Left atrial geometric and functional remodeling parameters measured by cardiac magnetic resonance imaging and outcome prediction in patients with severe aortic stenosis

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ABSTRACT

Background: Emerging studies are beginning to describe the role of afflicted left atrium (LA) function and strain in cardiovascular diseases including aortic stenosis (AS), especially for risk stratification and outcome prediction. Cardiac magnetic resonance imaging (CMR) is becoming increasingly useful in determining LA parameters; however, in patients with AS, this approach has not been applied yet.

Aims: This study sought to evaluate the role of CMR in characterizing LA geometry and function in patients with severe AS.

Methods: We prospectively evaluated 70 patients with symptomatic severe AS and 70 controls. LA volumes, function, and strain were determined using CMR. A composite outcome (cardiac death, ventricular tachyarrhythmias, and heart failure hospitalization) was evaluated over a median of 13 months. Time-to-event outcomes were analyzed accordingly.

Results: Besides increased LA volumes (LAVs) and LA sphericity index (LASI) (P <0.001), LA phasic functions and strain were considerably defective in patients with AS (all P <0.001). LV mass (LVM), end-diastolic and end-systolic volumes were also significantly associated withal LA strain parameters (P <0.001). Regarding outcome prediction, decreased total (LA-εt), active (LA-εa), and passive strain (LA-εp), along with enhanced LASI were independently associated with outcome (P <0.001). Time-to-event analysis showed a significantly higher risk to reach the composite outcome for LA-εt <31.1% (hazard ratio [HR], 6.981; 95% confidence interval [CI], 2.74–17.77; P <0.001), LA-εp <14.5% (HR, 2.68; 95% CI, 1.00–7.18; P <0.01), and LA-εa <21.2% (HR, 2.02; 95% CI, 1.07–3.83, P <0.03).

Conclusion: Patients with severe AS have a significantly remodeled LA, with impaired phasic function and strain. Amongst all CMR parameters, LAVmin, LASI, LAPF, and LA-εp appear to be independent predictors for outcomes.

Key words: aortic stenosis, cardiac magnetic resonance imaging, left atrial sphericity index, left atrial phasic functions, left atrial strain

WHAT'S NEW?

Patients with severe aortic stenosis (AS), besides having considerable left atrium (LA) enlargement, also present with important functional remodelling defined as impaired LA phasic function and strain on cardiac magnetic resonance imaging which are significantly associated with increased risk for cardiovascular outcome. Amongst them, minimum LA volume (LAVmin), LA passive emptying fraction (LAPF), left atrial passive strain (LA-εp), and LA sphericity index (LASI) are independent predictors of major adverse cardiovascular events, impacting survival. Further studies should be conducted to evaluate if they might become additional markers for accelerating aortic valve replacement procedures.

INTRODUCTION

Aortic stenosis (AS) is the most common valvular heart disease, having paramount consequences on life quality and survival [1]. Given that aortic valve replacement is the only effective therapy, the continuous search for non-invasive parameters which could improve risk stratification and prognosis prediction is a necessity [2]. The left atrium (LA) plays a decisive role in maintaining the integrity of heart physiology while its impairment has been shown to be considerably associated with mortality and poor outcomes in cardiovascular diseases [3, 4]. The constant development of cardiac magnetic resonance imaging (CMR) has widened its uses, and recent studies confirmed its ability to properly evaluate LA structure and function. Nonetheless, studies to characterize the LA measured by CMR and ascertain its utility in patients with AS are still lacking.

LA's physiology comprises three successive phases which have primary roles in preserving the cardiac output, even in those with left ventricular (LV) dysfunction, and it includes LA reservoir function, conduit function, and booster pump function [5–7]. On the other hand, it has been suggested that LV dysfunction promotes LA damage and dilation [3]. However, in patients with AS, O'Connor et al. [8] have shown that LA enlargement is not always accompanied by its dysfunction. Moreover, LA phasic dysfunction is closely related to the progression of LV dysfunction, which helps to predict independently cardiovascular outcomes [9]. Furthermore, LA strain measured by CMR has been shown to identify LV-impaired relaxation [10]. However, the prognosticating capacity of these parameters in patients with AS has not been evaluated yet.

Regarding LA geometry, LA volumes (LAVs) were shown shown to be important predictors of outcomes and mortality [11]. In patients with AS, Rusinaru et al. [12] have shown that echocardiography-based LAV was an independent predictor of mortality. As for the LA sphericity index (LASI), its importance in characterizing LA shape and remodeling and predicting recurrence of atrial fibrillation has been recently confirmed by several studies [13]. Nevertheless, in patients with AS, the role of LASI is still unknown.

Our study aimed to assess the role of LA geometry and function determined by CMR measurements in patients with severe AS.

METHODS

Study population

We conducted a prospective study on 70 patients with symptomatic severe AS and 70 controls (patients with cardiovascular risk factors and without clinically overt cardiovascular diseases) matched for age and sex, who were examined in the 2nd Department of Internal Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania, between March 2018 and May 2021. Severe AS was defined as peak aortic jet velocity ≥4 m/s, and/or mean transvalvular gradient ≥40 mm Hg, and/or [3] aortic valve area ≤1.0 cm^2 (indexed aortic valve area≤0.6 cm2/m2) determined by standard transthoracic echocardiography [14]. Patients with severe AS were considered symptomatic if they experienced dyspnea, angina, palpitation, and/or syncope. Figure 2 represents the study flowchart with the exclusion criteria.

