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CLINICAL RESEARCH

Atrial fibrillation substrate and impaired left atrial function: a cardiac MRI study

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Aims Structural and fibrotic remodelling is a well-known contributor to the atrial fibrillation (AF) substrate. Epicardial adipose tissue (EAT) is increasingly recognized as a contributor through electrical remodelling in the atria. We aimed to assess the association of LA fibrosis and EAT with LA strain and function using cardiac magnetic resonance (CMR) imaging in patients with AF.

Methods and results LA fibrosis was assessed using late gadolinium enhancement CMR, LA EAT was assessed using the fat-water separation Dixon sequence, and feature tracking was applied to assess global longitudinal strain in its three components [reservoir (GLRS), conduit (GLCdS), and contractile (GLCtS)]. LA emptying fraction and LA volume were measured using the cine sequences. All CMR images were acquired in sinus rhythm. One hundred one AF patients underwent pre-ablation CMR (39% female, average age 62 years). LA fibrosis was negatively associated with the three components of global longitudinal strain (GLRS: $R = -0.35$, $P < 0.001$; GLCdS: $R = -0.24$, $P = 0.015$; GLCtS: $R = -0.2$, $P = 0.046$). Out of the different sections of the LA, fibrosis in the posterior and lateral walls was most negatively correlated with GLRS ($R = -0.32$, $P = 0.001$, and $R = -0.33$, $P = 0.001$, respectively). LA EAT was negatively correlated with GLCdS ($R = -0.453$, $P < 0.001$). LA fibrosis was negatively correlated with LA emptying fraction but LA EAT was not ($R = -0.27$, $P = 0.007$, and $R = -0.22$, $P = 0.1$, respectively). LA EAT and fibrosis were both positively correlated with LA volume ($R = 0.38$, $P = 0.003$, and $R = 0.24$, $P = 0.016$, respectively).

Conclusion LA fibrosis, a major component of the AF substrate, and EAT, an important contributor, are associated with a worsening LA function through strain analysis by CMR.

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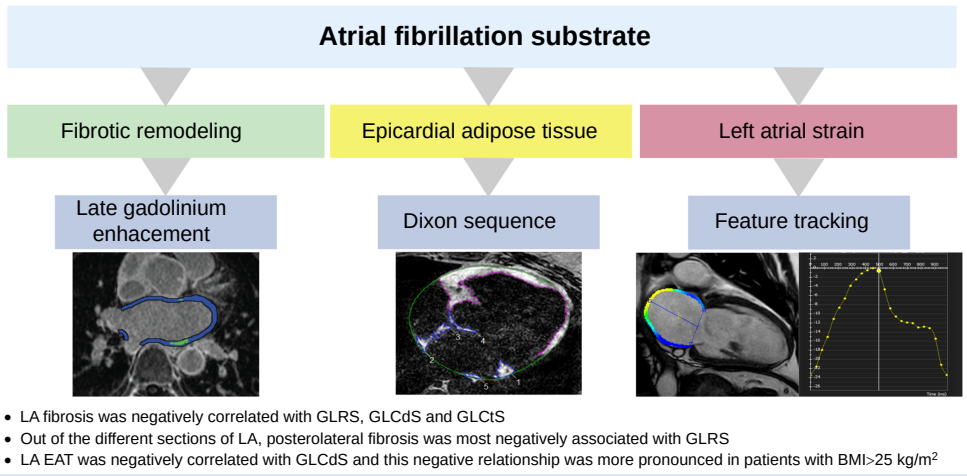
Graphical Abstract



Keywords Atrial fibrillation • Fibrosis • Epicardial adipose tissue • Strain • Cardiac MRI • Left atrial volume

What's new?

- Cardiac magnetic resonance has been used to detect the location and degree of LA fibrosis, epicardial adipose tissue (EAT), and LA strain. Previous data have shown that higher degrees of fibrosis are associated with lower LA strain rates. In addition to fibrosis, EAT is a well-known contributor to electrical and structural remodelling in the LA.
- The association and interaction of atrial fibrosis and EAT, and changes in atrial function measured through strain analysis, have not been previously elucidated.
- We used CMR imaging to simultaneously assess these associations of LA fibrosis and EAT, with LA volume, function, and compliance. We found that:
  - LA fibrosis was negatively correlated with GLRS, GLCdS, and GLCtS,
  - Out of the different sections of LA, posterolateral fibrosis was most negatively associated with GLRS, and
  - LA EAT was negatively correlated with GLCdS, and this negative relationship was more pronounced in patients with BMI > 25 kg/m^2.

