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Research paper

Relationship between left atrial myopathy and atrial fibrillation in adults with coarctation of aorta

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ABSTRACT

Background: Although patients with coarctation of aorta (COA) have clinical risk factors for atrial fibrillation (AF), there are limited data about AF prevalence, and role of left atrial (LA) indices for risk stratification in this population. We hypothesized that LA indices (LA reservoir strain and LA volume index) were associated with AF, and would identify patients at risk for AF progression.

Methods: We analyzed electrocardiograms/Holters, and echocardiograms of adult COA patients at Mayo Clinic (2000–2018).

Results: Of 776 patients, 726(94 %), 46(5.9 %) and 4(0.5 %) had no history of AF, paroxysmal AF, and persistent AF respectively; yielding AF prevalence of 6.4 %. LA reservoir strain (AUC 0.782 [0.751–0.808]) had more robust association with AF as compared to LA volume index (AUC difference −0.115, $p < 0.001$).

Among 726 patients without prior AF, 25(3.4 %) had new-onset AF during follow-up. LA reservoir strain <25 % and LA volume index >34 ml/m^2 were independent predictors of new-onset AF (HR 1.81 [1.15–3.85], and HR 1.41 [1.03–4.78], respectively). Of 46 patients with paroxysmal AF, 22(48 %) had recurrent AF, and LA reservoir strain <25 % was an independent predictor of recurrent AF (HR 1.94 [1.41–4.17]). LV pressure overload and stiffness indices were associated with progressive LA dysfunction and new-onset AF.

Conclusions: Collectively, these data suggest that LA strain can potentially be used for AF risk stratification. Further studies are required to determine whether LA strain can proactively identify patients that will respond favorably to different antiarrhythmic therapies, and whether interventions to reduce LV pressure overload will improve LA function and reduce AF progression.

1. Introduction

Atrial fibrillation (AF) is the most common sustained atrial arrhythmia in patients with acquired cardiovascular disease, and it is associated with heart failure, stroke and mortality [1]. Although the etiology of AF is multifactorial, left atrial (LA) inflammation and remodeling provides substrate for initiation of AF, and in turn, AF leads to more LA remodeling thereby creating a vicious cycle [2]. Because of the central role of LA remodeling in the pathogenesis of AF, echocardiographic assessment of LA structure and function is now routinely used for risk stratification and prognostication of AF in patients with acquired cardiovascular disease [3,4].

AF is also becoming increasingly common in adults with congenital heart disease, and it is now the most common atrial arrhythmia is patients older than 50 years of age [5,6]. The prevalence varies depending on the type of congenital heart lesion, and tends to be higher in lesions involving the left heart [5,6]. Coarctation of aorta (COA) is characterized by chronic left ventricular (LV) pressure overload, cardiomyocyte hypertrophy and fibrosis, and increased myocardial stiffness [7]. These hemodynamic changes lead to high LA filling pressures and LA remodeling, thus creating the perfect milieu for AF in this population [8–10]. However, there are limited data about the prevalence of AF, pathophysiologic interactions between LA remodeling and AF, and clinical indices for AF risk stratification in this population [10]. While such data already exist from studies conducted in older patients with acquired cardiovascular disease [2,3,11,12], it is unknown how well these data can be extrapolated to the COA population because of significant differences in demographic and clinical characteristics. Since

Abbreviations: AF, atrial fibrillation; COA, coarctation of aorta; LA, left atrium; LV, left ventricle; HR, hazard ratio; AUC, area under the curve.

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traditional risk factors for AF such as LV diastolic dysfunction, hypertension and coronary artery disease, and substrates for AF such as LA remodeling are common in the COA population [8,10,13,14], there is a need to delineate the prevalence of AF and the mechanistic interactions between LA remodeling and AF, as the initial step towards developing robust risk stratification models for improved clinical outcomes in this population. We hypothesized that LA remodeling (changes in LA volume and function in response to hemodynamic stress) is associated with AF, and that increasing severity of LA remodeling will identify patients at higher risk for AF progression.

2. Methods

2.1. Study population and design

This is a retrospective study of adults (age ≥18 years) with COA that underwent 12-lead electrocardiogram and transthoracic echocardiogram between January 1, 2000 and December 31, 2018. Patients were identified from the Mayo Adult Congenital Heart Disease (MACHD) registry [15,16]. We excluded patients with: (1) inadequate images to assess LA size and function; (2) significant mitral valve disease defined as a native mitral valve mean gradient >3 mmHg or >mild mitral regurgitation, severe mitral annular calcification based on qualitative assessment, or mitral valve prosthesis. The Mayo Clinic Institutional Review Board approved the study.