The research was approved by the Ethics Committee of the Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca. The study was conducted in accordance with the Declaration of Helsinki. All patients were informed about the investigation protocol and signed consent forms.

CMR imaging

CMR images were performed using a Siemens 1.5 T Open Bore scanner (Magnetom Altea, Siemens Medical Solutions, Erlangen, Germany). According to international recommendations, a standard scanning protocol used for the acquisition of fast imaging employing steady-state free precession (SSFP) sequences was performed to detect ventricular function and mass in short-axis and long-axis planes, to enclose both ventricles from base to apex [15]. Scanning parameters included repetition time (TR): 3.6 ms; echo time (TE): 1.8 ms; flip angle: 60°; slice thickness: 6 mm; field of view: 360 mm; image matrix of 192 × 192 pixels; voxel size: 1.9 × 1.9 × 6 mm; 25–40 ms temporal resolution reconstructed to 30 cardiac phases. Late gadolinium enhancement (LGE) was acquired 10 minutes after intravenous administration of 0.2 mmol/kg gadoxetic acid (Clariscan, GH Healthcare AS, Oslo, Norway) in long- and short-axis sequences, using a segmented inversion-recovery gradient-echo sequence (the repetition

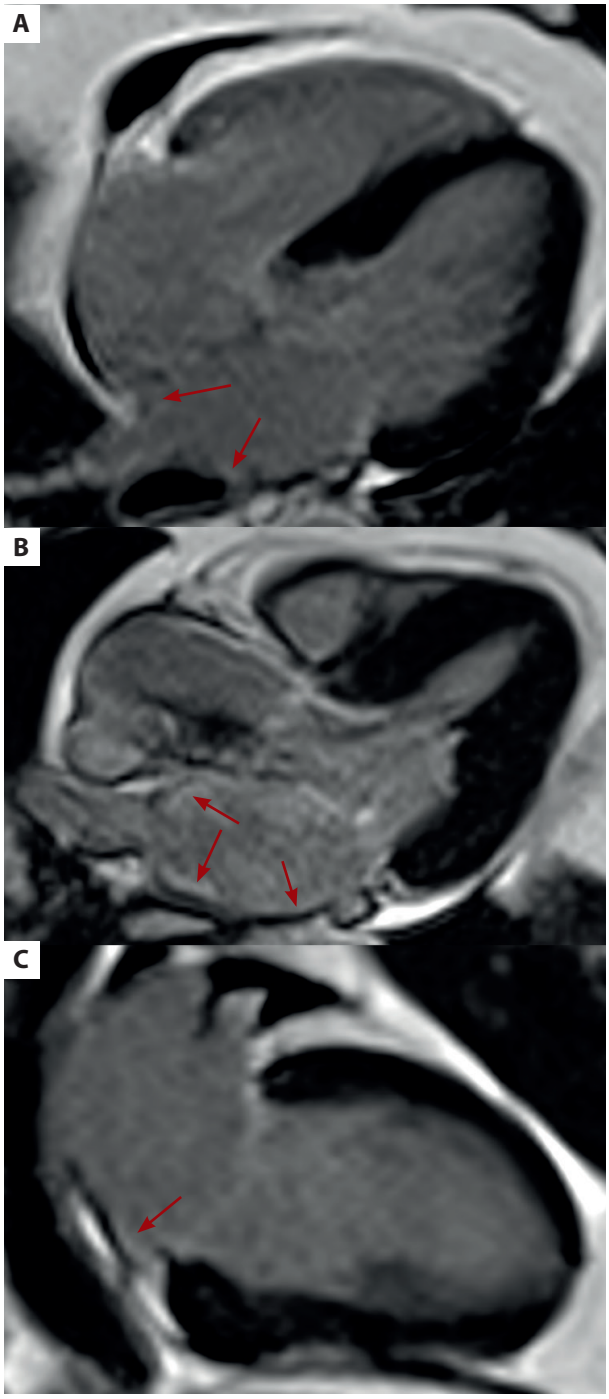

Figure 1. Cardiac magnetic resonance images representing a patient's left atrial late gadolinium enhancement in 4-(**A**) 4-chamber view, (**B**) 3-chamber view, and (**C**) 2-chamber view (arrows)

time [TR], 4.8 ms; the echo time [TE], 1.3 ms; inversion time, 200–300 ms). LA-LGE sequenced was performed during mid-ventricular diastole, using an ECG-triggered and navigator-gated, fat-saturated 3D gradient echo inversion recovery sequence, 15–25 minutes after administration of gadolinium contrast agent (Figure 1).

