Table 1)

The maximal and minimal volumes of LA ( $67.1 \pm 15.5$  vs  $71.6 \pm 15.1$  vs  $80.8 \pm 15.1$  mL,  $p < 0.05$ ;  $40.6 \pm 12.0$  vs  $43.7 \pm 11.7$  vs

**TABLE 1** The clinical and computed tomographic (CT) characteristics of the patients with atrial high-rate episodes (AHREs) =0, <6, and ≥6 min\*

	AHREs = 0 (n = 12)	AHREs <6 min (n = 45)	AHREs ≥6 min (n = 21)	p-value
<b>Clinical characteristics</b>				
Age	76.1±8.4	75.0±11.9	74.9±7.9	0.941
Female	7(58)	24(53)	12(57)	0.934
BMI	22.9±2.7	24.8±4.1	23.1±3.8	0.145
Hypertension	8(67)	35(78)	13(62)	0.384
Diabetes	3(25)	12(27)	7(33)	0.930
HF	2(17)	5(11)	2(10)	0.824
Prior stroke	1(8)	3(7)	1(5)	0.450
CAD	4(33)	12(27)	4(19)	0.640
CHA <sub>2</sub> DS <sub>2</sub> -VASc	3.7±1.0	3.5±1.5	3.3±1.2	0.934
<b>Medications</b>				
Anti-thrombotics	4(33)	19(42)	7(33)	0.728
β-blocker	5(42)	21(47)	9(43)	0.649
ACEi/ARB	4(33)	21(47)	13(62)	0.841
<b>Device type</b>				
Pacemaker	11(92)	39(87)	20(95)	0.648
ICD	0	5(11)	1(5)	-
CRT	1(8)	1(2)	0	-
<b>Indication</b>				
SSS	7(58)	14(31)	10(48)	0.303
AVB	4(33)	24(53)	11(52)	<0.001
Atrial pacing (%)	53.0±41.2	35.6±37.4	47.9±36.4	0.252
Ventricular pacing (%)	23.5±38.4	40.7±45.4	33.9±42.4	0.462
Mean AHREs burden (%)	-	0.11±0.07	1.83±4.04	<0.01
Median length of the Longest AHREs (hour:minute:second)	-	00:00:06	01:05:26	-
<b>CT characteristics</b>				
LAV max (mL)	67.1±15.5	71.6±15.1	80.8±15.1	<0.05
LAV min (mL)	40.6±12.0	43.7±11.7	54.6±18.1	<0.005
LAV precontraction (mL)	57.0±15.5	59.4±13.7	68.6±17.1	<0.05
LA total EF (%)	39.6±8.2	38.8±7.4	31.3±10.5	<0.05
LA passive EF (%)	15.6±8.3	16.8±9.9	15.6±10.6	0.876
LA active EF (%)	29.9±7.5	26.4±9.7	18.9±10.3	<0.05
LA AV max (mL)	5.1±2.1	7.6±3.2	8.5±2.4	<0.05
LA AV min (mL)	2.4±1.1	3.6±1.8	4.2±1.8	<0.05
LA AV precontraction (mL)	4.6±1.7	6.3±2.5	6.6±2.5	0.097
LAA total EF (%)	58.7±11.4	51.3±14.4	45.9±9.6	<0.05
LAA passive EF (%)	20.7±13.3	15.7±7.6	20.6±10.9	0.083
LAA active EF (%)	44.8±10.7	43.1±16.4	37.1±13.7	0.515
HU ratio of LAA/AA	0.97±0.05	0.98±0.03	0.91±0.18	<0.05
Total EAT (cm <sup>3</sup> )	25.0±11.8	26.2±8.5	20.7±9.2	0.084
LVEF (%)	59.0±12.9	54.0±13.6	53.0±9.5	0.707

\*Data are presented as n (%) or mean (SD) unless otherwise specified.

Abbreviations: AA, ascending aorta; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor antagonist; AVB, atrioventricular block; BMI, body mass index; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; EAT, epicardial adipose tissue; EF, emptying fraction; HF, heart failure; HU, Hounsfield unit; ICD, implantable cardioverter-defibrillator; LA, left atrium; LAA, left atrial appendage; LVEF, left ventricle ejection fraction; SSS, sick sinus syndrome; V, volume.

