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

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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 ≥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 ± 0.18 vs 0.98 ± 0.03 vs 0.97 ± 0.05, p < 0.05) were demonstrated in patients with AHREs ≥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 ≥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 ≥6 min. These findings may provide an incremental value for understanding SCAF.

KEYWORDS
atrial fibrillation, atrial high-rate episode, multidetector computed tomography, remodeling
1 | INTRODUCTION

Atrial fibrillation (AF) is a substantial risk factor for the development of stroke and adverse cardiovascular events.\(^1\)\(^,\)\(^2\) The evaluation and management of clinical AF, which is documented by electrocardiography (ECG), are relatively straightforward and well established.\(^3\) 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.\(^4\)\(^,\)\(^9\) 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.\(^15\) Previous studies have suggested that atrial remodeling is significantly associated with the development of AF and subsequent stroke.\(^11\)\(^,\)\(^12\) 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.\(^13\)\(^,\)\(^16\) 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 anticoagulants in high-risk patients with device-detected AHREs lasting longer than 6 min.\(^17\)\(^,\)\(^18\) 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 ≥6 min. The aim of this study was to explore the relationship between the structural and functional remodeling of atra 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 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.\(^16\) In brief,
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-cm² 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-cm² 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 ± 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 ≥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 ≥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 CHA2DS2-VASc score were similar between the three groups (Table 2).

3.2 | Comparison between AHREs =0, <6 min and AHREs ≥6 min in SCAF

3.2.1 | Left atrium size, and function and the association with AHREs ≥6 min (Table 1)

The maximal and minimal volumes of LA (67.1 ± 15.5 vs 71.6 ± 15.1 vs 80.8 ± 15.1 mL, p < 0.05; 40.6 ± 12.0 vs 43.7 ± 11.7 vs
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 |
|------------------|---------------------|-----------------------|-----------------------|---------|
| **Clinical**     |                     |                       |                       |         |
| Characteristics  |                     |                       |                       |         |
| 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   |
| CHA2DS2-VASc     | 3.7±1.0             | 3.5±1.5               | 3.3±1.2               | 0.934   |
| **Medications**  |                     |                       |                       |         |
| 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   |
| **Device type**  |                     |                       |                       |         |
| Pacemaker        | 11(92)              | 39(87)                | 20(95)                | 0.648   |
| ICD              | 0                   | 5(11)                 | 1(5)                  | –       |
| CRT              | 1(8)                | 1(2)                  | 0                     | –       |
| **Indication**   |                     |                       |                       |         |
| 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              | –       |
| **CT characteristics** |                 |                       |                       |         |
| 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   |
| LAAV max (mL)    | 5.1±2.1             | 7.6±3.2               | 8.5±2.4               | <0.05   |
| LAAV min (mL)    | 2.4±1.1             | 3.6±1.8               | 4.2±1.8               | <0.05   |
| LAAV 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 (cm³)  | 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.
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).

| 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) |
|-----------------|-----------------|-----------------|-----------------|
|                 | SCAF (n = 66)   | CIEDs with AF (n = 26) | AF for ablation (n = 40) |
| Clinical characteristics |                 |                 |                 |
| 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 | 40(6)     | 1(4)       | 8(20)       | 0.386 |
| CHA$_2$DS$_2$-VASc | 3.5±1.4     | 4.1±1.5      | 3.6±1.8      | 0.159 |
| Medications |                 |                 |                 |
| β-blocker | 30(45)       | 12(46)       | 20(50)       | 0.938 |
| ACEi/ARB | 34(52)       | 13(50)       | 24(60)       | 0.094 |
| Device type |                 |                 |                 |
| Pacemaker | 59(89)       | 21(81)       | –           | –     |
| ICD | 6(9)       | 1(4)       | –           | –     |
| CRT | 1(2)       | 4(15)       | –           | –     |
| Indication |                 |                 |                 |
| SS | 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      | –           | –     |
| CT characteristics |                 |                 |                 |
| 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±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$^3$) | 23.8±9.7      | 29.9±10.3     | 31.7±10.2     | <0.001 |

*Data are presented as n (%) or mean (SD) unless otherwise specified.
A multivariate analysis revealed that only the HU ratio of LAA/AA was significantly reduced (p < 0.05) between the groups of AHREs ≥6 min 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 ± 15.6 vs 85.6 ± 25.4 vs 107.9 ± 33.6 mL, p < 0.001) and LAA (7.9 ± 3.4 vs 9.9 ± 4.1 vs 9.8 ± 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 ± 9.7 vs 30.6 ± 11.0 vs 29.8 ± 12.7%, p < 0.001) and active EF (24.8 ± 10.2 vs 19.9 ± 10.5 vs 19.1 ± 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 ± 0.11 vs 0.89 ± 0.18 vs 0.88 ± 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 ± 9.7 vs 29.9 ± 10.3 vs 31.7 ± 10.2 cm³, 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.19,20
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 ≥5–6 min, ≥6 h, or ≥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.21-24 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 ≥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.25 In addition, we reported several studies in the context of atrial remodeling and AF- and AF-related stroke by MDCT images.15,16,26 Our recent report demonstrated that bialtrial 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.15 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 ≥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

| TABLE 3 | Logistic regression analysis of predictors of AHREs ≥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.
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.27 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.13,28,29 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.30 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 ≥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.31 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.22,23 There are inconsistent perceptions of the risk of stroke related to the temporal relationship and different durations of AHREs.34,35 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.3 To evaluate the net benefit of anticoagulation in patients with SCAF, two clinical trials are ongoing and have recruited patients with AHREs ≥6 min and additional risk factors for stroke.17,18 The comparative results between AHREs ≥ 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 ≥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 ≥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 CHA2DS2-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

![Graph showing comparison of left atrial (LA) function and structural changes between AHREs ≥6 min, CIEDs with AF, and AF for ablation.](image-url)
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 CHA₂DS₂-VASc score were similar between SCAF, CIEDs with AF and AF for ablation, CIEDs with AF patients are likely to have elderly and higher CHA₂DS₂-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 ≥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.

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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 enrolment. 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.

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