

Prognostic value of left atrial strain in patients with congenital aortic stenosis

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Received 22 November 2021; revised 25 February 2022; accepted 29 March 2022; online publish-ahead-of-print 6 April 2022

Handling Editor: Edit Nagy

Aim

To explore whether left atrial (LA) strain with speckle tracking echocardiography (STE) can contribute to prognostication in patients with congenital aortic stenosis (CAS).

Methods and results

In this prospective study, consecutive outpatients with stable CAS and healthy adults were enrolled between 2011 and 2015. Left atrial function was analysed with STE using Tomtec software. Associations between LA strain (LAS) measurements and primary composite outcome (any adverse cardiovascular event, hospitalization, or re-intervention) and secondary outcome (re-interventions) were assessed with Cox regression analysis. In total, 98 patients with CAS (mean age: 35.0 ± 11.9 year, female: 59.2%) and 121 controls (age: 43.9 ± 13.8 year, female: 55.4%) were included. The majority of patients were in NYHA class I: 97 (99%) at baseline. At baseline, LA conduit strain (LAS-cd) and strain rate (LASR-cd) were significantly lower in patients than in controls when corrected for age and sex (-18.1 ± 8.7 vs. $-23.5 \pm 9.9\%$, $P = 0.001$ and -0.73 ± 0.31 vs. $-1.02 \pm 0.43/s$, $P < 0.001$). During a median follow-up of 6.4 years (5.7–7.1), the primary composite outcome occurred in 48 (39.6%) patients. Kaplan–Meier analysis showed that decreased LAS-cd ($<21\%$) was associated with a higher occurrence of the primary outcome (log-rank: $P = 0.008$). Depressed LAS-cd and LASR-cd were both associated with the primary composite outcome [univariable hazard ratio (HR) = 0.64(0.46–0.88), $P = 0.005$ and HR = 0.68(0.55–0.83), $P < 0.001$, respectively]; adjusted HR (for LAS-cd and LASR-cd, respectively): 0.31(0.09–1.04), $P = 0.06$ and 0.49(0.26–0.89), $P = 0.02$.

Conclusion

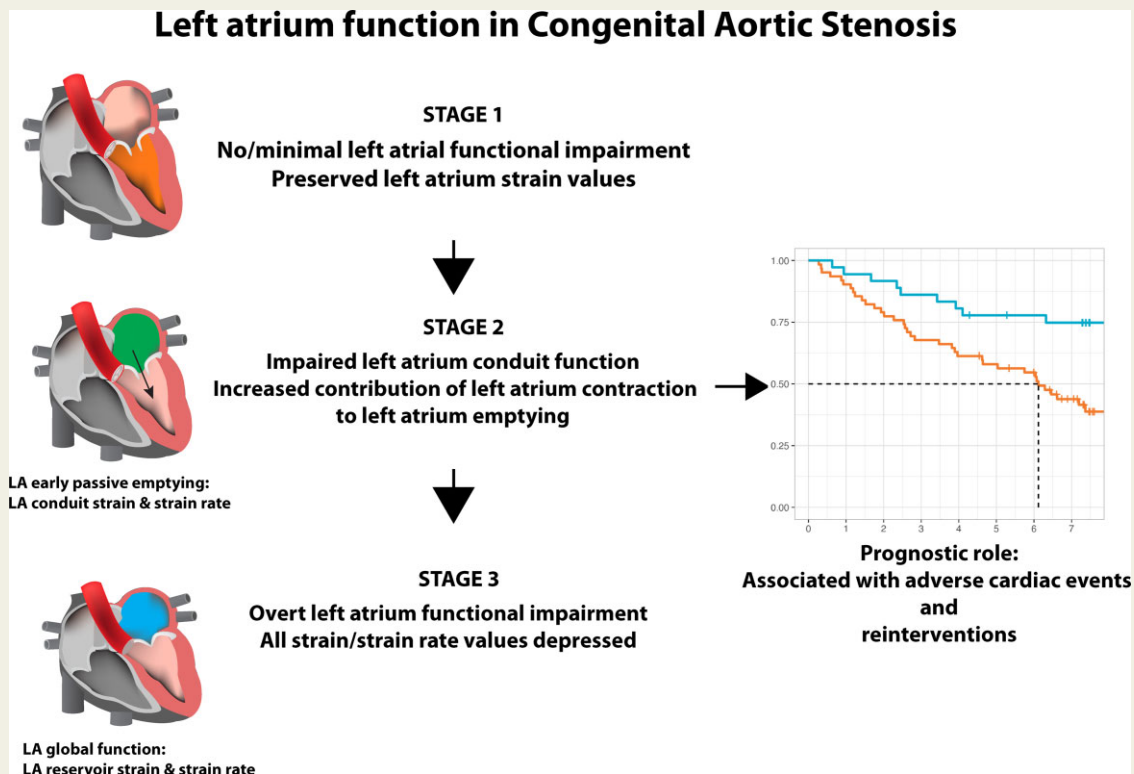
Impairment in LA conduit function assessed with STE carries prognostic value in patients with CAS and can be implemented in clinical management.