**TABLE 2** The clinical and computed tomographic (CT) characteristics of the patients with subclinical atrial fibrillation (SCAF), paroxysmal atrial fibrillation (AF) in CIEDs (CIEDs with AF) and who planning for catheter ablation (AF for ablation)<sup>\*</sup>

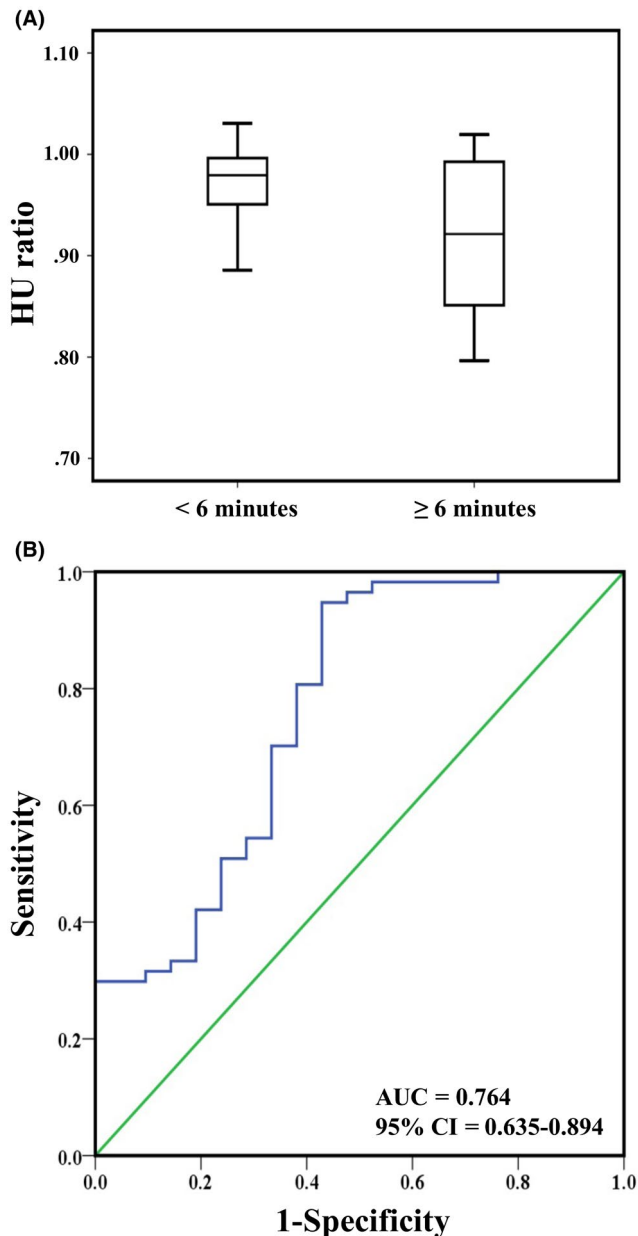
	SCAF (n = 66)	CIEDs with AF (n = 26)	AF for ablation (n = 40)	p-value
<b>Clinical characteristics</b>				
Age	74.9±10.7	75.2±9.7	74.4±7.9	0.945
Female	35(53)	19(73)	21(53)	0.203
BMI	24.2±4.1	24.9±3.0	24.3±5.2	0.756
Hypertension	45(68)	20(77)	23(58)	0.163
Diabetes	19(29)	13(50)	14(35)	0.160
HF	7(11)	7(27)	6(15)	0.054
Prior Stroke	4(6)	1(4)	8(20)	0.386
CHA <sub>2</sub> DS <sub>2</sub> -VASc	3.5±1.4	4.1±1.5	3.6±1.8	0.159
<b>Medications</b>				
β-blocker	30(45)	12(46)	20(50)	0.938
ACEi/ARB	34(52)	13(50)	24(60)	0.094
<b>Device type</b>				
Pacemaker	59(89)	21(81)	-	-
ICD	6(9)	1(4)	-	-
CRT	1(2)	4(15)	-	-
<b>Indication</b>				
SSS	24(36)	21(81)	-	-
AVB	35(53)	2(8)	-	-
Atrial pacing (%)	41.4±37.1	66.7±33.6	-	-
Ventricular pacing (%)	40.4±44.4	33.1±39.2	-	-
Mean AHREs burden (%)	0.6±2.0	4.4±9.3	-	-
Median length of the longest AHREs (hour:minute:second)	00:00:20	02:58:52	-	-
<b>CT characteristics</b>				
LAV max (mL)	74.5±15.6	85.6±25.4	107.9±33.6	<0.001
LA total EF (%)	37.5±9.7	30.6±11.0	29.8±12.7	<0.001
LA passive EF (%)	16.4±10.1	13.3±8.0	11.9±7.2	0.061
LA active EF (%)	24.8±10.2	19.9±10.5	19.1±11.2	<0.05
LAAV max (mL)	7.9±3.4	9.9±4.1	9.8±4.3	<0.05
LAA total EF (%)	52.8±14.3	43.6±10.5	41.2±10.3	0.260
LAA passive EF (%)	17.3±9.0	19.9±10.3	16.4.0±8.1	0.469
LAA active EF (%)	42.7±16.6	35.1±18.5	33.6±18.5	0.106
HU ratio of LAA/AA	0.95±0.11	0.89±0.18	0.88±0.17	<0.05
Total EAT (cm <sup>3</sup> )	23.8±9.7	29.9±10.3	31.7±10.2	<0.001