Evaluation of LV systolic and diastolic function

All images were evaluated by two experienced observers blinded to all clinical data. LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV), left ventricular ejection fraction (LVEF), and end-diastolic LV mass (LVM) were measured on short-axis cine-SSFP images. Epicardial and endocardial borders were traced semi-automatically at end-diastole and end-systole using specialized software (Syngo Virtual Cockpit). All volumes were indexed to body surface area. The presence, distribution, and mass of LV-LGE were assessed from short-axis images, using the 17-segment model, and we used a threshold of 5SD above the signal intensity of the normal myocardium. The extent of LV-LGE was expressed by gram (g) and as a percentage of LVM. Because LGE quantification with the threshold of 5SD demonstrated the best agreement with visual assessment and best reproducibility among different technique thresholds, we used a threshold of 5SD above the signal intensity of the normal myocardium [16, 17]. LV longitudinal function was assessed by LAS and defined as the difference in mitral annular displacement at end-systole vs. end-diastole and expressed as percentages [16].

Concerning LV diastolic function, blood flow, and myocardial velocity, phase-contrast CMR (PC-CMR) images were used to acquire: (1) transmitral through-plane flow velocity (encoding velocity Venc, 180 cm/s; TE, 3.1 ms; TR, 7.6 ms; views per segment, 2; temporal resolution, 15 ms), and (2) longitudinal myocardial velocity (Venc, 15 cm/s or 20 cm/s; TE, 5 ms; TR, 9.5 ms; views per segment, 2; temporal resolution, 20 ms). To minimize background offsets and to make acquisition duration compatible with breath holding, a 50% rectangular field of view was used [16]. Each PC-CMR dataset included a dynamic modulus series (providing information about the variation in mitral valve orifice geometry during the cardiac cycle) and the associated velocity-encoded dynamic series acquired during an entire cardiac cycle. These contours were then superimposed on velocity PC-CMR images for flow analysis.

Three basic waveforms were obtained which allowed measurements of the following parameters: transmitral early (E, in cm/s) and late (A, in cm/s) peak velocities and early (EQ, in mL/s) and late (AQ, in mL/s) peak flow rates; filling volume (FV), deceleration time (DT, in ms) and isovolumic relaxation time (IVRT, in ms). Myocardial longitudinal early (E′, in cm/s) and late (A′, in cm/s) peak velocity on LV lateral wall.

LA parameters were determined by CMR measurements using dedicated software (cvi42, Circle Cardiovascular Imaging Inc., Calgary, CA), following international guidelines, comprising maximum LA volume (LAVmax), pre-atrial contraction LA volume (LAVpre-A), and minimum LA volume (LAVmin); LA reservoir function was evaluated using LA total emptying fraction (LATF); LA conduit function was evaluated using LA passive emptying fraction (LAPF); and the atrial booster pump function was evaluated using LA active emptying fraction (LAAF), along with their specific LA strain: LA-εt, LA-εp, and LA-εa, respectively [6, 18, 19]. The LA sphericity index (LASI) was calculated using this formula: LA volume = maximum LA volume/(4 π/3)(maximum LA length/2) [20, 21].

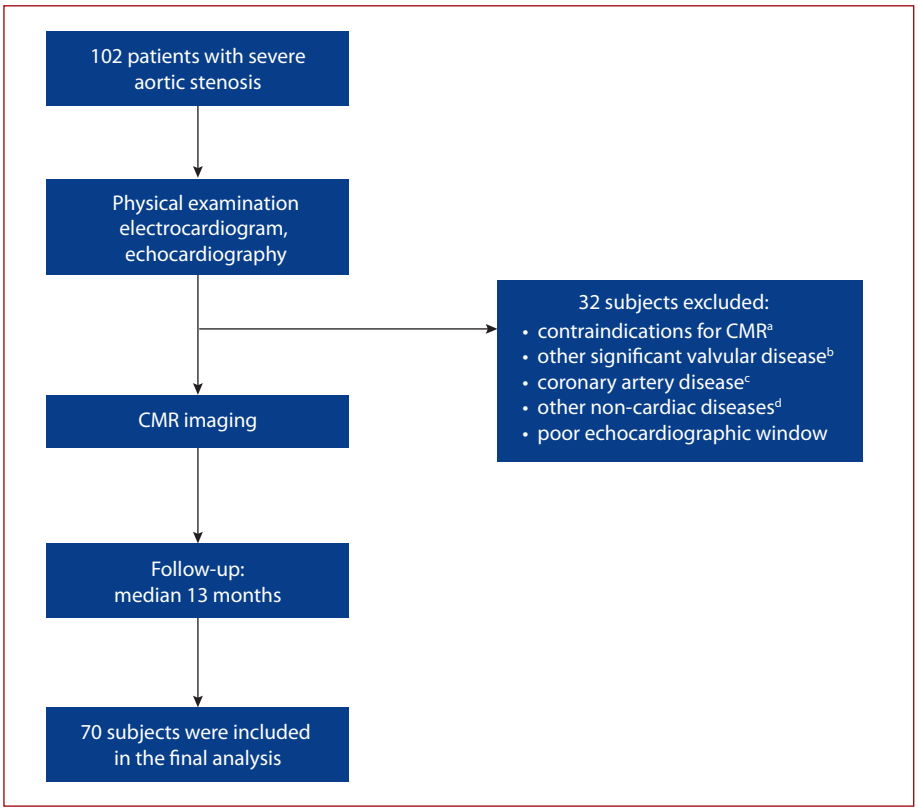

Figure 2. Study flowchart

[a]Incompatible metallic devices, significant chronic renal disease with estimated glomerular filtration rate <30 ml/min/1.73 m^2, or claustrophobia; [b]Moderate/severe mitral or aortic regurgitation; rhematic or post-irradiation aortic stenosis; previous surgery for valvular heart disease; [c]History of previous myocardial infarction with or without coronary revascularizaion by percutaneous coronary intervention and/or bypassoronary artery disease; [d]Active inflammatory, infectious diseases, or neoplasia, cirrhosis, pulmonary fibrosis
Abbreviations: CMR, cardiac magnetic resonance