The study objectives were to determine whether LA remodeling (changes in LA volume and function in response to hemodynamic stress) at baseline echocardiogram was associated with: (1) AF prevalence at the time of initial presentation, and (2) AF progression defined as new-onset AF in patients without prior history of AF or recurrent AF in patients with prior history of AF.

A subgroup analysis was performed to determine whether temporal deterioration in LA indices (calculated as values at baseline echocardiogram minus values at follow-up echocardiogram) was associated with new-onset AF (independent of baseline LA indices). This subgroup analysis was conducted in patients that had no history of AF at baseline echocardiogram, and had a subsequent echocardiogram performed at least 36 months from the baseline echocardiogram without any incident AF or interventions between echocardiograms.

2.2. Assessment of atrial rhythm

All electrocardiograms were manually reviewed by a staff cardiologist and verified by an electrophysiologist and used for cohort classification. Using the first echocardiogram, we divided the patients into 3 groups based on contemporary guidelines [17]. (1) No AF group: patients that were in sinus rhythm and without prior history of AF; (2) Paroxysmal AF group: patients that were in sinus rhythm at the time of baseline electrocardiogram but had prior history of AF or patients that were in AF but had spontaneous and chemical/electrical cardioversion to sinus rhythm within 7 days; (3) Persistent AF group: patients with AF lasting >7 days.

Electronic health records were reviewed to determine the type of antiarrhythmic therapy received. Antiarrhythmic drugs were classified using the Vaughan-Williams classification [18]. All electrocardiograms and Holter monitors performed during follow-up were reviewed to determine AF progression.

2.3. Assessment of LA structure and function

LA function was assessed using LA strain imaging which has 3 different components [3]: (1) LA reservoir strain which is dependent on LA compliance modulated by LV systolic function through descent of the base of the LV. (2) LA conduit strain which is dependent on LV relaxation and chamber stiffness. (3) LA booster strain which is dependent on intrinsic LA contractility and LV end-diastolic compliance. We chose LA reservoir strain as the primary metric of LA function based on previous data demonstrating superiority of LA reserve strain for prognostication as compared to LA conduit and booster strain [19]. LA dysfunction was defined as LA reservoir strain values >2 standard deviation from normative values which corresponds to a cut-off point of <25 % [10,20]. LA structural remodeling was assessed using LA volume index measured by biplane Simpson's method, and LA enlargement was defined as LA volume index >34 ml/m^2 [21]. These assessments were based on offline analyses of echocardiographic images by two experienced sonographers (JW and KT).

The procedural details for speckle tracking strain imaging in our laboratory have been described [22]. In brief, images were obtained using Vivid E9 and E95 (General Electric Co, Fairfield, Connecticut) with M5S and M5Sc-D transducers (1.5–4.6 MHz) at frame rate of 40 to 80 Hz, and these images were exported (DICOM) and then analyzed offline using TomTec (TomTec Imaging Systems, Unterschleissheim, Germany). LA reservoir strain, LA conduit strain, and LA booster strain were assessed using the QRS as the fiduciary point as shown in Supplementary Fig. 1. LV diastolic stiffness was estimated using LV diastolic stiffness constant (β), and LV afterload was estimated using effective arterial elastance index and valvuloaorterial impedance [7,23,24].

2.4. Statistical analysis

Between-group comparisons were performed using unpaired *t*-test, Wilcoxon test, Analysis of Variance, and Fisher's exact test as appropriate. Considering that only 4 patients had persistent AF at baseline, we excluded these patients from all subsequent analyses. Logistic regression was used to assess the relationship between LA indices (LA reservoir strain and LV volume index) and AF (modeled as a binary outcome: sinus rhythm vs paroxysmal AF), and the ability of the different LA indices to detect AF was compared using the area under the curve (AUC) for the different models. Time-to-event analyses were performed using Cox regression and Kaplan Meier method. All models were adjusted for current age, age at time of COA repair, sex, left ventricular global longitudinal strain, native COA (modeled as native COA vs repaired COA), and isolated COA (modeled as isolated COA vs associated left heart obstructive lesions). The single conditional imputation method was used to correct for missing data [25]. All statistical analyses were performed with JMP software (version 14.1; SAS Institute Inc., Cary NC), a $p < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics (n = 776)

Of 851 patients, 54 (6 %) were excluded because of mitral valve disease while additional 21 (3 %) patients were excluded because of suboptimal echocardiographic images. A total of 776 patients met the study inclusion criteria, and of these patients, 603 (78 %) had COA repair prior to age 18 years (median age 7 [0.3–13] years), 102 (13 %) had COA repair after age 18 years (median age at time of repair was 33 [19–46] years), and 71 (9 %) presented with native COA. Among the 705 patients with prior COA repair, the COA repair techniques were resection and end-to-end anastomosis (n = 282, 40 %), subclavian flap repair (n = 106, 15 %), patch aortoplasty (n = 117, 17 %), interposition graft repair (n = 113, 16 %), extra-anatomic bypass (n = 52, 7 %), balloon aortic dilation (n = 16, 3 %), and stent implantation (n = 19, 3 %).