Introduction

Atrial fibrillation (AF) is associated with structural, electrical, and functional alterations in the atrial myocardium, constituting a true atrial cardiomyopathy.[1,2] It can be an independent risk factor for adverse cardiovascular outcomes.[3] Left atrial (LA) fibrosis and enlargement are hallmarks of structural remodelling, and contribute to AF pathophysiology.[4] LA imaging is increasingly used in diagnosis and clinical management, offering valuable prognostic insights as a biomarker of subclinical atrial disease, particularly in cases like embolic stroke of undetermined source.[5–7] Cardiac magnetic resonance (CMR) imaging is the gold standard for evaluating LA volumes, and feature tracking in CMR is a reproducible technique for assessing LA function through strain.[8]

Epicardial adipose tissue (EAT) is increasingly recognized as another contributor through electrical, and possibly structural remodelling in the atria.[9] Epicardial adipose tissue is in direct contiguity with the underlying myocardium. This privileged location allows it to exert important paracrine and vasocrine effects on neighbouring cardiomyocytes. It secretes numerous pro-inflammatory cytokines and adipokines that can promote AF by inducing fibrotic remodelling in the LA, in addition to a localized inflammatory response.[10] Segmentation of EAT can be performed by cardiac computed tomography or magnetic resonance, and it is reported that EAT volume is associated with the incidence, severity, and recurrence of AF following catheter ablation.[11,12] Cardiac magnetic resonance has been used to detect the location and degree of LA fibrosis.[13,14] Previous data have shown that higher degrees of fibrosis are associated with lower LA strain rates.[15] In addition to fibrosis, EAT is a well-known contributor to electrical and structural remodelling in the LA.[9] The association and interaction of atrial fibrosis and EAT, and changes in atrial function measured through strain analysis, have not been previously elucidated. We used CMR imaging to simultaneously assess these associations of LA fibrosis and EAT, with LA volume, function, and compliance.

Methods

Study design and population

This is an observational study of 101 patients with AF undergoing cardiac MRI at the University of Washington Medical Center (Seattle, WA). Access to patient information was approved by the Institutional Review Board (IRB) of the University of Washington (HSD#6058), and all participants provided consent for use of their anonymized clinical data for research purposes. Study data were collected and managed using the REDCap system hosted at the University of Washington.[16,17] Exclusion criteria for AF patients included prior catheter ablation, severe claustrophobia, renal dysfunction, and other contraindications to MRI or gadolinium-based contrast. Persistent AF status was determined using standard ACC/AHA/HRS AF management guideline criteria.[18] Comorbidities and medications of the initial visit were determined using electronic medical record review. Of the patients included, 91 patients underwent catheter ablation and were followed for 1 year for arrhythmia recurrence. Arrhythmia recurrence was defined by at least 30 s of documented atrial arrhythmia after observing a 90-day blanking period.

MRI protocol

Images were obtained using a Philips Medical System Ingenia 1.5 T clinical scanner. To evaluate LA fibrosis, late gadolinium enhancement MRI (LGE-MRI) was acquired following the methods previously described.[19]

Scans were performed 15–25 min after contrast injection, using a 3D inversion-recovery, respiration-navigated, ECG-gated, gradient echo pulse sequence. Acquisition parameters included transverse imaging volume with a voxel size of 1.25 × 1.25 × 2.5 mm (reconstructed to 0.625 × 0.625 × 1.25 mm). To assess EAT, the 3D Dixon sequence was acquired with the following parameters: 1.5 mm slice thickness, repetition time (TR) = 5.4 ms, echo time 1/echo time 2 = 1.8/4.0 ms, flip angle (α) = 15°, voxel size = 1.5 × 1.5 × 3.0 mm^3 (reconstructed to 1.0 × 1.0 × 1.5 mm^3), parallel imaging factor (SENSE) = 1.5 in both phase encoding directions and water fat shift = 0.16 pixel.

Image analysis

Pre-ablation LGE-MRI based fibrosis quantification was carried out by a third-party image processing service (Merisight, Marrek Inc., Salt Lake City, UT) using previously described methods.[19] Briefly, the specific procedure for LA segmentation included: first defining the endocardium of the LA, next dilating the endocardial segmentation by 2 mm, and then manually editing it to create and estimate of the boundary of the epicardial LA surface, finally subtracting the endocardial segmentation from the epicardial segmentation to create a wall segmentation. The relative extent of fibrosis was quantified within the LA wall with a threshold-based algorithm described in detail in Oakes *et al.*[20] Atrial fibrosis was reported as a percentage of the LA wall volume. Epicardial adipose tissue was defined as adipose tissue located between the visceral layer of the pericardium and the outer surface of the myocardium. LA EAT was characterized by high signal intensity areas around the LA in a series of slices starting from the bifurcation of the pulmonary artery to the mitral annulus craniocaudally. The pericardium was identified in axial images and used as the external border for EAT. Areas of fat were segmented manually in the axial view using CVI42 software (Circle Cardiovascular Imaging Inc., version 5.6, Calgary, AB) contouring tools. Two investigators were involved in the analysis of the obtained images, both are medical doctors who received special training on EAT segmentation. Longitudinal LA strain analysis was performed using the feature tracking module in CVI42 software (Circle Cardiovascular Imaging, Inc.). Endocardial and epicardial contours of the LA were traced in the end-diastolic phase of the long-axis two-chamber and four-chamber cine images. The automatic contour tracking algorithm was used, and manual adjustments were applied, if necessary. This algorithm places a set of control points on the middle curve of the myocardial wall in the reference phase based on the drawn endocardial and epicardial contours. Subsequently, the position of the control points is detected based on the feature tracked boundaries in all the other phases to calculate longitudinal displacement. Longitudinal strain measurements were subdivided into global longitudinal reservoir, conduit, and contractile strain (GLRS, GLCdS, and GLCtS, respectively) (*Figure 1*). Similar methods for EAT segmentation and strain analysis have been described in the literature.[11,21] LA emptying fraction, LA volume index, and LA sphericity index were measured using the Cine