Clinical outcomes

Patients were followed up over a median time of 13 months (3 to 19 months) by completing surveys either during hospital visits, telephone calls, or both. The composite endpoint comprised major adverse cardiac events (MACE), including cardiac death, ventricular tachyarrhythmias, and heart failure (HF) hospitalizations. Hospitalizations for non-cardiac causes were not considered in the analysis.

Statistical analysis

The analysis was performed using MedCalc (Version 19.1.7, MedCalc Software, Belgium); *P*-values <0.05 were considered statistically significant. Data were presented as mean (SD), median with interquartile range (IQR), or percentages. Categorical data were assessed using the χ^2 test. Continuous data were tested using Student's t-test or the Mann-Whitney U test, depending on whether or not the data were normally distributed. The Pearson correlation (parametric) or Spearman correlation (non-parametric) was performed to investigate the potential relationship between LV conventional parameters, baseline parameters, and LA function. Cohen's Kappa inter- and intra-observer coefficients were determined to assess the reproducibility of CMR parameters. The Cox regression model was used to evaluate event predictions, and the results were presented as hazard ratios (HR). For each outcome, we considered all the significant variables in the univariate analysis and sought the best overall multivariable models for the composite endpoint by stepwise-forward selection. Event-free survival was generated by the Kaplan-Meier method and statistical significance was determined by the log-rank test.

RESULTS

Baseline characteristics and LV function measurements

Eventually, 70 patients with severe AS (mean [standard deviation, SD], 67 [8.8] year-old; 57.1% males) and 70 controls (mean [SD], 65 [8.6] year-old; 58.5% males) were included in the study, and their baseline clinical characteristics are presented in Table 1. In the diseased group, 47.1% [n = 33] of patients with severe AS presented with dyspnea, 34.2% (n = 24) with typical angina, and only 18.5% (n = 13) had syncope. Regarding the etiology of AS, 80% had a degenerative disease, 10% presented with a bicuspid aortic valve, 6% had rheumatic valvular disease, and in 4% etiology could not be determined.

CMR conventional parameters are presented in Supplementary material, *Table S1*. LVEDV, LVESV, LVM, LVEF, and LAS were significantly impaired in those with AS as compared to controls (all *P* <0.001). Furthermore, several LV diastolic parameters such as A, DT, E', E/A ratio, and E/E ratio (*P* <0.001) were also notably impaired. LGE was found in 34 patients with AS (48.5%). LGE was distributed midwall in 14 patients (20%), in the sub-epicardial myocardium in 5 patients (7.1%), was focal in 12 patients (17.1%), and diffuse in 3 patients (4.3%).

Regarding the agreements of the CMR parameters, LAVmax, LAVmin, LAVpre-A, LASI, and E/E' ratio, had Kappa

Table 1. Baseline characteristics of study patients

Variables	AS all patients (n = 70)	Controls (n = 70)	*P*-value
Clinical characteristics			
Age, mean (SD), years	67 (8.8)	65 (8.6)	0.110
Male sex, n (%)	40 (57.1)	41 (58.5)	0.102
Body Mass Index, mean (SD), kg/m^2	30.5 (4.9)	28.4 (4.2)	0.05
Hypertension, n (%)	49 (70)	37 (52.8)	0.05
Diabetes mellitus, n (%)	32 (45.7)	18 (25.7)	0.05
Electrocardiogram			
Paroxysmal atrial fibrillation, n (%)	6 (8.5)	—	NA
Left bundle branch block, n (%)	11 (15.7)	2 (2.8)	<0.001
Right bundle branch block, n (%)	10 (14.2)	1 (1.4)	<0.001
Significant Q waves, n (%)	3 (4.2)	—	NA
Echocardiography			
Peak aortic velocity, mean (SD), m/s	4.46 (0.46)	1.35 (0.33)	<0.001
Peak transaortic gradient, mean (SD), mm Hg	82.2 (17.8)	7.7 (2.31)	<0.001
Mean transaortic gradient, mean (SD), mm Hg	53.1 (14.6)	3.7 (0.74)	<0.001
AVA index, mean (SD), cm^2/m^2	0.51 (0.08)	3.2 (0.07)	<0.001
Medication			
Beta-blockers, n (%)	53 (75.7)	4 (5.7)	<0.001
ACEIs or ARBs, n (%)	47 (67.1)	10 (14.2)	<0.001
Calcium channel blockers, n (%)	23 (32.8)	5 (7.1)	<0.001
Diuretics, n (%)	43 (61.4)	6 (8.5)	<0.001
Antiarrhythmic, n (%)	15 (21.4)	—	NA
Anticoagulant, n (%)	13 (18.5)	—	NA
Biomarkers			
NT-proBNP, median (IQR), pg/ml	634.3 (172–1329)	215.7 (66–372)	<0.001
Galectin-3, median (IQR), ng/ml	16.4 (2.2–23.6)	5.6 (1–12.6)	<0.001
PICP, median, (IQR), ng/ml	1.16 (0.38–7.32)	0.75 (0.38–4.6)	0.05
PIIINP, median (IQR), ng/ml	10.7 (2.5–68.3)	8.1 (2.4–29.7)	0.05
eGFR, mean (SD), ml/min/1.73 m^2	82.1 (17.9)	89.3 (23.3)	0.05

