Effect of Bi-Atrial Size and Function in Patients With Paroxysmal or Permanent Atrial Fibrillation

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Atrial fibrillation (AF) remains the most common arrhythmia in clinical practice. The choice between a rate-control and rhythm-control strategy depends on various factors, including the anatomical and functional substrate. This study investigates the anatomical and functional characteristics of both atria in patients with AF and explores the potential therapeutic implications. From an ongoing registry of patients with paroxysmal or permanent AF, those who underwent cardiac computed tomography (CCT) were included. Left atrial (LA) and right atrial (RA) sizes were measured on CCT, whereas bi-atrial function was quantified with speckle tracking strain echocardiography. The mean LA volume index was 41.6 ± 5.6 ml/m^2, and the mean RA volume index was 71.0 ± 21.6 ml/m^2. Mean LA reservoir strain was 24.3 ± 15.1%, compared with the mean RA reservoir strain of 21.6 ± 13.2%. Patients with smaller LA volumes had higher LA reservoir strain values than those with larger LA volumes (24.6% [interquartile range (IQR) 15.8 to 35.8] vs 16.5% [IQR 11.2 to 25.0], p <0.001). Patients with permanent AF had larger LA volumes (44.0 [IQR 33.7 to 55.2] ml/m^2 vs 36.9 [IQR 30.1 to 47.1] ml/m^2, p = 0.025) compared with paroxysmal AF. Patients with permanent AF had more impaired LA reservoir strain (15.5% [IQR 11.6 to 22.7] vs 26.9% [IQR 17.4 to 35.6], p <0.001) compared with paroxysmal AF. Similar trends were observed in the RA. In conclusion, atrial substrate characterization by CCT and speckle tracking strain echocardiography may have therapeutic implications, especially for choosing between a rate-control and rhythm-control strategy. **(Am J Cardiol 2022;00:1−7)**

Introduction

Atrial fibrillation (AF) remains the most common arrhythmia, the prevalence of which continues to increase.[1] AF is associated with a 1.5-fold to twofold increased risk of all-cause mortality.[2] Identifying patients who will benefit from rhythm rather than rate-control remains challenging.[2] Although refractory symptoms are the primary indication for rhythm-control; recent evidence suggests that it might also translate into better long-term outcomes.[3,4] Characterization of the anatomical and functional atrial substrate of AF may support the choice between rhythm and rate-control because left atrial (LA) dilation and fibrosis are associated with AF.[5,6] Cardiac computed tomography (CCT) is frequently performed during the planning of AF catheter ablation and percutaneous LA appendage occlusion, permitting accurate measurement of cardiac chamber volumes because of its high spatial resolution.[7] Speckle tracking strain echocardiography is a sensitive technique to assess atrial function, reflecting LA compliance (an indirect marker of LA fibrosis).[6] This cross-sectional study aimed to investigate functional and anatomical atrial characteristics in a large cohort of patients with paroxysmal and permanent AF using CCT and speckle tracking strain echocardiography. We hypothesize that, on average, patients with permanent AF will have larger atria with more impaired strain values than patients with paroxysmal AF.

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Methods

From an ongoing institutional registry of patients with paroxysmal or permanent AF,[1] those who underwent CCT were included in the present analysis. The presence of AF was defined according to the European Society of Cardiology guidelines for AF management.[2] Indications for coronary CCT included evaluation of LA and pulmonary vein anatomy before catheter ablation of AF and the diagnosis of epicardial coronary artery disease. LA and right atrial (RA) volumes were measured from coronary CCT data. The transthoracic echocardiogram performed in the closest temporal proximity to the coronary CCT was used for atrial strain analysis. Patients were excluded from the present analysis if: (1) atrial volume or strain measurements were not feasible because of suboptimal CCT or echocardiography image quality, or (2) transthoracic echocardiography was not performed within 6 months of coronary CCT. Demographic and clinical data were collected from the departmental electronic information system (EPD-Vision, Leiden University Medical Center, Leiden, The Netherlands). For retrospective analysis of clinically acquired data, the Ethical Committee of the Leiden University

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Medical Center (The Netherlands) waived the need for patient written informed consent.