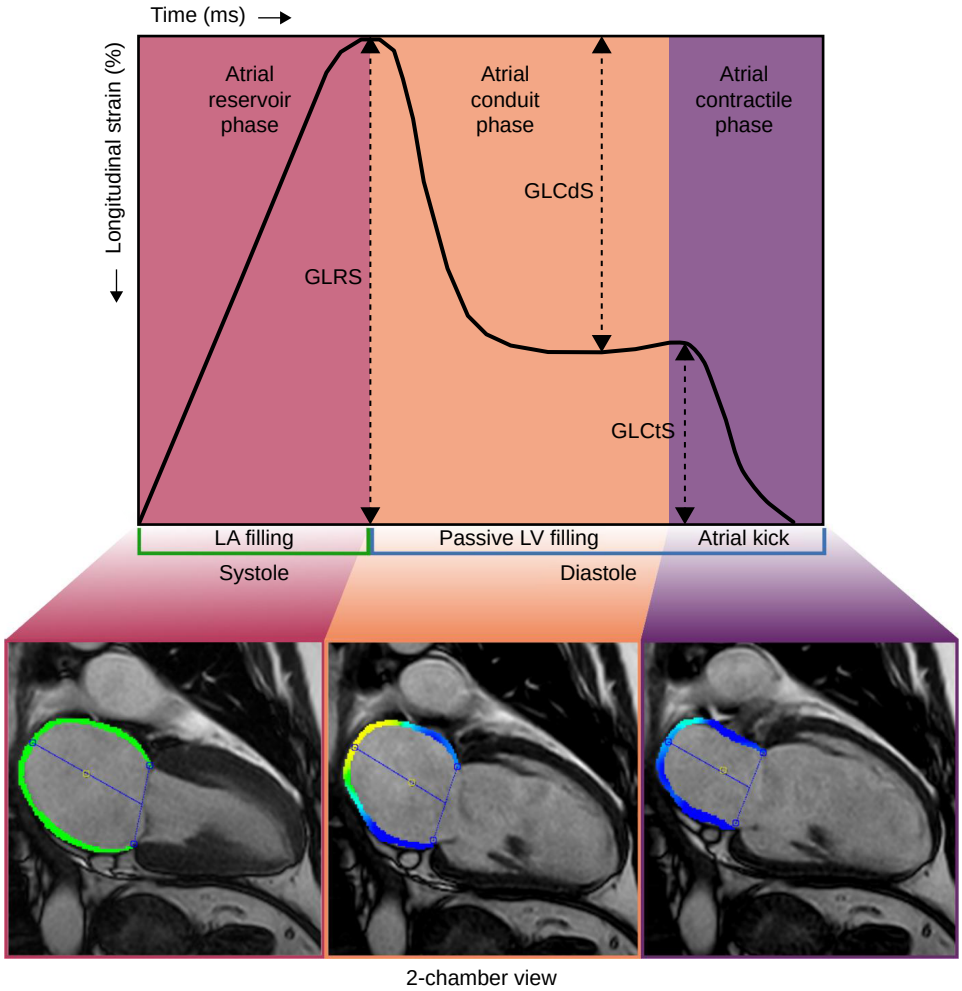


Figure 1 Left atrial global longitudinal strain curve during atrial reservoir phase, conduit phase, and contractile phase with corresponding two-chamber views of the left atrium. GLRS, GLCdS, and GLCtS, global longitudinal reservoir, conduit, and contractile strain, respectively. LA, left atrium; LV, left ventricle.

sequences. The LA sphericity index was calculated as the ratio of LA maximum volume to spherical volume. All CMR images were acquired in sinus rhythm. None of the patients included in the study had a cardioversion in the 3 weeks preceding their MRI. Supplementary material online, *Video S1*: panel A depicts a 3D model of the LA showing LGE fibrosis with superimposed 3D renderings of EAT, and panel B shows a two-chamber long-axis view of the heart with global longitudinal atrial strain rendering.

Statistical analysis

Categorical variables are expressed as percentages. Continuous variables were assessed for normality of distribution using the Shapiro–Wilk test and were reported as mean ± standard deviation if normally distributed, or median and interquartile range if not. Independent samples *t*-test was used to compare the mean LA EAT index, LA volume index, LA fibrosis, GLRS, GLCdS, and GLCtS based on patient comorbidities, and based on whether patients had AF recurrence post-ablation or not. A multivariable regression model was created with LA EAT volume as the dependent variable and GLCdS and LA fibrosis as the independent variables. All tests were two-sided, and a $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS Statistics (version 26.0, International Business Machines Inc.) and R Statistical Software version 4.1.1 (R Foundation for Statistical Computing) (*Figure 2*).