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AVA, aortic valve area; eGFR, estimated glomerular filtration rate; IQR, interquartile range; n, number of patients; NT-proBNP, N-terminal pro-brain natriuretic peptide; PICP, procollagen type I C-terminal propeptide; PIIINP, procollagen type III N-terminal propeptide; SD, standard deviation

coefficients for inter-observer agreements of 0.92, 0.94, 0.92, 0.94, and 0.91, respectively, and for intra-observer coefficients of 0.93, 0.95, 0.93, 0.94, and 0.91, respectively.

Characterization of LA phasic function and geometry

LA volumes were significantly increased in the AS group (all P <0.001). The LASI was considerably impaired in the diseased group (mean [SD], 0.50 [0.09] vs. 0.40 [0.05]; P<0.001) while 31.4% of them were positive for LA-LGE. As for LA phasic function, all three were significantly defective in the diseased group: LATF, LAPF, and LAAF (all P <0.001). Furthermore, LA strain CMR parameters (LA-εt, LA-εp, and LA-εa; P <0.001) were also substantially affected in those with AS as compared to controls.

Associations of LA phasic function and strain with LV functional parameters, LA volumes, and geometry

The best correlations between LA phasic functions and strain, LV parameters, and LA geometry are summarized in Supplementary material, *Table S2*. LA phasic functions and strain parameters were inversely associated with LA volumes and LASI. Hence, LAVmax, LAVpre-A, and LAVmin had the strongest correlations with LAAF, LA-εt, LA-εp and LA-εa (all P <0.001) while the LASI appeared to have the best associations mainly with LA-εt and LA-εa (P <0.001). Furthermore, LAAF, LA-εt, LA-εp, and LA-εa had the best correlations with conventional LV functional parameters (all P <0.001). The most significant associations were between LVM, LVEDV, and LVESV, and LA-εt, LA-εp and LA-εa (P<0.001).

The ability of LA parameters to predict composite endpoint in patients with AS

Patients with AS were followed up for a median period of 13 months. Of all patients, 1 patient experienced cardiac death, 3 ventricular tachyarrhythmias, and 11 HF hospitalization. In multivariable analysis, only few LA parameters remained independent predictors for outcomes: LAVmin (P <0.001), LASI (P <0.001), LAPF (P <0.001), LA-εp (P <0.001), LA-LGE (P <0.001), LV-LGE (P <0.001), and E/E' ratio (P <0.001) (Table 3).

Time-to-event analysis was performed to test LA parameters' abilities to predict the composite outcome (Figure 4). Thus, a threshold of >22 ml/m^2 for LAVmin (HR, 1.75; 95% CI, 1.04–4.07; P <0.001), >34% for LAPF (HR, 4.13;

Table 2. Comparison between left atrial function and geometry parameters between AS patients and healthy volunteers

Variables	AS patients (n = 70)	Controls (n = 70)	*P*-value
LA volumes indexed			
LAV_{max} index, ml/m², mean (SD)	42.2 (4.8)	26.9 (3.5)	<0.001
LAV_{min} index, ml/m², mean (SD)	20.3 (5.9)	10.5 (1.3)	<0.001
$LAV_{pre\text{-}A}$ index, ml/m², mean (SD)	31.7 (6.2)	18.9 (2.4)	<0.001
LA geometry and fibrosis			
LASI, mean (SD)	0.50 (0.09)	0.40 (0.05)	<0.001
LA-LGE, n, mean (SD)	22 (31.4)	—	N/A
LA phasic functions			
LATF, %, mean (SD)	58.2 (2.1)	60.7 (1.8)	<0.001
LAPF, %, mean (SD)	34.9 (2.8)	29.6 (4.9)	<0.001
LAAF, %, mean (SD)	36.3 (4.1)	43.9 (3.9)	<0.001
LA strain parameters			
LA-ε_t, %, mean (SD)	31.1 (2.4)	39.8 (3.3)	<0.001
LA-ε_p, %, mean (SD)	14.5 (1.9)	18.3 (3.0)	<0.001
LA-ε_a, %, mean (SD)	21.2 (2.8)	28.8 (4.1)	<0.001