CCT was performed using a 320-slice CT-scanner (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) with collimation of 320 × 0.5 mm, a temporal resolution of 175 milliseconds, and a gantry rotation time of 350 milliseconds. Depending on the body mass index of the patient, peak tube voltage ranged from 100 to 135 kV and tube current from 140 to 580 mA. Coronary CCT data were acquired with electrocardiographic gating, covering between 70% and 80% of the R-R interval. Administration of contrast agent (60 to 90 ml; Iomeron 400, Bracco, Milan, Italy) was performed using a triphasic injection protocol, and CCT data acquisition was triggered after a threshold of 300 HU was exceeded in the descending aorta.

Transthoracic echocardiography was performed using a commercially available ultrasound transducer and equipment (M5S probe, Vivid E9, GE-Vingmed, Horten, Norway) with the patient in the left lateral decubitus position. According to prevailing recommendations, M-mode, 2-dimensional, color, pulsed, and continuous-wave Doppler data were acquired on standard views adjusting depth, sector width, and gain settings, as required. In addition, tissue Doppler data were acquired to assess diastolic function. All images were digitally stored for offline analysis (EchoPAC, version 113 1.1, GE-Vingmed, Horten, Norway).

Atrial volumes were measured on coronary CCT data using a dedicated software package (IntelliSpace Portal, version 10.1, Philips Healthcare, Eindhoven, The Netherlands). The LA and RA borders were automatically traced to obtain a 3-dimensional (3-D) volume-rendered image of both atria. The LA and RA borders were manually corrected according to prespecified anatomical landmarks: the LA border was defined by the ostia of the pulmonary veins, the mitral annulus, and the ostium of the LA appendage. In contrast, the RA border was defined by the entrance of the superior and inferior vena cavae and the tricuspid annulus. The RA appendage was included in the RA volume (Figure 1). Atrial volumes were calculated during end-diastole (i.e., 70% to 80% of the R-R interval) and were indexed to body surface area. Population median values of atrial volume index were used to categorize patients as having "small" or "large" atria.

As previously described, LA and RA reservoir strains were measured using 2-dimensional speckle tracking on transthoracic echocardiographic images obtained from the apical 4-chamber view. The electrocardiogram was referenced to the onset of the QRS complex, and the region of interest was adjusted manually to encompass the LA and RA walls. Pulmonary vein ostia and the LA appendage were excluded from the tracings. The peak longitudinal strain during ventricular systole defined the LA and RA reservoir strain and was derived from atrial strain versus time plots (Figure 2). Patients were categorized as having "compliant" or "stiff" atria based on median reservoir strain values.

Categorical variables are expressed as numbers and percentages and were compared with Pearson's chi-square test. Continuous variables are presented as mean ± SD or median and interquartile range. Normally distributed variables were compared with the Student *t* test and non-normally distributed variables with the Mann-Whitney U test. Relations between continuous variables of atrial volume index and strain were expressed as Pearson's *r* correlation, with corresponding confidence intervals according to the Fisher's *r* to *z*-transformation. Two-sided p values <0.05