Results

Baseline characteristics

One hundred one patients were included in the study (61% male, mean age 62.7 years). The mean body mass index of our study population was 29.6 ± 6.96 kg/m^2, and the majority had paroxysmal AF (81.2%). Median LA volume index was 45.16 mL/m^2 [36.64, 56.5], LA fibrosis percentage was 15.5% [9.6, 19], and LA sphericity index was 54.09% [46.44, 64.58]. LA EAT volume was 28.48 mL [19.14, 34.39]. GLRS was 17.4% [14.95, 20.1], GLCdS was 9.2% [6.75, 12], and GLCtS was 8.1% [6.5, 9.8]. Other baseline characteristics are summarized in *Table 1*. The intraclass correlation coefficients for inter-observer and intra-observer reliability for EAT measurements were 0.927 (95% CI, 0.734–0.981) and 0.968 (95% CI, 0.877–0.992), respectively. The Bland–Altman analysis for inter-observer reliability revealed a good agreement between the results of EAT measurements performed by two different readers. The mean difference between the observers was −0.59 mL with 95% limits of agreement of (−25.11; 23.93) mL for EAT volume. The Bland–Altman analysis for intra-observer reliability revealed a good agreement between the results of repeated EAT measurements performed by the same reader. The mean difference between the repeated measurements was −0.29 mL with 95% limits of agreement of (−16.75; 16.17) mL for EAT volume.

Table 1 Baseline characteristics of our study population

Age, years	62 ± 11
Male sex, *n* (%)	62 (61.4%)
BMI, kg/m^2	29.6 ± 7
Hypertension, *n* (%)	45 (44.6%)
Coronary artery disease, *n* (%)	22 (21.8%)
Heart failure with reduced ejection fraction, *n* (%)	12 (11.9%)
Heart failure with preserved ejection fraction, *n* (%)	5 (5%)
Stroke, *n* (%)	8 (7.9%)
Obstructive sleep apnoea, *n* (%)	28 (27.7%)
Hyperlipidaemia, *n* (%)	41 (40.6%)
Diabetes mellitus, *n* (%)	11 (10.9%)
Paroxysmal AF, *n* (%)	82 (81.2%)
Imaging parameters	
LA volume index, mL/m^2	45.16 [36.64, 56.5]
LA fibrosis percentage, %	15.5 [9.6, 19]
LA sphericity index, %	54.09 [46.44, 64.58]
LA emptying fraction, %	56.3 [48.84, 63.53]
LA EAT volume, mL	28.48 [19.14, 34.39]
Global longitudinal reservoir strain, %	17.4 [14.95, 20.1]
Global longitudinal conduit strain, %	9.2 [6.75, 12]
Global longitudinal contractile strain, %	8.1 [6.5, 9.8]

AF, atrial fibrillation; BMI, body mass index; EAT, epicardial adipose tissue; LA, left atrium.

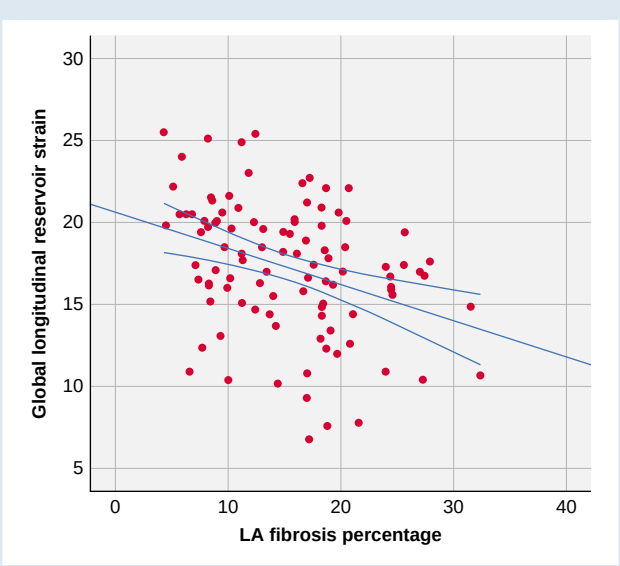


Figure 2 Scatter plot showing the association between LA fibrosis percentage and GLRS. LA fibrosis was negatively associated with GLRS ($R = -0.35$, $P < 0.001$).

Table 2 shows a comparison of mean LA EAT index, LA volume index, LA fibrosis, GLRS, GLCdS, and GLCtS based on patient comorbidities. Patients with hypertension had higher LA EAT index (16.21 ± 6.32 vs. 12.30 ± 4.59 mL/m^2, $P = 0.021$). Patients with a history of coronary artery disease had lower GLRS than those who did not (15.55 ± 4.29 vs. 17.75 ± 3.85, $P = 0.038$). Patients with a history of obstructive sleep apnoea had higher LA fibrosis (17.99 ± 6.33 vs. 14.20 ± 6.24%, $P = 0.009$), lower GLRS (15.55 ± 3.83 vs. 17.93 ± 3.94, $P = 0.008$), and lower GLCdS (8.29 ± 2.98 vs. 9.90 ± 3.55, $P = 0.025$). Patients with a history of stroke had lower GLCdS (7.46 ± 2.17 vs. 9.62 ± 3.51, $P = 0.028$). Patients with diabetes had a lower GLRS (14.95 ± 3.53 vs. 17.55 ± 4.02, $P = 0.04$). Patients with hyperlipidaemia had higher LA fibrosis (17.01 ± 6.48 vs. 14.04 ± 6.23%, $P = 0.024$). There was no difference in LA EAT index, LA volume index, LA fibrosis, GLRS, GLCdS, and GLCtS between patients who had paroxysmal or persistent AF.