The overall AF prevalence was 6.4 % (50/776), with 726 (94 %), 46 (5.9 %) and 4 (0.5 %) being classified into the No AF, Paroxysmal AF and Persistent AF groups respectively. As compared to the No AF group, the Paroxysmal AF group and Persistent AF group were older, had higher prevalence of coronary artery disease and renal dysfunction, and were more likely to have associated left heart obstructive lesions, Table 1. AF prevalence differed by age group: 2.5 % (13/512) among patients ≤40

Table 1
Baseline characteristics (n = 776).

	No AF (n = 726)	Paroxysmal AF (n = 46)	Persistent AF (n = 4)	p	p*
Age, years	31 (20–44)	48 (27–66)	50 (38–63)	<0.001	<0.001
Male	420 (58 %)	28 (61 %)	2 (50 %)	0.7	0.9
Body mass index, kg/m^2	26 ± 6	27 ± 7	27 ± 4	0.1	0.07
Associated lesions					
Bicuspid aortic valve	449 (62 %)	29 (63 %)	2 (50 %)	0.8	0.9
Isolated COA*	599 (83 %)	32 (72 %)	2 (50 %)	0.001	0.02
Subaortic stenosis	70 (10 %)	2 (4 %)	1 (25 %)	0.09	0.1
Aortic valve disease*	109 (15 %)	13 (28 %)	2 (50 %)	0.01	0.02
Repaired VSD	18 (3 %)	2 (4 %)	–		0.9
Comorbidities					
Hypertension	389 (54 %)	27 (59 %)	3 (75 %)	0.1	0.6
Coronary artery disease	42 (6 %)	9 (19 %)	1 (25 %)	<0.001	<0.001
Hyperlipidemia	140 (19 %)	13 (28 %)	2 (50 %)	0.08	0.2
Diabetes	31 (4 %)	4 (9 %)	1 (25 %)	0.1	0.2
AAD therapy					
Class I	–	2 (4 %)	–	–	–
Class II	199 (27 %)	24 (51 %)	3 (75 %)	<0.001	0.0005
Class III	–	5 (11 %)	3 (75 %)	–	–
Class IV	80 (11 %)	18 (38 %)	2 (50 %)	<0.001	<0.001
Laboratory data					
Hemoglobin, g/dl	13.7 ± 2.2	13.4 ± 0.1.6	12.9 ± 1.4	0.6	0.8
GFR, ml/min/1.73m^2	97 ± 19	87 ± 16	81 ± 11	<0.001	0.02
NT-proBNP, pg/ml	159 (53–359)	383 (211–722)	422 (276–654)	0.005	0.01

AAD: Antiarrhythmic drug; AF: Atrial fibrillation; VSD: Ventricular septal defect; GFR: Glomerular filtration rate; Aortic valve disease defined as aortic velocity >2 m/s and/or ≥mild aortic regurgitation; Isolated COA* denotes absence of other left heart obstructive lesions such as aortic or subaortic stenosis.
p denotes comparison across all 3 groups while p* denotes comparison between the No AF group and the Paroxysmal AF group.

years vs 10.3 % (20/194) among patients 41–60 years vs 24 % (17/70) among patients >60 years (p < 0.001).

3.2. LA structure and function (n = 776)

Compared to the No AF group, the Paroxysmal AF and Persistent AF groups had lower LA reservoir strain and higher LA volume index (Table 2). Similarly, the Paroxysmal AF and Persistent AF groups also had higher LV diastolic stiffness and filling pressures, more LV systolic dysfunction and hypertrophy, and higher LV afterload (Table 2). There was good intraobserver, interobserver and test-retest reproducibility for all LA function indices based on analysis of 20 randomly selected

Table 2
Echocardiography (n = 776).