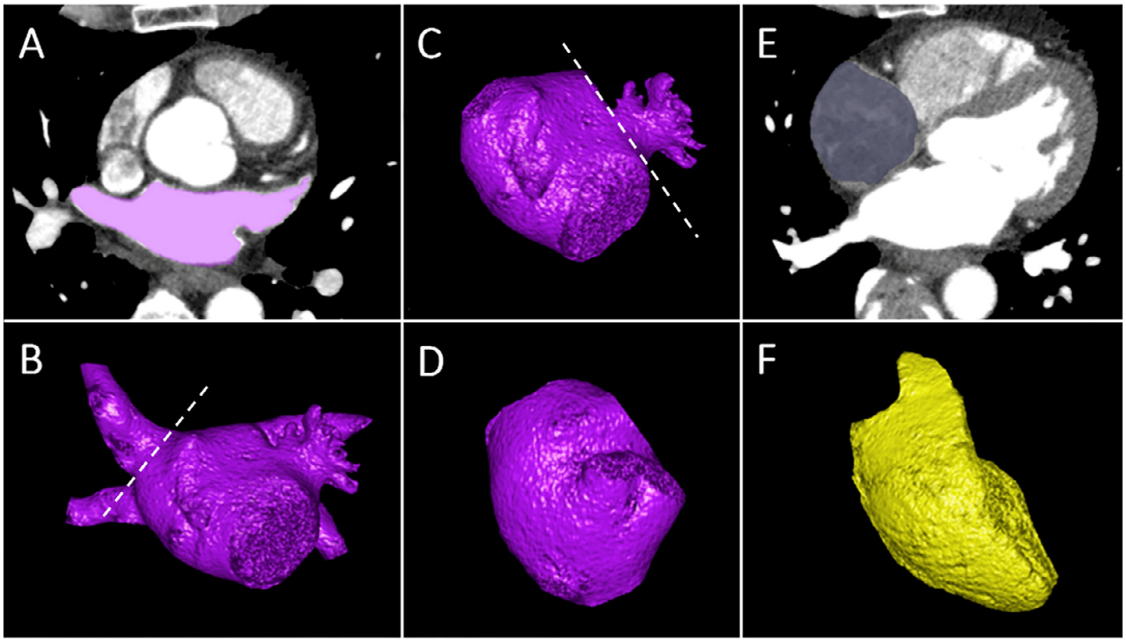

Figure 1. Steps in the measurement of atrial volumes on computed tomography data. (*A*) Identification of the left atrium on a transverse image. (*B*) Cropping of the pulmonary veins on a volume-rendered image. (*C*) Cropping of the left atrial appendage. (*D*) Final volume-rendered image of the left atrium used for volume calculation. (*E*) Identification of the right atrium on a horizontal long axis image. (*F*) Final volume-rendered image of the right atrium used for volume calculation, after following steps A, B, and D for the right atrium.