<sup>\*</sup>Data are presented as n (%) or mean (SD) unless otherwise specified.

54.6 ± 18.1 mL,  $p < 0.005$ ) and LAA (5.1 ± 2.1 vs 7.6 ± 3.2 vs 8.5 ± 2.4 mL,  $p < 0.05$ ; 2.4 ± 1.1 vs 3.6 ± 1.8 vs 4.2 ± 1.8 mL,  $p < 0.05$ ) were significantly increased in patient with AHREs ≥6 min compared to those without AHREs and AHREs <6 min. The total EF and active EF of LA and total EF of LAA were significantly reduced in patients with AHREs ≥6 min compared to the other two groups ( $p < 0.05$ ).

### 3.2.2 | The HU ratio of LAA/AA and EAT and the associations with AHREs ≥6 min

The amount of EAT was similar between the patients without AHRE and those with AHREs <6 min or ≥6 min. However, the HU ratio of LAA/AA was significantly decreased in patients with AHREs ≥6 min compared to those with AHREs <6 min (Figure 2A).



**FIGURE 2** A. Box-whisker graph of the LAA/AA HU ratio in patients with AHREs <6 min and ≥6 min. The HU ratio of LAA/AA was significantly decreased in patients with AHREs ≥6 min compared to those with AHREs <6 min ( $0.91 \pm 0.18$  vs  $0.98 \pm 0.03$ ,  $p < 0.05$ ). B. ROC curve analysis of the HU ratio to predict the occurrence of AHREs ≥6 min. A cutoff point of 0.92 was established with a 95% sensitivity and 43% specificity. \*AA, ascending aorta; AUC, area under the curve; CI, confidence interval; HU, Hounsfield unit; LAA, left atrial appendage; ROC, receiver operating characteristic

A multivariate analysis revealed that only the HU ratio of LAA/AA was significantly reduced ( $p < 0.05$ ) between the groups of AHREs ≥ and <6 min (Table 3). Receiver-operating characteristic curve analysis was performed to determine the cutoff value of the HU ratio to predict the occurrence of AHREs ≥6 min. The area under the curve (AUC) was found to be statistically significant (AUC = 0.764, 95% confidence interval = 0.635–0.894) (Figure 2B). A cutoff point of 0.92 was

established with a 95% sensitivity and 43% specificity. The reproducibility of the HU ratio and EAT measurements was evaluated by two independent investigators and the results showed high agreement in the intra- and inter-observer measurements. (Supplement Figure 1).

### 3.3 | Comparison between patients with SCAF, CIEDs with AF and AF for ablation

#### 3.3.1 | Left atrium size and function and the associations with SCAF and clinical AF (Table 2)

The maximal volumes of the LA ( $74.5 \pm 15.6$  vs  $85.6 \pm 25.4$  vs  $107.9 \pm 33.6$  mL,  $p < 0.001$ ) and LAA ( $7.9 \pm 3.4$  vs  $9.9 \pm 4.1$  vs  $9.8 \pm 4.3$  mL,  $p < 0.05$ ) were significantly increased in patients with clinical AF either in CIEDs with AF or AF for ablation groups compared to SCAF. The total EF ( $37.5 \pm 9.7$  vs  $30.6 \pm 11.0$  vs  $29.8 \pm 12.7\%$ ,  $p < 0.001$ ) and active EF ( $24.8 \pm 10.2$  vs  $19.9 \pm 10.5$  vs  $19.1 \pm 11.2\%$ ,  $p < 0.05$ ) were significantly better in SCAF compared to the groups of CIEDs with AF and AF for ablation. Analyzing into subgroups, total and active EF of LA and LAA in patients with AHREs ≥6 min have no statistical differences between the groups of CIEDs with AF and AF for ablation except the larger LAV max and total EAT were noted in clinical AF groups than those with AHREs ≥6 min. (Figure 3 and supplement Table 1).