	No AF (n = 726)	Paroxysmal AF (n = 46)	Persistent AF (n = 4)	p	p*
LA structure and function					
LA reservoir strain, %	39 ± 8	26 ± 10	21 ± 7	<0.001	<0.001
LA conduit strain, %	25 ± 6	14 ± 7 [n = 43]♯	–	–	0.002
LA booster strain, %	15 ± 5	12 ± 6 [n = 43]♯	–	–	0.09
LA volume index, ml/m^2	26 ± 9	36 ± 13	44 ± 11	<0.001	<0.001
Other indices of diastolic function					
Mitral E velocity, m/s	1.1 ± 0.3	1.1 ± 0.3	1.2 ± 0.2	0.9	0.9
Mitral deceleration time, ms	189 ± 43	185 ± 38	167 ± 33	0.3	0.6
Septal e′ velocity, cm/s	9 ± 3	7 ± 3	6 ± 2	0.005	0.03
Lateral e′ velocity, cm/s	13 ± 3	9 ± 2	7 ± 2	<0.001	<0.001
Averaged e′	11 ± 3	8 ± 3	7 ± 2	0.007	0.006
Septal E/e	11 ± 4	14 ± 5	16 ± 3	<0.001	0.01
Lateral E/e	8 ± 2	10 ± 2	13 ± 2	0.006	0.02
Averaged E/e′	9 ± 3	12 ± 3	15 ± 2	<0.001	<0.001
Tricuspid regurgitation velocity, m/s	2.5 ± 0.3	2.7 ± 0.5	2.9 ± 0.6	0.008	0.1
Other echo indices					
LV end-diastolic volume index, ml/m^2	58 ± 12	57 ± 9	58 ± 8	0.6	0.7
LV end-systolic volume index, ml/m^2	20 ± 9	22 ± 10	23 ± 7	0.3	0.1
LV ejection fraction, %	64 ± 7	59 ± 11	56 ± 7	0.006	0.03
LV global longitudinal strain, %	22 ± 12	19 ± 12	16 ± 3	<0.001	<0.011
LV mass index, g/m^2	91 ± 18	118 ± 21	106 ± 15	0.03	<0.001
LV diastolic stiffness constant (β)	6.61 ± 0.54	6.82 ± 0.49	7.03 ± 0.31	0.02	0.007
Valvuloarterial impedance, mmHg/ml*m^2	3.0 ± 0.4	3.6 ± 0.7	3.5 ± 1.2	0.3	0.003
EaI, mmHg/ml*m^2	2.8 ± 0.7	3.3 ± 0.8	3.1 ± 0.5	0.009	<0.001
≥Moderate aortic regurgitation	50 (7 %)	4 (9 %)	1 (25 %)	0.2	0.9
Aortic valve peak velocity, m/s	1.8 (1.5–2.5)	1.9 (1.4–2.7)	2.1 (1.8–2.4)	0.2	0.6
COA peak velocity, m/s	2.4 (1.7–2.8)	2.5 (2.0–2.9)	2.2 (1.8–2.6)	0.5	0.7
COA mean gradient, mmHg	13 (9–19)	12 (5–20)	11 (8–14)	0.7	0.8

COA: Coarctation of aorta; LA: left atrium; LV: Left ventricle; E: Mitral early diastolic velocity; e′: Mitral annular tissue Doppler early velocity; AF: Atrial fibrillation; EaI: Effective arterial elastance.
Of the 46 patients in the Paroxysmal AF group, 3 patients were in AF at the time of echocardiogram and hence LA conduit and booster strain were not measured in these 3 patients. [n = 43]♯ show that values were based on the 43 patients that were in sinus rhythm at the time of echocardiogram.
p denotes comparison across all 3 groups while p* denotes comparison between the No AF group and the paroxysmal AF group.

patients (Supplementary Table 1).

LA reservoir strain, LA conduit strain, LA booster strain, and LA volume index were associated with AF at the time of presentation. Using LA reservoir strain as the reference, LA conduit strain (AUC difference −0.023, p = 0.02), LA booster strain (AUC difference −0.035, p = 0.007), and LA volume index (AUC difference −0.115, p < 0.001) had less robust discriminatory ability for AF (Table 3). Of the 772 patients (No AF and Paroxysmal AF groups), 135 (18 %) had LA dysfunction while 150 (19 %) had LA enlargement. There was an interaction between LA reservoir strain and LA enlargement defined as LA volume index >34 ml/m^2 (p < 0.001) such that the AUC for LA reservoir strain to predict AF among patients with LA enlargement was 0.866, as compared to those without LA enlargement where the AUC was only 0.712 (p interaction = 0.008). This means that the relationship between LA volume and LA strain was not uniformed across the spectrum of measurements. The correlation between LA strain and LA volume was stronger among patients with LA dilation (as evidenced by higher AUC) as compared to patients with normal LV volume.