Association between LA volume and fibrosis, and LA strain and function

Feature tracking was applied to the LA to assess the three components of the global longitudinal strain: reservoir, conduit, and contractile. LA fibrosis was negatively associated with all three components (GLRS:

Table 2 Comparison of the mean LA EAT index, LA volume index, LA fibrosis, GLRS, GLCdS, and GLCtS based on patient comorbidities

		LA EAT index		LA volume index		LA fibrosis		GLRS		GLCdS		GLCtS	
		Mean ± SD	*P*-value	Mean ± SD	*P*-value	Mean ± SD	*P*-value	Mean ± SD	*P*-value	Mean ± SD	*P*-value	Mean ± SD	*P*-value
HTN	Yes	16.21 ± 6.32	0.021	47.11 ± 10.84	0.977	16.21 ± 7.51	0.197	16.40 ± 4.28	0.056	8.76 ± 3.55	0.075	8.04 ± 2.34	0.390
	No	12.30 ± 4.59		47.18 ± 14.32		14.48 ± 5.44		17.97 ± 3.72		10.01 ± 3.32		8.46 ± 2.62	
CAD	Yes	14.30 ± 6.37	0.663	47.60 ± 15.07	0.874	17.50 ± 6.28	0.068	15.55 ± 4.29	0.038	8.26 ± 3.19	0.060	7.50 ± 2.35	0.096
	No	13.47 ± 5.30		47.03 ± 12.29		14.62 ± 6.42		17.75 ± 3.85		9.79 ± 3.48		8.49 ± 2.51	
HFrEF	Yes	12.83 ± 5.30	0.696	50.15 ± 11.84	0.370	18.35 ± 7.50	0.144	16.20 ± 2.97	0.225	8.21 ± 2.24	0.074	8.16 ± 2.31	0.857
	No	13.77 ± 5.60		46.74 ± 12.98		14.83 ± 6.24		17.41 ± 4.15		9.62 ± 3.58		8.29 ± 2.53	
HFpEF	Yes	16.26 ± 11.10	0.790	44.03 ± 11.24	0.609	17.08 ± 7.44	0.598	20.46 ± 5.59	0.252	12.00 ± 3.39	0.153	10.46 ± 3.20	0.185
	No	13.58 ± 5.40		47.28 ± 12.94		15.15 ± 6.44		17.10 ± 3.90		9.32 ± 3.44		8.16 ± 2.42	
OSA	Yes	17.29 ± 6.60	0.055	47.13 ± 13.02	0.993	17.99 ± 6.33	0.009	15.55 ± 3.83	0.008	8.29 ± 2.98	0.025	7.94 ± 2.34	0.385
	No	12.81 ± 4.94		47.16 ± 12.87		14.20 ± 6.24		17.93 ± 3.94		9.90 ± 3.55	0.025	8.40 ± 2.56	
Stroke	Yes	16.69 ± 5.66	0.214	50.91 ± 11.13	0.389	16.44 ± 7.06	0.631	17.15 ± 3.39	0.921	7.46 ± 2.17		10.00 ± 3.78	0.208
	No	13.32 ± 5.46		46.87 ± 12.97		15.15 ± 6.44		17.28 ± 4.10		9.62 ± 3.51	0.028	8.13 ± 2.33	
DM	Yes	14.61 ± 6.39	0.684	49.43 ± 15.46	0.608	17.83 ± 4.89	0.096	14.95 ± 3.53	0.040	7.64 ± 3.29	0.076	7.45 ± 2.03	0.186
	No	13.54 ± 5.46		46.87 ± 12.56		14.93 ± 6.58		17.55 ± 4.02		9.68 ± 3.44		8.38 ± 2.54	
HLD	Yes	14.35 ± 5.21	0.503	47.36 ± 13.67	0.892	17.01 ± 6.48	0.024	16.36 ± 4.45	0.071	8.91 ± 3.80	0.207	7.89 ± 2.85	0.220
	No	13.33 ± 5.72		47.00 ± 12.36		14.04 ± 6.23		17.89 ± 3.63		9.83 ± 3.20		8.54 ± 2.21	
AF type	Paroxysmal	13.78 ± 5.70	0.300	47.32 ± 12.85	0.719	14.82 ± 6.41	0.165	17.53 ± 4.11	0.182	9.66 ± 3.56	0.210	8.36 ± 2.58	0.459
	Persistent	12.25 ± 2.23		46.42 ± 13.17		17.11 ± 6.53		16.15 ± 3.56		8.55 ± 2.94		7.89 ± 2.13	

AF, atrial fibrillation; CAD, coronary artery disease; DM, diabetes mellitus; EAT, epicardial adipose tissue; GLRS, global longitudinal reservoir strain; GLCdS, global longitudinal conduit strain; GLCtS, global longitudinal contractile strain; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HLD, hyperlipidaemia; HTN, hypertension; LA, left atrial; OSA, obstructive sleep apnoea.