Abbreviations: AS, aortic stenosis; n, number of patients; LA-ε_t, left atrial total strain; LA-ε_p, left atrial passive strain; LA-ε_a, left atrial active strain; LAV, left atrial volume; LASI, left atrial sphericity index; LA-LGE, left atrial late gadolinium enhancement; LAPF, left atrial passive emptying fraction; LAAF, left atrial active emptying fraction; LATF, left atrial total emptying fraction

Table 3. Univariate and multivariate Cox Analysis testing between studied parameters and MACEs

	Univariable analysis		Multivariable analysis	
	Unadjusted HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
Age, years	1.02 (0.97–1.07)	0.516		
Sex, male	1.01 (0.45–2.19)	0.612		
Body mass index, kg/m²	1.01 (0.93–1.09)	0.090		
LVEDV index, ml/m²	1.01 (1.00–1.03)	0.047		
LVESV index, ml/m²	1.02 (1.00–1.04)	0.018		
LVEF, %	1.01 (0.93–1.07)	0.721		
LVM index, g/m²	1.09 (1.07–1.33)	<0.001		
LV-LGE	2.75 (1.25–7.97)	<0.001	1.73 (1.02–5.91)	<0.001
LAS, %	1.28 (1.13–2.12)	<0.001		
LAV max index, ml/m²	1.12 (1.01–1.17)	0.019		
LAV min index, ml/m²	1.45 (1.23–1.89)	<0.001	1.37 (1.08–1.66)	<0.01
LAV preA index, ml/m²	1.31 (1.17–1.37)	<0.001		
LASI	1.20 (1.18–1.43)	<0.001	1.13 (1.01–1.43)	<0.01
LA-LGE	3.36 (1.35–9.35)	<0.001	3.56 (1.02–12.47)	<0.001
LATF, %	1.66 (1.44–1.72)	<0.001		
LAPF, %	2.16 (1.73–2.64)	<0.001	1.76 (1.09–2.34)	<0.01
LAAF, %	1.61 (1.52–1.81)	<0.001		
LA-εt, %	1.25 (1.19–1.43)	<0.001		
LA-εp, %	1.54 (1.35–1.86)	<0.001	1.31 (1.12–2.01)	<0.01
LA-εa, %	1.43 (1.32–1.61)	<0.001		
E /E′ ratio	1.59 (1.19–2.22)	<0.001	1.20 (1.00–1.44)	<0.01
DT, ms	1.13 (1.01–1.26)	0.012		
NP-proBNP, pg/ml	1.01 (0.81–1.02)	0.978		
Galectin-3, ng/ml	0.99 (0.94–1.05)	0.254		

Abbreviations: cMRI, cardiac magnetic resonance imaging; LV, left ventricle; LVEDV; left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVM, left ventricular mass; LVEF, left ventricular ejection fraction; LV-LGE, left ventricular late gadolinium enhancement; LAV, left atrial volume; LASI, left atrial sphericity index; LA-LGE, left atrial late gadolinium enhancement; LAPF, left atrial passive emptying fraction; LAAF, left atrial active emptying fraction; LATF, left atrial total emptying fraction;-ε_t, left atrial total strain; LA-ε_p, left atrial passive strain; LA-ε_a, left atrial active strain; E, early peak mitral flow velocity; E′, myocardial longitudinal early diastolic peak myocardial velocity; MACEs, major adverse cardiovascular events; NT-proBNP, N-terminal pro-brain natriuretic peptide

Adjustment models: age, sex with the addition of significant parameters of univariable analysis