3.3. LA dysfunction and new-onset AF (n = 726)

The 726 patients in the No AF group were followed for 79 (34–109) months, and during this period, 2858 electrocardiograms (average of 4 electrocardiograms per patient) and 166 Holter monitors (average of 0.2 Holter monitors per patient) were performed. Of the 726 patients, 25 (3.4 %) patients developed new-onset AF (all paroxysmal AF), all 25 cases were confirmed by an electrophysiologist prior to therapy. Supplementary Fig. 1 shows the different antiarrhythmic therapies received by these patients. The 5- and 10-year cumulative incidence of new-onset AF was significantly higher in patients with LA dysfunction vs normal LA function (5.8 % vs 0.4 % and 13 % vs 4.2 %, log-rank p < 0.001), and in patients with LA enlargement vs normal LA volume (4.3 % vs 1.3 % and 11 % vs 6.8 %, p = 0.01), Fig. 1. LA dysfunction (hazard ratio [HR] 1.81 [1.15–3.85], p < 0.001) and LA enlargement (HR 1.41 [1.03–4.78], p = 0.008) were independent predictors of new-onset AF (Supplementary Table 2A).

The median age at the time of new-onset AF was 38 (26–57) years, and the CHA_2DS_2-VASc scores were as follows: CHA_2DS_2-VASc score of 0 (n = 9), 1 (n = 13) and 2 (n = 3). Of the 25 patients, 9 (36 %) patients received warfarin, 6 (24 %) patients received direct oral anticoagulants, and 10 (40 %) patients were on antiplatelet therapy only. Four of the 25 patients (16 %) had ischemic stroke during follow-up. Of the 4 patients, 3 patients (CHA_2DS_2-VASc score of 1 [n = 2] and CHA_2DS_2-VASc score of 0 [n = 1]) were receiving antiplatelet therapy at the time of stroke while one patient (CHA_2DS_2-VASc score of 1) was on warfarin and had subtherapeutic INR at the time of stroke. All 4 patients had LA dysfunction.

Table 3
Multivariate logistic regression models showing relation between LA indices and AF at baseline.

	AUC (95%CI)	p	AUC comparison	p
Model 1				
LA reservoir strain	0.782 (0.751–0.808)	<0.001	reference	–
Model 2				
LA conduit strain	0.759 (0.722–0.802)	<0.001	−0.023 (−0.029 to −0.006)	0.02
Model 3				
LA booster strain	0.747 (0.698–0.795)	<0.001	−0.035 (−0.053 to −0.013)	0.007
Model 4				
LA volume index	0.669 (0.644–0.681)	<0.001	−0.115 (−0.078 to −0.131)	<0.001

LA: Left atrium; AUC: Area under the curve; CI: confidence interval; AF: Atrial fibrillation.
Each model was adjusted for current age, age at time of COA repair, sex, left ventricular global longitudinal strain, native COA (modeled as native COA vs repaired COA), Isolated COA (modeled as isolated COA vs associated left heart obstructive lesions).

3.4. LA dysfunction and recurrent AF (n = 46)

Of the 46 patients in the Paroxysmal AF group, the median age at the time of first episode of AF was 44 (23–61) years. Table 1 shows the different classes of antiarrhythmic drugs used by the patients at the time of baseline electrocardiogram. These 46 patients were followed for 84 (51–133) months, and underwent 388 electrocardiograms (average of 9 electrocardiograms per patient) and 138 Holter monitors (average of 3 Holter monitors per patient). Of the 46 patients, 22 (48 %) had recurrent AF, and all 22 cases were confirmed by an electrophysiologist prior to therapy. Supplementary Fig. 2 shows the different antiarrhythmic therapies at baseline and during follow-up. The 5-year cumulative risk of recurrent AF was significantly higher in patients with LA dysfunction vs normal LA function (42 % vs 19 %, p = 0.02), but not between patients with LA enlargement vs normal LA volume (38 % vs 26 %, p = 0.08), Fig. 1. LA dysfunction (but not LA enlargement) was an independent predictor of recurrent AF after multivariate adjustment (HR 1.94 [1.41–4.17], p < 0.001), Supplementary Table 2B.

The CHA_2DS_2-VASc scores at the time of baseline electrocardiogram were as follows: CHA_2DS_2-VASc score of 0 (n = 24), 1 (n = 18) and 2 (n = 4). Twelve patients were on warfarin (8 of them also had mechanical aortic valve prostheses), 4 patients were on direct oral anticoagulants, and 17 patients were on antiplatelet therapy. Of the 46 patients, 2 (4 %) had history of ischemic stroke prior to the beginning of the study period, while another 5 (11 %) had ischemic stroke during follow-up. Two of the 5 cases of stroke occurred in patients with mechanical aortic valve prostheses, of which one had subtherapeutic INR. The other 3 cases occurred in patients on aspirin, and their CHA_2DS_2-VASc score at the time of ischemic stroke was 1. Three of the 5 patients had LA dysfunction.