#### 3.3.2 | The HU ratio of LAA/AA and peri-atrial EAT

The HU ratio of LAA/AA was significantly greater in patients with SCAF than the groups of CIEDs with AF and AF for ablation ( $0.95 \pm 0.11$  vs  $0.89 \pm 0.18$  vs  $0.88 \pm 0.17$ ,  $p < 0.05$ ). The EAT was significantly lower in patients with SCAF than the groups of CIEDs with AF and AF for ablation ( $23.8 \pm 9.7$  vs  $29.9 \pm 10.3$  vs  $31.7 \pm 10.2$  cm<sup>3</sup>,  $p < 0.001$ ).

## 4 | DISCUSSION

### 4.1 | Major findings

The present study provides two major findings: (1) patients with SCAF detected by CIEDs have a distinct LA remodeling process that differs from patients with clinical AF, and (2) among the patients with SCAF, patients with AHREs ≥6 min have worse remodeling features of LA structure and function than those with AHREs <6 min and without AHREs. The circulation stasis of LAA presenting with a reduced HU ratio of LAA/AA was associated with the occurrence of an AHREs ≥6 min in the next 6 months.

### 4.2 | Clinical significance of SCAF

A growing body of evidence has shown that CIEDs-detected AHREs increase the risk of systemic embolization and stroke.<sup>19,20</sup>

**TABLE 3** Logistic regression analysis of predictors of AHREs  $\geq 6$  min in cardiac implanted electronic device patients

	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.00	0.95–1.05	0.986	–	–	–
Sex	1.16	0.41–3.31	0.772	–	–	–
BMI	0.89	0.77–1.03	0.115	–	–	–
Hypertension	0.46	0.15–1.43	0.182	–	–	–
Diabetes	1.38	0.45–4.22	0.578	–	–	–
HF	0.84	0.15–4.74	0.842	–	–	–
Prior stroke	0.84	0.26–2.67	0.764	–	–	–
CAD	0.82	0.22–3.01	0.769	–	–	–
LAV max	1.05	1.01–1.08	<0.05	–	–	–
LAV min	1.06	1.02–1.10	<0.01	1.02	0.92–1.08	0.572
LAV precontraction	1.04	1.01–1.08	<0.05	–	–	–
LA total EF	0.90	0.84–0.97	<0.01	0.91	0.81–1.01	0.068
LA passive EF	0.99	0.94–1.04	0.664	–	–	–
LA active EF	0.91	0.86–0.97	<0.01	–	–	–
LAAV max	1.15	0.97–1.36	0.115	–	–	–
LAAV min	1.30	0.99–1.74	0.071	–	–	–
LAAV precontraction	1.09	0.89–1.35	0.384	–	–	–
LAA total EF	0.96	0.93–1.00	<0.05	0.97	0.93–1.01	0.161
LAA passive EF	0.99	0.98–1.10	0.130	–	–	–
LAA active EF	0.98	0.95–1.01	0.258	–	–	–
HU ratio of LAA/AA	0.86	0.75–0.98	<0.05	0.91	0.79–1.02	<0.05
Total EAT	0.94	0.86–0.98	<0.05	0.94	0.90–1.03	0.267