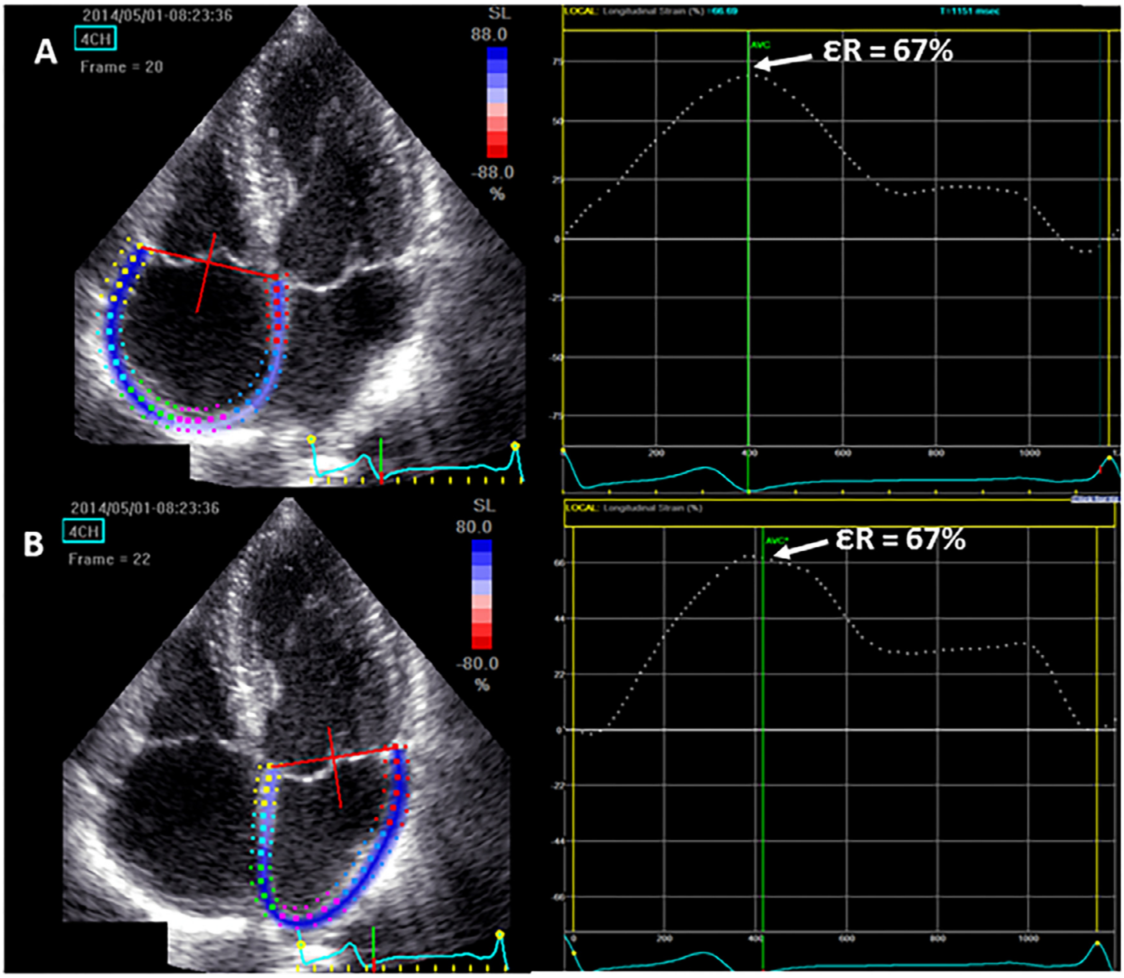

Figure 2. Echocardiographic speckle tracking strain analysis of the right (*A*) and left (*B*) atria. Both left atrial and right atrial strain was measured from an apical four-chamber view, using the R-wave as a reference point. The global atrial strain versus time curves are demonstrated on the right, from which peak reservoir strain was measured. AVC = aortic valve closure; εR = reservoir strain.

were considered statistically significant. Statistical analyses were performed with SPSS for Windows version 23.0 (IBM Corp Released 2015; IBM SPSS Statistics for Windows, Version 23.0; IBM Corp., Armonk, New York) and Prism version 8.0.1 (GraphPad, San Diego, California).

Results

From n = 196 patients with available CCT and echocardiography imaging with an interval <6 months, n = 13 were excluded because of poor imaging quality, leaving n = 183 patients for the analysis (mean age 59 ± 9 years, 75% male). Table 1 lists the clinical characteristics of patients. Diagnosis of AF was classified as paroxysmal in 96 patients (53%), whereas 87 (47%) had permanent AF. The median duration of AF was 45 months (interquartile range 18 to 81), and 78 patients (43%) were treated with class I or III antiarrhythmic drugs. Median LA volume index was 38.5 (30.9 to 49.6) ml/m^2, whereas median RA volume index was 68.0 (54.4 to 84.4) ml/m^2. The median LA reservoir strain was 21.4% (13.6 to 31.2), and the median RA reservoir strain was 18.4% (12.1 to 27.8) (Table 1).

On average, patients had larger right than left atria (paired *t* test p <0.001). Patients with small left atria (as defined by the population median) had significantly higher values of LA reservoir strain as compared to patients with large left atria (24.6% [15.8 to 35.8] vs 16.5% [11.2 to 25.0], p <0.001, Figure 3). Similarly, RA reservoir strain values were significantly higher in patients with small than enlarged right atria (24.8% [16.7 to 32.7] vs 14.9% [10.7 to 20.0], p <0.001, Figure 3). When stratifying for cardiac rhythm at the time of echocardiography, differences between patients with paroxysmal and permanent AF largely persisted (Supplementary Figure 1).

Figure 4 demonstrates atrial volumes and reservoir strain values according to the type of AF. Patients with permanent AF demonstrated significantly larger volume indexes of the LA (44.0 [33.7 to 55.2] vs 36.9 [30.1 to 47.1] ml/m^2, p = 0.025) and RA (76.3 [64.2 to 94.7] vs 59.8 [50.5 to 73.8] ml/m^2, p <0.001) than patients with paroxysmal AF. Furthermore, patients with permanent AF had significantly more impaired LA reservoir strain (15.5% [11.6 to 22.7] vs 26.9% [17.4 to 35.6], p <0.001) and RA reservoir strain (13.9% [10.2 to 21.5] vs 23.9% [17.2 to 32.5], p <0.001) than patients with paroxysmal AF. Correlations between

Table 1
Clinical, echocardiographic, and cardiac computed tomography characteristics