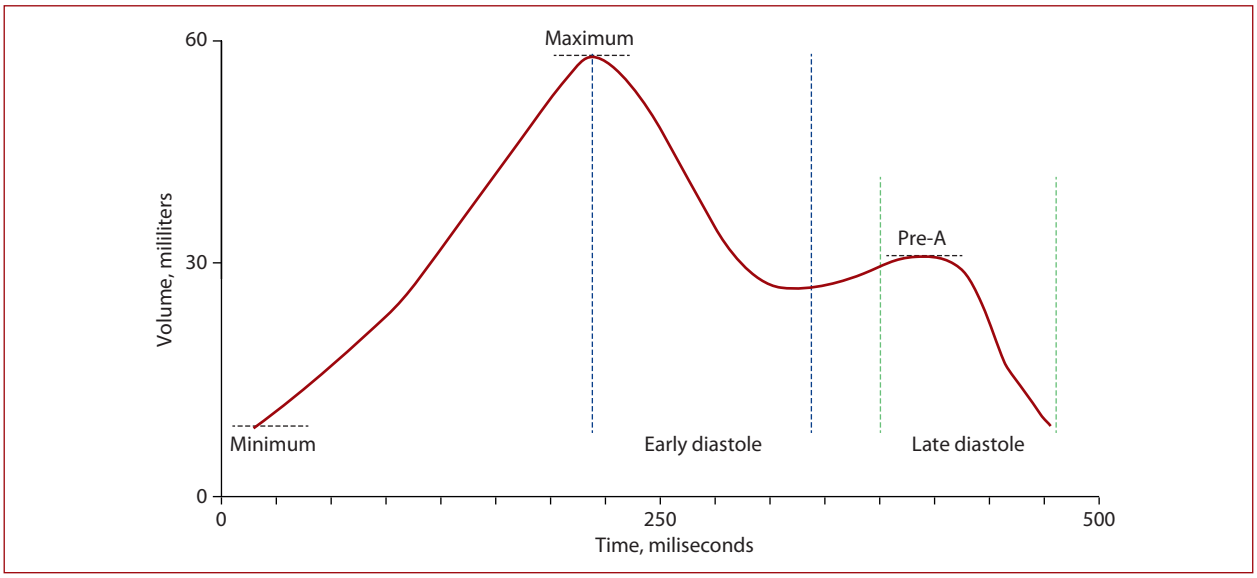

Figure 3. Left atrial volume curves during the cardiac cycle

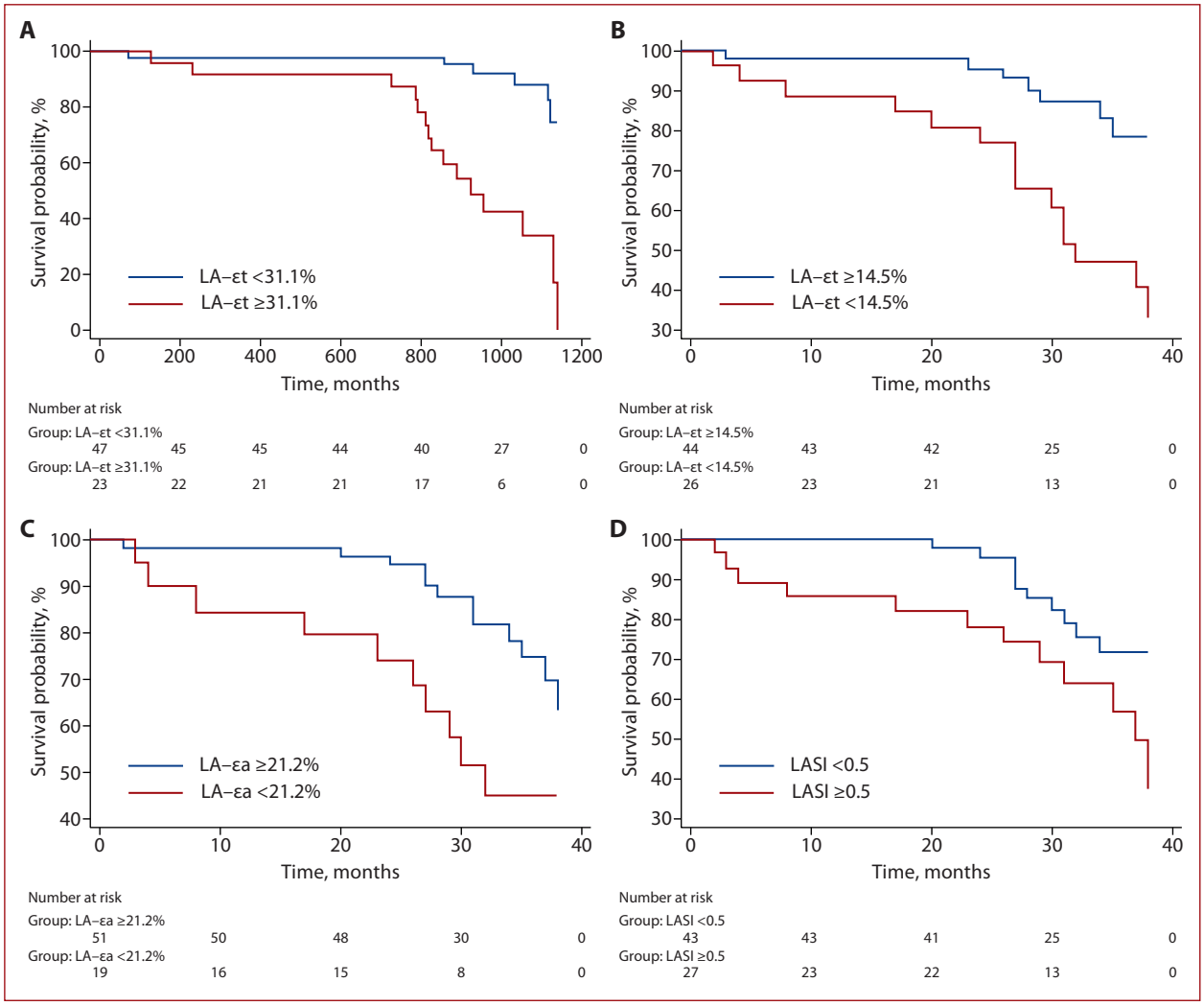

Figure 4. Log-rank analyses for left atrial parameters in determining the outcome

Abbreviations: LA-εa, left atrial active strain; LA-εp< left atrial passive strain; LA-εt, left atrial total strain; LASI, left atrial sphericity index

95% CI, 1.32–12.21; P <0.001), and >0.5 for LASI (HR, 2.24; 95% CI, 1.06–3.99; P = 0.04) significantly predicted the outcome. As for LA strain parameters, LA-εt<31.1% (HR, 6.981; 95% CI, 2.74–17.77; P <0.001), LA-εp <14.5% (HR, 2.68; 95% CI, 1.00–7.18; P = 0.01), and LA-εa <21.2% (HR, 2.02; 95% CI, 1.07–3.83; P = 0.03) also predicted the outcome. As for cardiac fibrosis, the presence of both LA-LGE (HR, 2.78; 95% CI, 1.07–7.16; P = 0.01) and LV-LGE (HR, 2.58; 95% CI, 1.11–5.97; P = 0.03) significantly predicted the outcome.