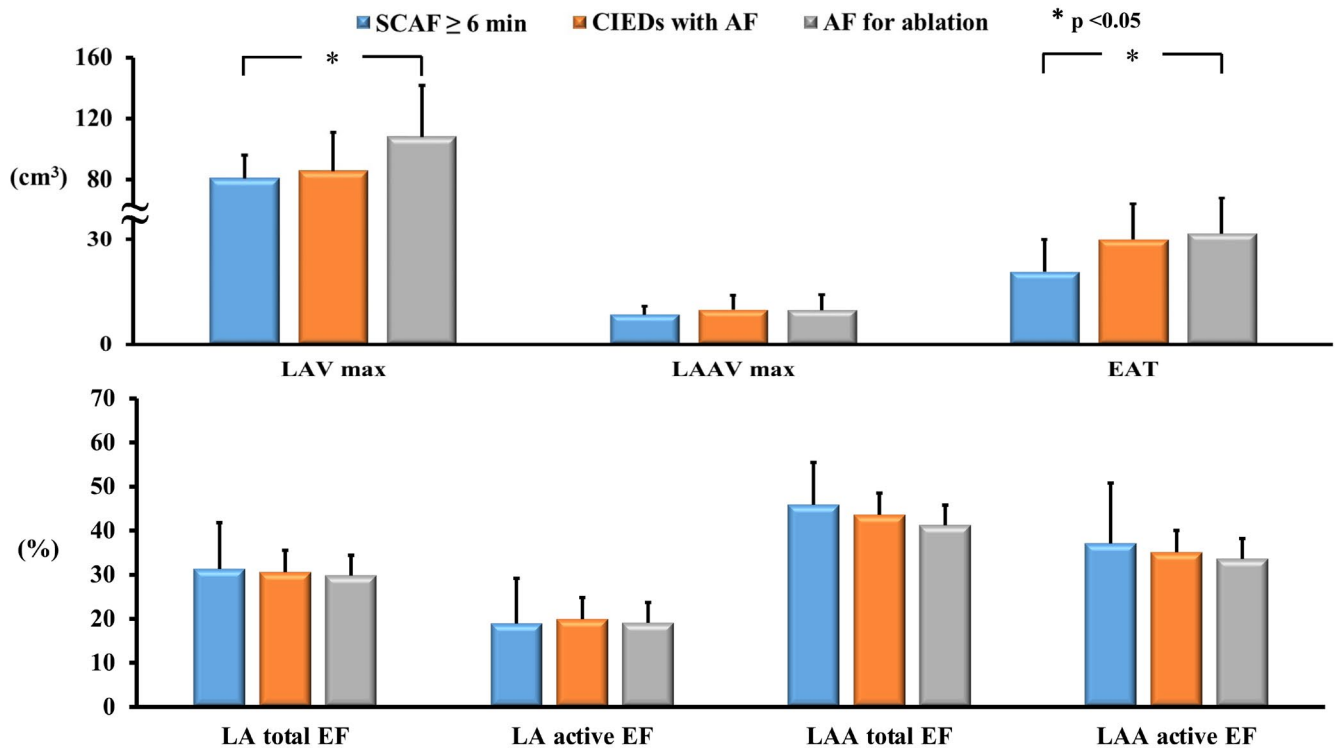
Abbreviations: OR, odds ratio; CI, confidence interval.

However, it is difficult to define the threshold of duration and burden of AHREs that can indicate the need for clinical treatment to prevent negative outcomes. Brief episodes (<20 s/day) are rarely associated with systemic embolism and are considered clinically irrelevant. However, prolonged episodes of  $\geq 5$ –6 min,  $\geq 6$  h, or  $\geq 24$  h were related to a higher risk of cerebrovascular events in various clinical studies. On the contrary, some publications show inconsistent results in supporting a positive relationship between duration and further complications.<sup>21–24</sup> Our findings offered biological evidence to delineate the changes in the atrial substrate between patients with SCAF and clinical AF. We depicted the distinct remodeling between patients with AHREs < and  $\geq 6$  min by CT images, which may elucidate the pathophysiological mechanism of SCAF.

### 4.3 | Atrial remodeling is associated with AF and AF-related complications

Previous studies have demonstrated the process of atrial remodeling in AF using echocardiography and MDCT. Dilated and impaired contractile function of the LA was shown in the patients with paroxysmal and permanent AF. Ciuffo et al. reported that

atrial mechanical dyssynchrony can be detected during sinus rhythm using echocardiography in patients with AF and stroke.<sup>25</sup> In addition, we reported several studies in the context of atrial remodeling and AF- and AF-related stroke by MDCT images.<sup>15,16,26</sup> Our recent report demonstrated that biatrial mechanical dysfunction was linked to the development of stroke in AF patients. We have also shown that the circulation stasis of the LAA and periatrial EAT was significantly related to the occurrence of cerebrovascular accidents in patients with clinical AF.<sup>15</sup> The present study bolsters these findings by demonstrating a milder degree of atrial remodeling in SCAF that can partly explain the better outcome of AHREs compared to clinical AF. In contrast, incremental AF burdens were associated with worsening LA function from SCAF to clinical AF. AF for ablation patients is likely to have the more advanced atrial disease than recent onset or drug responsive AF. We further investigated the CT variables between the AHRE patients with a cutoff value of 6 min and demonstrated the reduced LAA/AA HU ratio as a potential indicator for future development of AHREs  $\geq 6$  min. The plausible mechanism of this observation may be attributed to the atrial myopathy formed by the interplay of aging, atrial stretch, and inflammation. The atrial substrates in these patients show a typical feature of dilated atria and reduced contractile function of the LA and LAA and may result in