3.5. Determinants and implications of progressive LA dysfunction (n = 611)

A pre-specified subgroup analysis was performed in the 611 (84 %) of the 726 patients that had additional LA function assessment performed during follow-up. The mean interval between the baseline and follow-up assessments was 41 ± 4 months, and the temporal change in LA reservoir strain (ΔLA reservoir strain) was 2.2 (1.3–2.9) % while the temporal change in LA volume index (ΔLA volume index) was +4.8 (−1.2 to +9.4) ml/m^2. Of these 611 patients, 22 (3.6 %) patients developed new-onset AF during follow-up. Temporal decline is LA reservoir strain (ΔLA reservoir strain) was independently associated with new-onset AF after adjustment for baseline LA reservoir strain (HR 1.08 [1.03–1.14] per unit change, p = 0.004). Temporal change in LA volume was not associated with new-onset AF.

Of these 611 patients, 559 (91 %) and 52 (9 %) had normal LA function and LA dysfunction respectively at the time of baseline echocardiogram. Of the 559 patients with normal LA function at baseline, 21 (3.8 %) developed LA dysfunction, while all the 52 patients with LA dysfunction at baseline continued to have LA dysfunction at follow-up echocardiogram. Using the time of the follow-up echocardiogram as 'time zero', the 5-year cumulative incidence of AF was significantly different across the 3 groups (Fig. 2).

Exploratory analysis was performed to identify the determinants of temporal decline in LA function in the subgroup of patients with normal LA function at baseline (n = 559). In this subgroup, the temporal change in LA function (ΔLA reservoir strain) was 2.3 (1.7–2.8) %, and was