PATIENTS	(N=183)
AGE (YEARS)	59.2±9.1
MEN	137 (75%)
BODY SURFACE AREA (m2)	2.08±0.21
TYPE OF AF AT TIME OF DIAGNOSIS	
• PAROXYSMAL	96 (53%)
• PERMANENT	87 (47%)
DURATION OF AF (MONTHS)	45 (18 − 81)
HYPERTENSION	115 (63%)
HYPERCHOLESTEROLEMIA	66 (36%)
SMOKER	43 (24%)
DIABETES MELLITUS	10 (6%)
KNOWN CORONARY ARTERY DISEASE	27 (15%)
KNOWN VALVULAR HEART DISEASE	43 (23.5%)
STATIN USER	66 (36%)
BETA-BLOCKER USER	120 (66%)
CALCIUM ANTAGONIST USER	35 (19%)
CLASS I OR III ANTIARRHYTHMIC DRUG	78 (43%)
ACE-INHIBITOR/ANGIOTENSIN RECEPTOR BLOCKER	80 (44%)
DIURETIC	35 (19%)
CCT MEASUREMENTS	
LA VOLUME INDEX (ml/m2)	38.5 (30.9-49.6)
RA VOLUME INDEX (ml/m2)	68.0 (54.4-84.4)
CARDIAC RHYTHM AT TIME OF ECHOCARDIOGRAPHY	84 (45.9%)
• SINUS RHYTHM	77 (42.0%)
• AF	
LA RESERVOIR STRAIN (%)	21.4 (13.6-31.2)
RA RESERVOIR STRAIN (%)	18.4 (12.1-27.8)
LV EJECTION FRACTION (%)	57.2±9.6

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; CCT = cardiac computed tomography; LA = left atrium; LV = left ventricle; RA = right atrium.

atrial volumes and reservoir strain values per type of AF are presented in Supplementary Figure 2.

Table 2 lists the prevalence of atrial substrates (i.e., anatomical remodeling and functional impairment) according to the type of AF. Patients with permanent AF most frequently had enlarged, stiff LA, whereas patients with paroxysmal AF most frequently had small, compliant LA ($p < 0.001$; Table 2). Similar results were found for the RA (Table 3). Notably, 27.1% of patients with paroxysmal AF had enlarged yet compliant LA, whereas 23.0% of patients with permanent AF had small yet stiff LA.

Discussion

The main findings in the present study can be summarized as follows: (1) patients with large atria had more impaired bi-atrial reservoir strain; (2) patients with permanent AF had larger atria, whereas having more impaired atrial reservoir strain than patients with paroxysmal AF; (3) significant numbers of patients had ‘discordant’ LA volume index and strain: 27.1% of patients with paroxysmal AF had large yet compliant LA, whereas 23.0% of patients with permanent AF had small, stiff LA.

LA size has been linked to incident AF in a population without known atrial arrhythmias.[8] In the present study population, the median LA volume index was 38.5 (30.9 to 49.6) ml/m^2. In contrast, normal 3-D echocardiographic references ranges are 15 to 42 ml/m^2 for men and 15 to 39 ml/m^2 for women.[9] Normal CCT references for LA size have been less well established, although echocardiography may underestimate LA volume, compared with CCT.[7] LA volume has been found to be an independent predictor of AF recurrence after catheter ablation in studies of patients with different types of AF.[10,11] In a study of 170 patients who underwent catheter ablation for AF, those with larger LA sizes generally had higher values of integrated backscatter (an indirect marker of LA fibrosis). However, there was a large variation in integrated backscatter across different LA sizes.[12] Impaired LA function has been associated with new-onset AF and AF recurrence after catheter ablation.[8,13] In a large meta-analysis (including >2,500 normal subjects) LA reservoir strain was 39% (95% confidence interval 38 to 41%), compared with 21.4% (13.6 to 31.2) in the present population.[14] In addition, reduction in LA reservoir strain (measured with speckle tracking echocardiography) correlates with LA wall fibrosis on cardiac magnetic resonance imaging.[6] Both functional and anatomical LA remodeling are typical of AF, with various (ultra)structural changes being described, such as interstitial collagen deposition.[6]

In line with the studies previously mentioned, the present report found a higher degree of LA remodeling in terms of more enlarged size and more impaired function in patients with permanent as compared with paroxysmal AF, reflecting different stages of the disease.

The role of the RA in the pathogenesis, progression, and treatment of AF has been less well explored than that of the LA. Greater RA size was associated with incident AF in patients without cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis (MESA).[15] In the present study, the median RA volume index was 68.0 (54.4 to 84.4) ml/m^2 − larger than normal 3-D echocardiographic reference ranges (25 ± 7 ml/m^2 for men and 21 ± 6 ml/m^2 for women).[16] RA volumes have been less well studied by CT.[17] Larger RA size in 97 patients with AF was associated with less successful ablation.[18] The normal reference range for RA reservoir strain has been reported as 19% ± 7%, whereas in the present study, it was 18.4% (12.1 to 27.8), both less impaired than LA reservoir strain.[19] The link between RA size, function, and fibrosis remains largely speculative.[15] Our results suggest that the remodeling interplay between RA size and function is similar to what is observed for the LA.