DISCUSSION

This is the first CMR study to characterize the predictive ability of LA geometry and function in patients with AS. Hence, the main findings of this study are as follows: (1) LA volumes, phasic functions, strain, and geometry were considerably impaired; (2) LA strains were strongly related to LA volumes, LASI, and LV function; (3) LAVmin, LAPF, LA-εp, and E/E' ratio were independently associated with the outcome; (5) LASI and LA strains were notably related with higher risk of the composite endpoint.

As a direct response to LV impairment, the LA dilates and becomes defective [3]. Studies have shown that regardless of cardiovascular disease, LA phasic functions commonly become impaired [3, 9, 22] and are firmly associated with HF, LV dysfunction, and atrial fibrillation [8, 22, 23]. LA reservoir function often becomes impaired even before LV hypertrophy and dilation and is closely related to LV diastolic dysfunction. Additionally, LA reservoir dysfunction independently predicted HF hospitalization and cardiac mortality [24].

We demonstrated that LA parameters were significantly impaired in those with AS and these findings were confirmed using healthy volunteers. Hence, LA volumes, phasic functions, and strains were considerably defective in patients with AS. Thus far, some studies have shown the utility of CMR in assessment of LA parameters [9, 24, 25]; however, in patients with AS such research has never been conducted. Echocardiography-based studies have concluded that patients with severe AS had all three LA phasic functions defective, and LA reservoir and conduit functions were associated with impaired LV filling pressures and relaxation and with AS's severity [26, 27]. Additionally, Ferreira et al. have shown that defective LA emptying fraction was a strong predictor for all-cause mortality [28]. As for LA strain, studies have shown that LA strain was related to LV dysfunction and AS severity and was also an independent predictor for HF hospitalization, all-cause mortality, and new-onset atrial fibrillation, regardless of LA dilation [29, 30]. Recently, Kim et al. [31] conducted a CMR study in which they suggested that LA peak longitudinal strain might predict cardiovascular events in AS, but several studies have shown that traditional CMR methods might have questionable reliability, requiring further adjustments [32]. In conclusion, more work is still required to properly assess the prognosis ability of CMR-based LA parameters.

Furthermore, all three LA volumes turned out to have the strongest associations with LAAF, LA-εt, LA-εp and LA-εa, strengthening even more the pathogenetic duality of which LA dilation and dysfunction are two complementary processes. These measurements were also closely related to parameters of LV systolic dysfunction, thus suggesting the mutuality of LA and LV impairment. Similar results have been found in other cardiovascular diseases, but so far there has been no such study conducted on patients with AS. Recently published data have demonstrated similar associations between LV systolic dysfunction and LA enlargement and impairment [9, 33]. Moreover, in our diseased group, LVEF deterioration was closely related to LA dysfunction, similar to other reports [34].

What is more, in the actual study, the predictive ability of relevant LA parameters was tested. In univariate analysis, all LA volumes, LA phasic functions, LA strains, and the LASI were associated with the composite endpoint; however, after adjustment for confounders, only a few remained significant. Hence, LAVmin, LA conduction function, LA passive strain, and the LASI were independent predictors for cardiovascular outcomes in patients with AS. Furthermore, we performed Kaplan-Meier analysis to test the ability of time-to-event prediction for these LA parameters, and all of them reached statistical significance. Similarly, some studies have shown the predictive ability of LA volumes, phasic functions, and strain for outcomes in various cardiovascular diseases [25, 35]. Nonetheless, as we are aware, this is the first research article that evaluates the comprehensive predictive ability of LA parameters measured by CMR in patients with AS.

Lastly, regarding the LASI, in comparison with other LA parameters, this was significantly associated with parameters of LA strain only. Moreover, time-to-event analysis has shown that it significantly increases the risk of outcome for a threshold of >0.5. Lately, the LASI determined by both echocardiography and CMR has been shown to be a marker of LA remodeling, atrial fibrillation recurrence, and HF hospitalization [36–38]. These findings suggest a close relationship between the LASI as a marker of LA remodeling and dysfunction and defective LA strains, thereby indicating that although LA dilation and dysfunction are at some point co-dependent, these pathogenetic processes are also independent of one another. Additionally, this is the first study to assess the predictive ability of the LASI in patients with AS.

Regarding the limitations, firstly, this was a single-center study. Secondly, more advanced LA parameters such as atrial displacement were not evaluated. Finally, a second diagnosis method, such as cardiac catheterization or echocardiography, was not performed.

CONCLUSIONS

Patients with severe AS have significantly remodeled LA, with impaired phasic function and strain. Amongst all CMR parameters, LAVmin, LASI, LAPF, and LA-εp are independent predictors for outcomes.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska

Article information

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