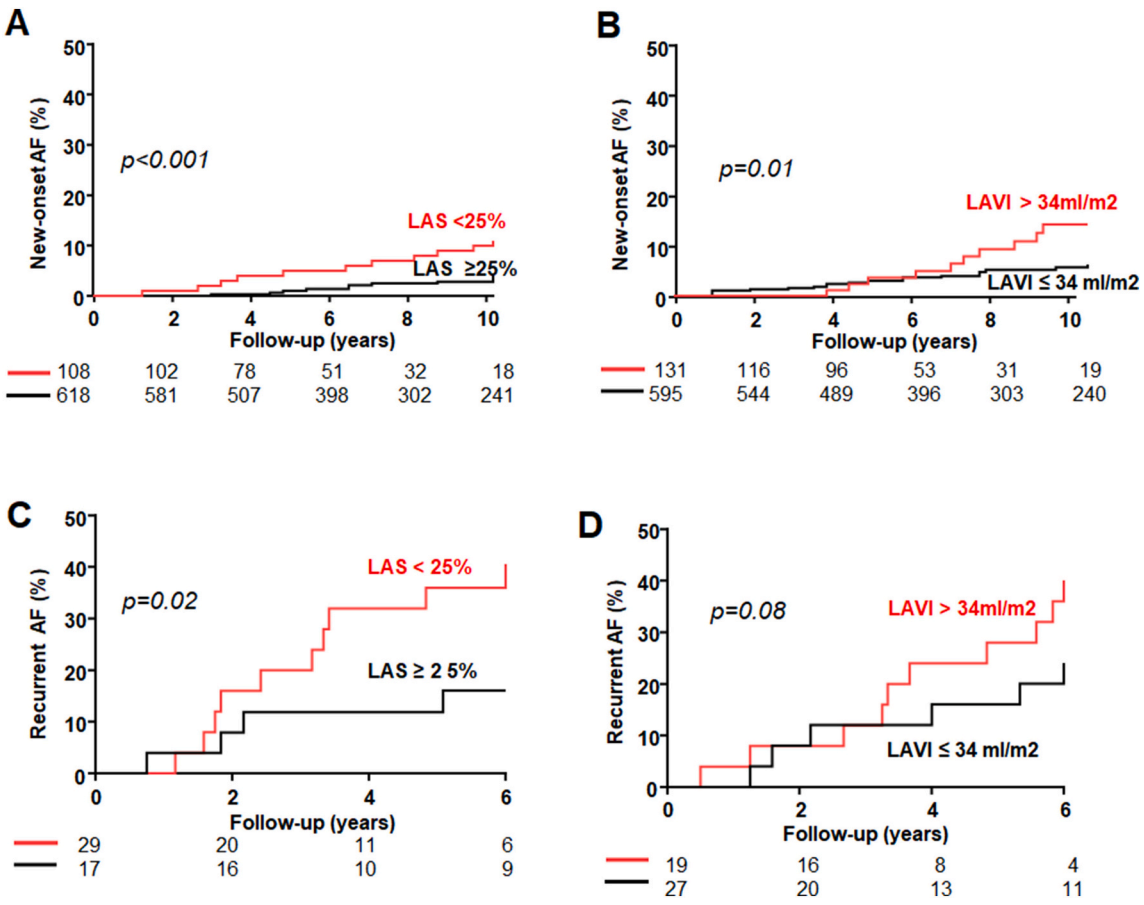

Fig. 1. Kaplan-Meier curves comparing the cumulative incidence of new-onset atrial fibrillation (AF) based on left atrial (LA) remodeling indices.
Patients with LA dysfunction defined as left atrial reservoir strain (LAS) <25 % and those with LA enlargement defined as LA volume index >34 ml/m^2, had higher incidence of new-onset AF and recurrent AF as compared to those with normal LA function and LA volume respectively.

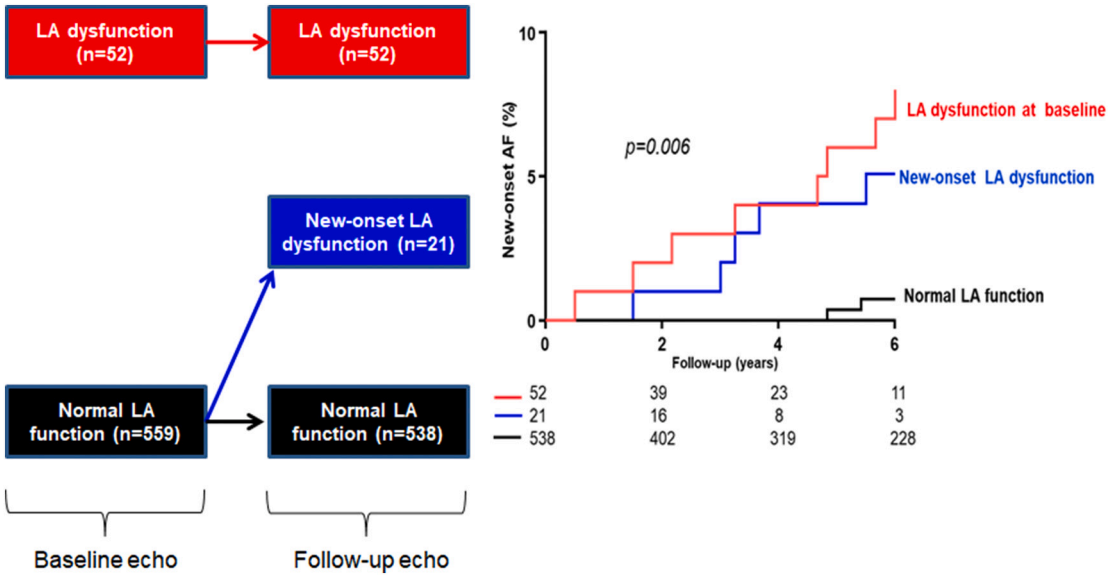

Fig. 2. Flowchart and Kaplan-Meier curves showing temporal deterioration in LA function and its impact of new-onset AF during follow-up.
The highest incidence of new-onset AF occurred in patients with LA dysfunction at baseline, followed by those that developed new-onset LA dysfunction during follow-up, and then those that had normal LA function at baseline and follow-up.

associated with older age, LV mass index, LV diastolic stiffness, and arterial afterload (both arterial elastance and valvuloarterial impedance), Table 4. These data suggest that patients with LV pressure overload resulting in increased LV hypertrophy and stiffness were at a higher risk for developing progressive LA dysfunction, and new-onset AF.

Table 4
Multivariate linear regression models showing determinants of progressive LA dysfunction (ΔLA reservoir strain).

Determinants of LA reservoir strain	Beta ± SE	p
Current age, per years	−0.11 ± 0.04	<0.001
Male sex	–	–
Body mass index, per kg/m^2	–	–
Age at COA repair, per years	–	–
Transcatheter COA repair	–	–
Isolated COA*	–	–
Arterial elastance index, per mmHg/ml*m^2	−0.26 ± 0.19	<0.001
LV diastolic stiffness constant (β), per unit	−1.64 ± 0.22	<0.001
LV mass index, per 10 g/m^2	−1.2 ± 0.06	0.002

COA: coarctation of aorta; LV: left ventricle; LA: left atrium; SE: standard error; Isolated COA (model as isolated COA vs associated left heart obstructive lesions). Note that valvuloarterial impedance and arterial elastance were both significant predictors of ΔLA reservoir strain. However we did not include the 2 variables in the same model because of collinearity.
–: denotes non-significant beta estimates and p values.