Although refractory symptomatology remains the primary indication for rhythm control in patients with hemodynamically stable AF, recurrence rates up to 45% have been reported after catheter ablation.[20] Ablation, especially pulmonary vein isolation, is the principal technique employed in restoring sinus rhythm in patients with AF. Knowing in which patients rhythm control will be sustainable will greatly assist clinicians in the decision-making process. Several clinical, biochemical, and imaging risk factors for AF recurrence postablation have been described, including patient age, renal function, AF type (i.e.,

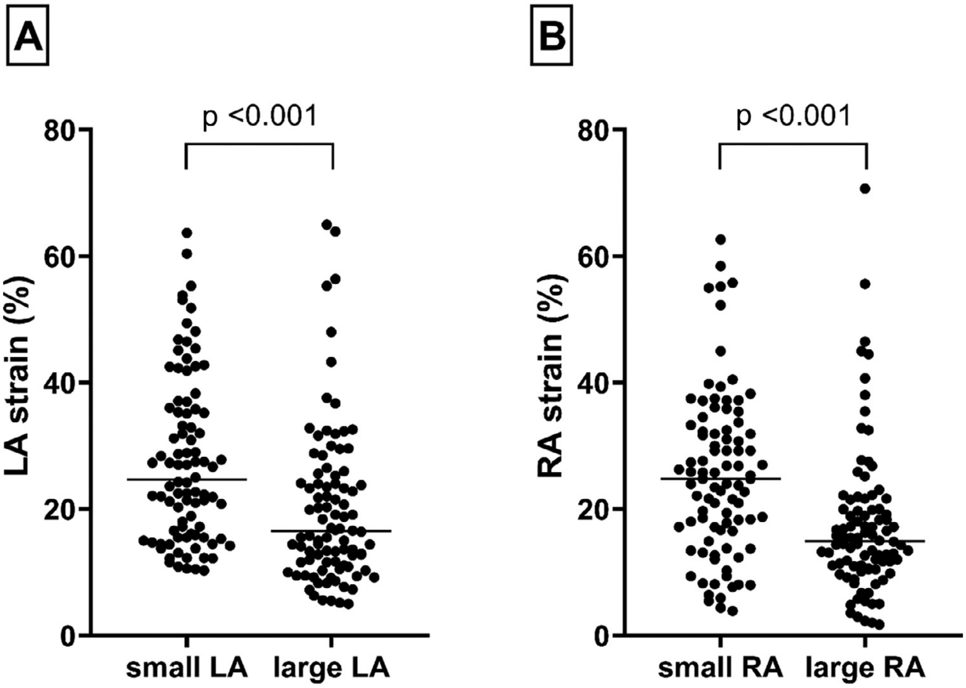

Figure 3. Distribution of left atrial (*A*) and right atrial (*B*) strain values according to atrial volume. Strain values are expressed as percentages and represent atrial reservoir strain. Horizontal bars represent median values. Median atrial reservoir strain values were more impaired in large atria and more preserved in small atria. LA = left atrium; RA = right atrium.

paroxysmal or permanent), brain natriuretic peptide, LA size and deformation, and LA late gadolinium enhancement (LGE).[2,11,13,20,21] Imaging the AF substrate is probably the best approach for predicting postablation AF recurrence. In the Delayed-Enhancement MRI Determinant of Successful Radiofrequency Catheter Ablation of AF study, LA LGE was associated with postablation AF recurrence.[21] Although some data have suggested that atrial fibrosis is more common in patients with paroxysmal AF, this has not been borne out by all investigators.[5,6] A large degree of variation exists in the degree of atrial fibrosis between patients with different AF types, and only a weak association between LA fibrosis and strain was found in an LGE cardiac magnetic resonance study.[6,22]

LA size is predictive of AF recurrence but is also influenced by, for example, left ventricular filling pressure and mitral valve disease. Nevertheless, LA size has been demonstrated to be a better predictor of AF recurrence postablation than AF type.[23] LA function, assessed with speckle tracking strain echocardiography, has also been demonstrated to predict postablation AF. However, our results demonstrate that LA size and function are not always concordant. This may be a reason why LA size and function are only moderately accurate on an individual level when predicting postablation AF recurrence. The present report highlights that large yet compliant atria are prevalent in paroxysmal AF, whereas in persistent AF, small, stiff atria are more frequently seen. This could imply a more advanced stage of disease in patients with impaired strain, whereas patients with atrial enlargement only, have a greater likelihood of successful AF ablation.