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Graphical Abstract



Staging of left atrial damage in congenital aortic stenosis.

Keywords

Left atrium • Strain • Speckle tracking echocardiography • Aortic stenosis • Congenital heart disease • Outcome

Introduction

Congenital aortic stenosis (CAS) accounts for 3–6% of congenital heart defects.¹ Accelerated valvular degeneration leading to severe aortic valve stenosis and regurgitation, and aortopathy leading to increased incidence of aortic complications in patients with CAS, necessitate close surveillance.² Several clinical factors related to prognosis have been defined; however, imaging biomarkers, particularly markers of diastolic dysfunction, might improve risk stratification and might have utility in the surveillance of asymptomatic patients with CAS.³

Increased filling pressures and diastolic dysfunction is the hallmark of aortic valve disease and might be evident in early stages, even in asymptomatic patients.⁴ The left atrium (LA) functions as a buffer between the pulmonary circulation and the left ventricle (LV), and as a conductance element for the blood passing to the LV during diastole. Thus, an assessment of LA structure and function plays an important role in the assessment of diastolic dysfunction.⁵ Left atrial maximal volume indexed (LAVi) for body surface area (BSA) forms the basis of assessing the LA and carries prognostic value in patients with aortic stenosis (AS). It was shown that AS patients with marked LA enlargement (LAVi > 50 mL/m²) have lower chances of survival than patients with mild-to-moderate enlargement.⁶ However, functional changes in LA usually precede structural changes. In addition, LA function is an

important determinant of LV filling pressures.⁷ Previous studies have shown that LA functional impairment might be present even when no structural changes are observed and might be an earlier indicator of cardiac damage in patients with AS.^{8,9} As a result, an assessment of LA functions in asymptomatic patients might be more sensitive in predicting outcomes in CAS patients compared with an assessment of structure.

Recently, speckle tracking echocardiography (STE) emerged as a novel modality for the assessment of LA function. Left atrial phasic functions could be assessed by means of phasic volumes or strain measurements with this modality. Previously, LA strain (LAS) was shown to predict the occurrence of symptoms and death in asymptomatic degenerative AS patients with normal left ventricular ejection fraction.¹⁰ Nevertheless, data regarding the role of LA phasic functions assessed with STE in patients with congenital AS are scarce.

The main aim of this study was to prospectively investigate LA function in adult patients with CAS and its relation with adverse cardiovascular outcomes.

Methods

Study population

This prospective observational study included clinically stable patients with CAS visiting the outpatient clinic between 2011 and 2015 at our

tertiary centre. Exclusion criteria were age <18 years, a prosthetic valve or baseline rhythm other than sinus rhythm, inability to understand and sign informed consent form; or poor echocardiographic image quality. The study was carried out in accordance with the Declaration of Helsinki and approved by the local ethics committee (EMC 05-01-43-01-05). Written informed consent was obtained from every participant. To be able to compare the LAS and LASR data, we used a control group consisting of self-declared healthy volunteers, described previously.¹¹

Data collection

Detailed medical history, physical examination, 12-lead electrocardiogram, transthoracic echocardiogram with STE analysis, and venous blood sampling were obtained on the same day at inclusion. Follow-up data were acquired during yearly clinical appointments and a thorough review of electronic medical records.

Echocardiographic acquisition

Two-dimensional greyscale harmonic images were obtained in the left lateral decubitus position using an iE33 or EPIQ7 ultrasound system (Philips Medical Systems, Best, The Netherlands) with a transthoracic broadband X5-1 matrix transducer (composed of 3040 elements with 1–5 MHz). Standard apical 4-chamber (A4C), 2-chamber (A2C), and 3-chamber (A3C) views were obtained for STE, with the focus in LV and LA zone, respectively. At least two consecutive heart beats were recorded. A standardized sequential segmental analysis protocol was used.¹² Conventional measurements were assessed according to the recommendations of the European Association of Cardiovascular Imaging.¹³ Left ventricular ejection fraction was measured using the modified Simpson rule. Images were stored in 'Digital Imaging and Communications in Medicine' format.