**FIGURE 3** Left atrial (LA) function and structural changes comparison between AHREs  $\geq 6$  min, CIEDs with AF and AF for ablation. The maximal volumes of the LA ( $107.9 \pm 33.6$  vs  $85.6 \pm 25.4$  vs  $80.8 \pm 15.1$  mL,  $p < 0.001$ ) and total EAT ( $31.7 \pm 10.2$  vs  $29.9 \pm 10.3$  vs  $20.7 \pm 9.2$  cm<sup>3</sup>,  $p < 0.001$ ) were significantly increased in patients of AF for ablation compared to the group of CIEDs with AF and those with AHREs  $\geq 6$  min. \*EAT, epicardial adipose tissue

a prothrombotic state corresponding to the reduced HU ratio of the LAA/AA. Romero et al. suggested that the HU ratio of LAA to AA is the most frequently used measure to quantify LAA contrast attenuation.<sup>27</sup> Several studies have shown that a reduced LAA/AA HU ratio reflects circulation stasis within the LAA and correlates with decreased TEE velocity. The filling defect of the LAA may indicate the propensity of stroke occurrence in patients with AF.<sup>13,28,29</sup> A markedly reduced LAA/AA HU ratio may also correlate with the clinical situation of spontaneous echo contrast or thrombus formation in patients with AF.<sup>30</sup> In the present study, we also analyzed the phasic function of LA and showed that the total EF and booster pump function (active EF) of LA and LAA were significantly reduced in patient with AHREs  $\geq 6$  min. However, the conduit function (passive EF) was similar between the two groups. Booster pump function indicates the intrinsic atrial contraction using ATP energy, and the passive function may correlate with the extension of atrial fibrosis.<sup>31</sup> This observation may reflect the potential reversibility of LA and LAA function and calls for appropriate management at this stage of the disease.

#### 4.4 | Clinical implication

The optimal treatment strategy, including anticoagulation and anti-arrhythmia, for AHREs remains an area of uncertainty.<sup>32,33</sup> There are inconsistent perceptions of the risk of stroke related to

the temporal relationship and different durations of AHREs.<sup>34,35</sup> Therefore, the initiation of anticoagulants varies according to the clinical scenario. The ESC 2020 AF guideline highlighted the importance of risk factor evaluation in patients with SCAF in addition to the duration of AHREs and suggested that the use of anticoagulants should be considered in patients with AHREs  $>24$  h and estimated high stroke risk.<sup>3</sup> To evaluate the net benefit of anticoagulation in patients with SCAF, two clinical trials are ongoing and have recruited patients with AHREs  $\geq 6$  min and additional risk factors for stroke.<sup>17,18</sup> The comparative results between AHREs  $\geq$  or  $<6$  min in the present study might offer imaging evidence to justify the use of anticoagulants in patients with high stroke risk and AHREs  $\geq 6$  min, especially in patients with HU ratio of LAA/AA at a cutoff point of 0.92 that may predict the occurrence of an AHREs  $\geq 6$  min in the next 6 months.

#### 4.5 | Limitations

The study has several limitations. First, this is a single-institution, observational analysis with a relatively small patient number. Second, these patients are relatively high risk with an average CHA<sub>2</sub>DS<sub>2</sub>-VASc score = 3.6. These findings might not be applicable to low-risk patients. Otherwise, AHREs presented atrial tachyarrhythmias including SCAF within the detection window. Third, stroke or transient ischemic attack information cannot be assessed because of



the short follow-up period. Fourth, the temporal correlation of CT imaging with ECG waves cannot be perfectly precise because only 10 serial images within a cardiac cycle were analyzed. However, using the ECG-gating methodology, we can adjust the most appropriate imaging to match the ECG waveform. Fifth, despite age, sex, comorbidities, and CHA<sub>2</sub>DS<sub>2</sub>-VASc score were similar between SCAF, CIEDs with AF and AF for ablation, CIEDs with AF patients are likely to have elderly and higher CHA<sub>2</sub>DS<sub>2</sub>-VASc score that may partially contribute to worsening LA function and structural changes. Another minor limitation due to different settings of device manufactures should be noted. The CIEDs may oversense or undersense the AHREs. However, every electrogram documentation is collected and reviewed by our investigators to minimize bias.

## 5 | CONCLUSION

Patients with SCAF show a more favorable remodeling process of LA structures and function than those with clinical AF. Among the patients with device-detected AHREs, dilatation and dynamic dysfunction of the LA and a reduced LAA/AA HU ratio are associated with AHREs  $\geq 6$  min. These CT imaging findings may provide an incremental value for understanding the pathophysiology of SCAF and become a component of therapeutic decision making for SCAF.