This was a single-center study with a retrospective design. Imaging tests were performed for clinical indications, resulting in larger time intervals between echocardiography and CCT. The RA appendage could not be cropped from the CCT-derived RA volume data before

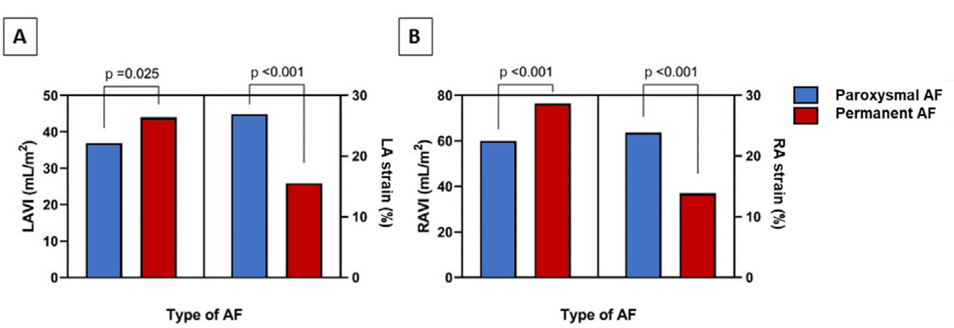

Figure 4. Left (*A*) and right (*B*) atrial volume and strain values, stratified according to the type of AF. Strain values are expressed in percentages and represent atrial reservoir strain. Patients with permanent AF were characterized by large atria and impaired reservoir strain, and patients with paroxysmal AF by small atria and preserved reservoir strain. LAVI = left atrial volume index; RAVI = right atrial volume index.

Table 2
Atrial anatomic remodeling and functional impairment according to the type of atrial fibrillation: left atrium

	Paroxysmal AF (n=96)	Permanent AF (n=87)	p Value*
Atrial substrate†			**<0.001**
Small and compliant LA	41 (42.7%)	17 (19.5%)	
Large but compliant LA	26 (27.1%)	8 (9.2%)	
Small but stiff LA	13 (13.5%)	20 (23.0%)	
Large and stiff LA	16 (16.7%)	42 (48.3%)	

AF = atrial fibrillation; LA = left atrium.
* Pearson's chi-square test.
† Atrial substrate was categorized according to population median values of atrial volume index and reservoir strain.

Table 3
Atrial anatomic remodeling and functional impairment according to the type of atrial fibrillation: right atrium

	Paroxysmal AF (n=96)	Permanent AF (n=87)	p Value*
Atrial substrate†			**<0.001**
Small and compliant RA	49 (51.0%)	14 (16.1%)	
Large but compliant RA	16 (16.7%)	13 (14.9%)	
Small but stiff RA	14 (14.6%)	14 (16.1%)	
Large and stiff RA	17 (17.7%)	46 (52.9%)	

AF = atrial fibrillation; RA = right atrium.
* Pearson's chi-square test.
† Atrial substrate was categorized according to population median values of atrial volume index and reservoir strain.

obtaining the final RA volume, which is a limitation of the postprocessing software. Echocardiographic strain is vendor-dependent and cannot be directly compared across platforms. The evolution of bi-atrial size and function over time could not be reported because CCT follow-up data were not systematically acquired. Because of the cross-sectional nature of the study, no distinction could be made between LA remodeling as the cause or consequence of AF, although it is by no means clear that this impacts the success or long-term outcome of ablation. Outcome data were not systematically collected in the registry and are not presented. Ideally, future research would be focused on patients who will undergo AF ablation, with a large enough sample to analyze the independent effect of atrial strain on the outcome of AF ablation.

In conclusion, our report shows that patients with permanent AF had a higher degree of atrial anatomical remodeling and functional impairment than patients with paroxysmal AF, reflecting different stages of the disease. However, volume and strain were not always concordant, with a high prevalence of enlarged yet compliant LA in the paroxysmal AF group and small yet stiff LA in the permanent AF group. Therefore, both anatomical remodeling and functional impairment could have implications for the success of AF ablation.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.07.024.

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