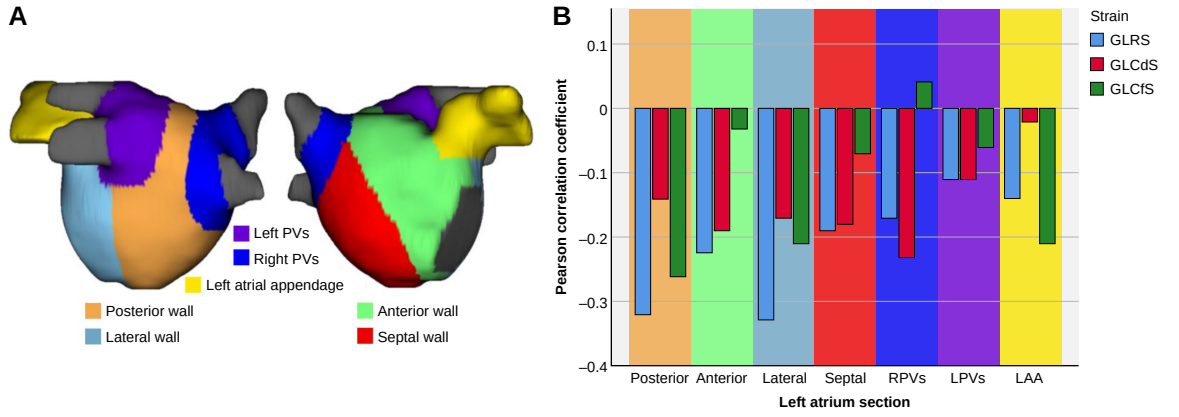


Figure 3 (*A*) The LA can be divided into seven different anatomical regions: left PVs, right PVs, left atrial appendage, septal wall, anterior wall, lateral wall, and posterior wall. (*B*) Barplot showing the Pearson correlation coefficient for the relationship between fibrosis in each of the LA sections and each of the three components of the global longitudinal strain, it shows that fibrosis in the posterior and lateral walls was most negatively correlated with GLRS ($R = -0.32$, $P = 0.001$, and $R = -0.33$, $P = 0.001$, respectively). GLRS, GLCdS, and GLCtS, global longitudinal reservoir, conduit, and contractile strain, respectively. LAA, left atrial appendage; LPVs, left pulmonary veins; PV, pulmonary vein; RPVs, right pulmonary veins.

$R = -0.35$, $P < 0.001$ (*Figure 2*); GLCdS: $R = -0.24$, $P = 0.015$; GLCtS: $R = -0.2$, $P = 0.046$). The LA was divided into seven anatomical regions: left PVs, right PVs, left atrial appendage, septal wall, anterior wall, lateral wall, and posterior wall (*Figure 3A*). *Figure 3B* shows the Pearson correlation coefficient for the relationship between fibrosis in each of the LA sections and each of the three components of the global longitudinal strain. Out of the different anatomical sections of the LA, fibrosis in the posterior and lateral walls was most negatively correlated with GLRS ($R = -0.32$, $P = 0.001$, and $R = -0.33$, $P = 0.001$, respectively). LA fibrosis was positively correlated with LA volume ($R = 0.24$, $P = 0.016$).

LA volume index was negatively correlated with GLRS ($R = -0.37$, $P < 0.001$). *Figure 4* shows a scatter plot of the association between LA volume index and (*A*) GLRS, and (*B*) LA emptying fraction.

Association between LA epicardial adipose tissue and LA strain and function

LA EAT volume was negatively correlated with GLCdS ($R = -0.453$, $P < 0.001$). However, LA EAT volume did not correlate with GLRS or GLCtS ($R = -0.251$, $P = 0.06$ and $R = 0.209$, $P = 0.118$ respectively. *Figure 5* shows a scatter plot of the association between LA EAT volume and GLCdS. When we divide the patients into two groups, those with a BMI ≤ 25 kg/m^2 and those with a BMI > 25 kg/m^2, the correlation between LA EAT and GLCdS became more negative in the obese patients [$R = -0.501$, $P = 0.002$ (BMI > 25 kg/m^2), vs. $R = -0.346$, $P = 0.115$ (BMI ≤ 25 kg/m^2)].

Multivariable regression shows that the correlation between LA EAT volume and GLCdS was independent of LA fibrosis (b coefficient for LA EAT volume −0.12; 95% CI, −0.19 to −0.05, $P < 0.001$). LA EAT was positively correlated with LA volume ($R = 0.38$, $P = 0.003$).