## ACKNOWLEDGEMENTS

The authors would like to thank all the technical staffs including Yu-Fen Chen and Wei-Liang Lin that aided with the completion of this study.

## DISCLOSURE

The authors have no conflicts of interest to declare.

## ETHICAL APPROVAL

The study protocols and consent forms were approved by Institutional Review Board of National Yang Ming Chiao Tung University Hospital (IRB No. 2018A017) before participants enrollment. The study was conducted in accordance with Good Clinical Practice guidelines and the ethical principles outlined in the Declaration of Helsinki.

## AUTHOR CONTRIBUTIONS

Sung-hao Huang drafted the manuscript with input from Professor Shih-Ann Chen and Hsuan-Ming Tsao. All authors made substantial contributions to the conception and design of the manuscript, revised it critically for intellectual context and gave final approval of the final version.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ORCID

Hsuan-Ming Tsao  <https://orcid.org/0000-0003-2792-4927>

## REFERENCES

- Lip GY, Tse HF, Lane DA. Atrial fibrillation. *Lancet*. 2012;379(9816):648-661.
- Chao T-F, Liu C-J, Tuan T-C, et al. Lifetime risks, projected numbers, and adverse outcomes in Asian patients with atrial fibrillation: a report from the Taiwan nationwide AF cohort study. *Chest*. 2018;153(2):453-466.
- Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42(5):373-498.
- Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012;366(2):120-129.
- Boriani G, Glotzer TV, Ziegler PD, et al. Detection of new atrial fibrillation in patients with cardiac implanted electronic devices and factors associated with transition to higher device-detected atrial fibrillation burden. *Heart Rhythm*. 2018;15(3):376-383.
- Mahajan R, Perera T, Elliott AD, et al. Subclinical device-detected atrial fibrillation and stroke risk: a systematic review and meta-analysis. *Eur Heart J*. 2018;39(16):1407-1415.
- Khan AA, Boriani G, Lip GY. Are atrial high rate episodes (AHREs) a precursor to atrial fibrillation? *Clin Res Cardiol*. 2020;109(4):409-416.
- Glotzer TV, Hellkamp AS, Zimmerman J, et al. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MODE Selection Trial (MOST). *Circulation*. 2003;107(12):1614-1619.
- Boriani G, Glotzer TV, Santini M, et al. Device-detected atrial fibrillation and risk for stroke: an analysis of >10000 patients from the SOS AF project (Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted devices). *Eur Heart J*. 2014;35(8):508-516.
- Shen MJ, Arora R, Jalife J. Atrial myopathy. *JACC: Basic Translat Sci*. 2019;4(5):640-654.
- Wazni OM, Tsao H-M, Chen S-A, et al. Cardiovascular imaging in the management of atrial fibrillation. *J Am Coll Cardiol*. 2006;48(10):2077-2084.
- Guglielmo M, Baggiano A, Muscogiuri G, et al. Multimodality imaging of left atrium in patients with atrial fibrillation. *J Cardiovasc Comput Tomograph*. 2019;13(6):340-346.
- Hur J, Kim YJ, Lee H-J, et al. Cardioembolic stroke: dual-energy cardiac CT for differentiation of left atrial appendage thrombus and circulatory stasis. *Radiology*. 2012;263(3):688-695.
- Wong CX, Abed HS, Molaee P, et al. Pericardial fat is associated with atrial fibrillation severity and ablation outcome. *J Am Coll Cardiol*. 2011;57(17):1745-1751.
- Tsao H-M, Hu W-C, Tsai P-H, et al. The abundance of epicardial adipose tissue surrounding left atrium is associated with the occurrence of stroke in patients with atrial fibrillation. *Medicine*. 2016;95(14):e3260.
- Tsao H-M, Hu W-C, Wu M-H, et al. Quantitative analysis of quantity and distribution of epicardial adipose tissue surrounding the left atrium in patients with atrial fibrillation and effect of recurrence after ablation. *Am J Cardiol*. 2011;107(10):1498-1503.
- Lopes RD, Alings M, Connolly SJ, et al. Rationale and design of the apixaban for the reduction of thrombo-embolism in patients with device-detected sub-clinical atrial fibrillation (ARTESiA) trial. *Am Heart J*. 2017;189:137-145.
- Kirchhof P, Blank BF, Calvert M, et al. Probing oral anticoagulation in patients with atrial high rate episodes: rationale and design of the Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes (NOAH-AFNET 6) trial. *Am Heart J*. 2017;190:12-18.