4. Discussion

Patients with COA have clinical risk factors and substrates for AF. However, there are limited data about the prevalence, pathophysiologic interaction between LA remodeling and AF, and clinical indices for risk stratification for AF in this population. The current study addressed some of these knowledge gaps.

4.1. Atrial fibrillation

The AF prevalence in our cohort was 6.4 %, and it ranged from 2.5 % in patients younger 40 years of age to 24 % in patients older than 60 years of age. These estimates are significantly higher than the 2 % prevalence of AF in the general population, but comparable to the 22 % prevalence in older patients with heart failure with preserved ejection fraction [1,2]. This relatively high age-adjusted prevalence of AF observed in our COA cohort may be related to the high burden of risk factors such as hypertension, coronary artery disease, arterial stiffening and LV diastolic dysfunction that have been described in this population [8,13,14,26]. Although AF has been reported in COA patients [10], there are no systematic analyses of the disease burden of AF in the COA population, and hence the novelty of our results.

4.2. Left atrial dysfunction

We observed LA enlargement and LA dysfunction in 18 % and 19 % of our cohort respectively, and a progressive deterioration in LA function during a relatively short follow-up period especially in the patients LV pressure overload and increased LV diastolic stiffness. In a cross-sectional study of 56 adult COA patients using speckle tracking echocardiography, Labombarda et al. [10] reported LA dysfunction (defined as LA reservoir strain less negative that 25 %) in 41 % of the patients, and that atrial arrhythmias and ischemic stroke were more common in patients with LA dysfunction. In another study utilizing cardiac magnetic resonance imaging for the assessment of LA function in 51 COA patients, Voges et al. [27] showed that LA dysfunction can occur even in the absence of hemodynamically significant re-coarctation, and was associated with aortic stiffness. While these studies provide important insight about LA dysfunction in patients with repaired COA, the small sample size and the cross-sectional study design limits the prognostic inferences that can be drawn from these studies. Building on the existing literature, the current study showed that LA strain analysis can identify patients at risk for new-onset and recurrent AF, and hence can be used for risk stratification.

4.3. Clinical implications and future directions

The above results open new horizons for further investigations in three important areas. First, there is a need to determine whether LA strain indices can potentially be used to identify patients that will respond favorably to different antiarrhythmic therapies.

Second, the temporal relationship between LV pressure overload and stiffness, progressive LA dysfunction and new-onset AF in the current study provides mechanistic insight into the pathogenesis of AF in this population. Building on these data, further studies are needed to determine whether interventions that reduce LV afterload and stiffness will improve LA function and reduce AF progression. Such potential intervention may include intensification of antihypertensive therapy with lower systolic blood pressure target, and lower threshold for re-intervention for recurrent COA.

Third, we observed ischemic stroke in 16 % and 11 % of patients with new-onset and recurrent AF respectively even though these patients had CHA_2DS_2-VASc score of 1 or less at the time of stroke. More importantly, most of these cases of ischemic stroke occurred in patients with LA dysfunction. Historically, COA has been associated with an increased risk of stroke [28], and hence it is unclear whether the use of CHA_2DS_2-VASc scores underestimates the risk of stroke in this population. We cannot confidently draws inferences regarding the interaction between LA dysfunction, AF, anticoagulation, COA intervention type, and subsequent risk of stroke based on our data because confounders. There is a need for more rigorous studies to determine whether CHA_2DS_2-VASc score accurately reflects stroke risk in COA patients, whether the integration of LA strain indices will improve risk stratification.

4.4. Limitations

We did not control for the confounding effect of antiarrhythmic therapies and structural interventions on the incidence of new-onset and recurrent AF during follow-up, thus limiting the strength of our results. Because of the retrospective study design, there were no set protocols for rhythm monitoring, and thus we could have underestimated the cumulative incidence of AF. Additionally, the current study did not provide data regarding the relative efficacy of the different antiarrhythmic therapies for prevention of AF progression.

5. Conclusions

Patients with COA have a high prevalence of AF relative to their age, and a high cumulative incidence of new-onset and recurrent AF during follow-up. LA dysfunction was associated with the AF prevalence at the time of initial presentation, as well as incident AF during follow-up. LV pressure overload and stiffness are risk factors for progressive LA dysfunction and new-onset AF. Collectively, these findings suggest that LA strain analysis can potentially be used for AF risk stratification in COA patients, and also provides the scientific premise for further studies to determine whether interventions to reduce LV pressure overload and stiffness will result in improvement of LA function and reduce the risk of AF.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2023.100284.

Ethical statement

This study was approved by Mayo Clinic institutional review board and conducted according to the highest ethical standards.

Disclosures

None.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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