Association between LA emptying fraction and LA strain, volume, epicardial adipose tissue, and fibrosis

There was a positive correlation between LA emptying fraction and the three components of longitudinal strain GLRS ($R = 0.658$, $P < 0.001$), GLCdS ($R = 0.570$, $P < 0.001$), and GLCtS ($R = 0.330$, $P < 0.001$). There was a negative correlation between LA emptying fraction and

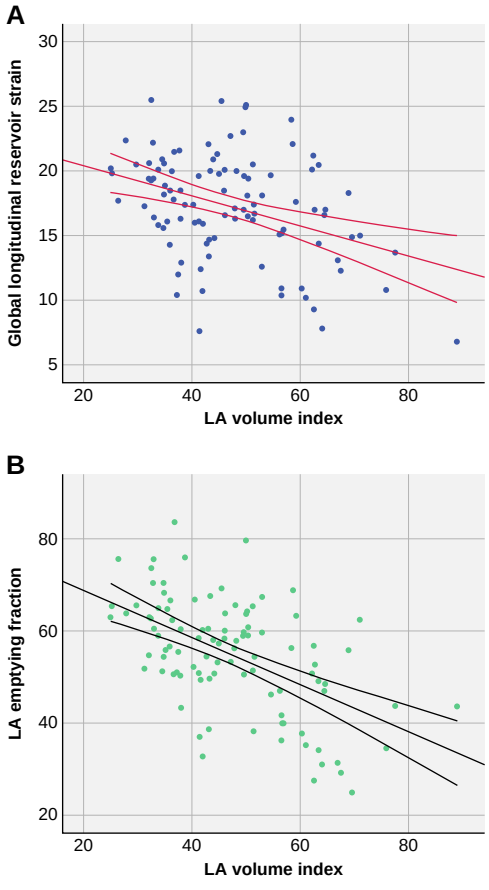


Figure 4 Scatter plots showing the association between LA volume index and (*A*) GLRS, and (*B*) LA emptying fraction. LA volume index was negatively correlated with GLRS and LA emptying fraction ($R = -0.37$, $P < 0.001$ and $R = -0.54$, $P < 0.001$, respectively). LA, left atrium.

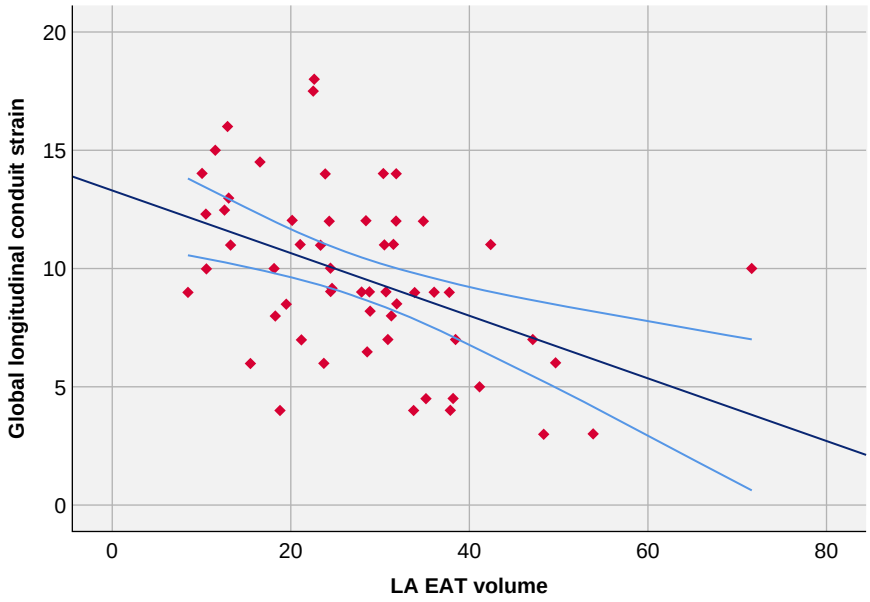


Figure 5 Scatter plot showing the association between LA EAT volume and GLCdS. LA EAT volume was negatively correlated with GLCdS ($R = -0.453$, $P < 0.001$). EAT, epicardial adipose tissue; LA, left atrium.

LA volume index ($R = -0.54$, $P < 0.001$), LAA surface area ($R = -0.319$, $P = 0.001$), and LA fibrosis ($R = -0.265$, $P = 0.007$). LA emptying fraction was not correlated with LA EAT ($R = -0.219$, $P = 0.1$).

AF recurrence post-ablation

Twenty-five out of 91 patients (24.8%) had AF recurrence after catheter ablation. Patients who had AF recurrence post-ablation had significantly larger LA volume index (52.55 ± 13.71 vs. 45.6 ± 12.04 mL/m^2, $P = 0.032$), and significantly larger LA EAT index (17.73 ± 6.64 vs. 12.79 ± 5.02 mL/m^2, $P = 0.048$) compared to those who did not have AF recurrence. Regarding strain analysis, patients with AF recurrence had significantly lower GLRS (15.87 ± 3.3 vs. 17.92 ± 4.12, $P = 0.017$) and GLCdS (8.23 ± 2.74 vs. 9.99 ± 3.58, $P = 0.023$) but not GLCtS (8.19 ± 1.74 vs. 8.4 ± 2.74, $P = 0.663$).