19. Kaufman ES, Israel CW, Nair GM, et al. Positive predictive value of device-detected atrial high-rate episodes at different rates and durations: an analysis from ASSERT. *Heart Rhythm*. 2012;9(8):1241-1246.
20. Van Gelder IC, Healey JS, Crijns HJGM, et al. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. *Eur Heart J*. 2017;38(17):1339-1344.
21. Witt CT, Kronborg MB, Nohr EA, Mortensen PT, Gerdes C, Nielsen JC. Early detection of atrial high rate episodes predicts atrial fibrillation and thromboembolic events in patients with cardiac resynchronization therapy. *Heart Rhythm*. 2015;12(12):2368-2375.
22. Al-Gibbawi M, Ayinde HO, Bhatia NK, et al. Relationship between device-detected burden and duration of atrial fibrillation and risk of ischemic stroke. *Heart Rhythm*. 2021;18(3):338-346.
23. Healey JS, Alings M, Ha A, et al. Subclinical atrial fibrillation in older patients. *Circulation*. 2017;136(14):1276-1283.
24. Swiryn S, Orlov MV, Benditt DG, et al. Clinical implications of brief device-detected atrial tachyarrhythmias in a cardiac rhythm management device population: results from the registry of atrial tachycardia and atrial fibrillation episodes. *Circulation*. 2016;134(16):1130-1140.
25. Ciuffo L, Tao S, Gucuk Ipek E, et al. Intra-atrial dyssynchrony during sinus rhythm predicts recurrence after the first catheter ablation for atrial fibrillation. *JACC Cardiovasc Imaging*. 2019;12(2):310-319.
26. Tsao H-M, Hu W-C, Tsai P-H, et al. Functional remodeling of both atria is associated with occurrence of stroke in patients with paroxysmal and persistent atrial fibrillation. *Acta Cardiologica Sinica*. 2017;33(1):50-57.
27. Romero J, Cao JJ, Garcia MJ, Taub CC. Cardiac imaging for assessment of left atrial appendage stasis and thrombosis. *Nat Rev Cardiol*. 2014;11(8):470-480.
28. Funabashi N, Takaoka H, Uehara M, Murayama T, Ozawa K, Kobayashi Y. LAA CT contrast defects correlate with TEE LAA velocity and CHADS<sub>2</sub>-score and are a prognostic indicator for embolism in subjects with atrial fibrillation or flutter. *Int J Cardiol*. 2015;185:297-300.
29. Chang AD, Ignacio GC, Akiki R, et al. Increased left atrial appendage density on computerized tomography is associated with cardioembolic stroke. *J Stroke Cerebrovasc Dis*. 2020;29(4): 104604.
30. Hur J, Pak H-N, Kim YJ, et al. Dual-enhancement cardiac computed tomography for assessing left atrial thrombus and pulmonary veins before radiofrequency catheter ablation for atrial fibrillation. *Am J Cardiol*. 2013;112(2):238-244.
31. Deferm S, Bertrand PB, Churchill TW, et al. Left atrial mechanics assessed early during hospitalization for cryptogenic stroke are associated with occult atrial fibrillation: a speckle-tracking strain echocardiography study. *J Am Soc Echocardiogr*. 2021;34(2):156-165.
32. Freedman B, Boriani G, Glotzer TV, Healey JS, Kirchhof P, Potpara TS. Management of atrial high-rate episodes detected by cardiac implanted electronic devices. *Nat Rev Cardiol*. 2017;14(12):701-714.
33. Belkin MN, Soria CE, Waldo AL, et al. Incidence and clinical significance of new-onset device-detected atrial tachyarrhythmia: a meta-analysis. *Circ Arrhythm Electrophysiol*. 2018;11(3):e005393.
34. Brambatti M, Connolly SJ, Gold MR, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation*. 2014;129(21):2094-2099.
35. Noseworthy PA, Kaufman ES, Chen LY, et al. Subclinical and device-detected atrial fibrillation: pondering the knowledge gap: a scientific statement from the American Heart Association. *Circulation*. 2019;140(25):e944-e963.

### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Huang S-H, Liao C-F, Chen Z-Y, Chao T-F, Chen S-A, Tsao H-M. Distinct atrial remodeling in patients with subclinical atrial fibrillation: Lessons from computed tomographic images. *Pharmacol Res Perspect*. 2022;10:e00927. doi:[10.1002/prp2.927](https://doi.org/10.1002/prp2.927)