Discussion

The major findings of the present study are as follows: (i) LA fibrosis was negatively correlated with GLRS, GLCdS and GLCtS, (ii) out of the different sections of LA, posterolateral fibrosis was most negatively associated with GLRS, and (iii) LA EAT was negatively correlated with GLCdS, and this negative relationship was more pronounced in patients with BMI > 25 kg/m^2.

Cardiovascular magnetic resonance-derived parameters of LA function and dimensions have been previously studied in association with markers of electrical and structural remodelling.[22] LA strain was shown to detect subclinical changes related to physiologic conditions, with worsening LA strain measures with aging,[23,24] in men compared to women and with differences between races.[25] It has also gained considerable attention as a cardiovascular imaging biomarker due to its prognostic importance, with functional abnormalities often preceding adverse LA structural remodelling and overt clinical disease. In the Multi-Ethnic Study of Atherosclerosis (MESA), lower LA longitudinal reservoir strain assessed by CMR feature tracking reflecting LA dysfunction was an independent marker of incident heart failure in the asymptomatic multi-ethnic population.[26] Cardiac magnetic resonance feature tracking has higher spatial resolution and better ability to define the endocardial border, overcoming the challenges related to speckle tracking echocardiography, particularly the anatomic location of LA and thinness of the atrial wall.[8]

In our study, using cardiac CMR we simultaneously assessed LA fibrosis and EAT and their relationship with changes in atrial strain. We showed that LA fibrosis was negatively correlated with all three components of global longitudinal strain and that out of the different sections of LA, posterolateral fibrosis was most negatively associated with GLRS. Assaf *et al.*[27] showed that atrial fibrosis does not uniformly affect the LA, and that regional fibrosis can be a significant predictor of AF recurrence. Ferro *et al.*[28] showed that increased LA sphericity, global LA fibrosis, and fibrosis in the lateral wall are independently associated with arrhythmia recurrence. Habibi *et al.*[15] showed that lower LA strain rates were associated with higher degrees of fibrosis. Histological analysis showed that increased LA remodelling was significantly related to altered LA strain. Huber *et al.*[29] showed that decreased peak LA strain was correlated to the histologic degree of LA fibrofatty myocardial replacement, a substrate of AF cardiomyopathy, however, LA volume did not correlate with the degree of fibrofatty infiltration.

In addition to the role of fibrosis in the pathophysiology of AF, there is growing interest in EAT as a metabolically active visceral adipose tissue in direct contiguity with the myocardium. The secretome of EAT contains a host of inflammatory adipokines, growth factors, and cytokines that can induce fibrosis.[30] Epicardial adipose tissue volume is associated with fibrotic remodelling by MRI imaging.[31] In addition, fibrotic remodelling of EAT is associated with myocardial fibrosis[32] and can be detected by per cent change in fat attenuation using CT scan.[33,34]

Commonly, only GLRS (peak LA strain during systole) is reported in clinical studies. While other strain measurements seem to follow the same trajectory, they may hold other information. In our study, we show that EAT is negatively correlated with conduit strain. Similarly, recent studies promoted the evaluation of the contractile strain,

worsening LA function was associated with incident AF.[35] In addition, obesity was associated with impaired LA reservoir and conduit function assessed using echocardiography in middle-aged adults and improved pump function that may be compensatory.[36]

Obese patients were shown to have higher volumes of EAT and EAT was positively associated with LA enlargement,[31] however using LA enlargement as a measure of atrial remodelling may not differentiate compensatory LA remodelling in obesity from pathologic remodelling. We showed that EAT is negatively correlated with conduit strain, and that this negative relationship is more pronounced in patients with BMI > 25 kg/m^2, suggesting that increased EAT volume is linked to atrial dysfunction. Therefore, EAT and LA dysfunction may be better at identifying adverse remodelling than LA volume in obesity.

We also showed that patients who had AF recurrence post-ablation had larger LA volume and LA EAT volume and had lower reservoir strain and conduit strain. This suggests that both structural and functional remodelling in AF are associated with worse outcomes and falls in line with results from previous studies.[12,37]

Limitations

Our study has some limitations. It is a single centre observational study with a relatively small sample size. The process of EAT quantification and LA wall segmentation for strain analysis are performed manually and can benefit from artificial intelligence and automation. Similar methods for EAT segmentation and strain analysis have been described in the literature.[11,21] There is currently no consensus regarding fibrosis quantification, multiple methods have been described in the literature, and different optimal scar thresholds can be used,[38–40] however the method we implemented in fibrosis quantification in this study has been used in previous large clinical studies and trials.[19,41]

Conclusion

LA fibrosis and EAT, two important contributors to the AF substrate, are associated with a worsening LA function through strain analysis by CMR. AF patients with extensive fibrosis have impaired reservoir, conduit, and contractile strain, whereas AF patients with increased EAT volume have impaired conduit strain. LA strain may act as a non-invasive surrogate of LA fibrofatty remodelling and may ultimately be useful for clinical decisions in patients with AF.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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