Speckle tracking analysis

Speckle tracking analysis was performed with dedicated commercially available software (Image Arena version 4.6 TomTec Imaging Systems, Unterschleissheim, Germany). Left atrial volumes, strain, and strain rate were measured according to the latest consensus document. Left atrial reservoir function was expressed as peak reservoir strain (LAS-r) and strain rate (LASR-r), conduit function as LA conduit strain (LAS-cd) and strain rate (LASR-cd), and contraction function as contraction strain (LAS-ct) and strain rate (LASR-ct), according to this consensus.¹⁴

R–R gating was used for the initiation of the strain calculation. The strain curve itself was used as the guide for determining the atrial end systolic, end-diastolic, and pre-contraction phases. The nadir of the strain curve was set as the zero strain reference point, the peak of the curve as the LAS-r, and the time point just before the steep decline corresponding to the LA contraction as the LAS-ct. LAS-cd was calculated with the formula $LAS-cd = -(LAS-r) - (LAS-ct)$ (Supplementary material online, Figure S1A).

Left atrial reservoir, conduit, and contraction strain rates were measured from the LASR curve. The value at the peak of the curve was recorded as the LA reservoir strain rate (LASR-r), the first dip during the diastolic phase as the conduit strain rate (LASR-cd), and the second dip during the diastole as the contraction strain rate LASR-ct (Supplementary material online, Figure S1B). Associations of inequality were used according to the absolute values for the conduit and contraction strain and strain rate, since these parameters take negative values. Left atrial maximal, minimal, and pre-contraction volumes were identified on the LA volume curve, which is automatically generated by the analysis software. The LA conduit volume (LAV-cd) was calculated by subtracting LA pre-contraction volume from the LAV-max. Left atrial contraction

volume (LAV-ct) was calculated by subtracting LA minimum volume (LAV-min) from LA pre-contraction volume. The volumes were indexed to the BSA for the statistical analysis. Global left ventricle strain (GLS) was analysed in the LV-focused apical 2-chamber, 3-chamber, and 4-chamber views, using the same analysis software.

Definition and assessment of outcomes

The primary composite outcome was defined as any of the following adverse events: all-cause mortality, heart failure (requiring initiation or change in heart failure medication, or requiring hospital admission), hospitalizations due to cardiovascular disease, arrhythmias requiring treatment, thromboembolic events, or surgical or percutaneous interventions. The secondary outcome was surgical or percutaneous re-interventions. All patients were prospectively followed by a yearly protocolized clinical evaluation. When necessary, we retrieved information from electronic patient charts and from correspondence with referring hospitals. The survival status of all patients was checked in the Municipal Population Register on 20 October 2020.

For patients with multiple events, event-free survival was defined as the time from enrolment to the occurrence of the first event. Patients without any cardiovascular event were censored on the day of the last contact with the patient. Every patient was treated according to the physician's discretion, while not being aware of the myocardial deformation measurements and in accordance with the European Society of Cardiology guidelines.

Statistical analysis

Normality was assessed using histograms and the Shapiro–Wilk test. Continuous data were presented as mean \pm SD in case of a normal distribution, and as median (25th–75th percentile) otherwise. Categorical data were presented as frequencies and percentages. The student's *t*-test or Mann–Whitney *U* test was used to assess differences between groups for continuous data depending on the distribution, and the χ^2 test or Fisher's exact test was used for categorical data as appropriate. To assess if the differences in LAS and LA volume parameters between patients and controls persist when adjusted for age and sex, linear regression analysis was additionally performed, with the strain and volume parameters as dependent variables and patient/control status as the independent variable.

To investigate the association of LAS, LASR, and volume parameters with case-control status as well as baseline characteristics, univariable and multivariable linear regression analyses were performed on the overall study group. Echocardiographic parameters were used as the dependent and clinical characteristics were used as the independent variables. The assumptions of homoscedasticity were tested by assessing the residual plots. The results are presented as beta's (β), which signify the difference in echocardiographic parameter (unit: percentage for LAS and 1/s for LASR) per unit of the clinical characteristic. Subsequently, multivariable linear regression models were estimated using backward elimination, to investigate which set of variables is independently associated with strain parameters. An elimination threshold of $P = 0.10$ was used. Age and gender were included in all of the multivariable models to account for the differences between the study groups. A complete case analysis was performed.

To compare clinical outcome between groups with depressed and preserved LAS-cd, the reference range for healthy individuals from a recent meta-analysis by Pathan *et al.*¹⁵ on healthy individuals was used. In this meta-analysis, a reference range of 20.7–25.2% was determined. Based on this data, we considered LAS-cd depressed when the values were $< -21\%$ and preserved when $\geq -21\%$. For LASR-cd, Youden's index was used to determine the cut-off point by assessing the area under

Table 1 Characteristics of the study population

Clinical assessment	Patients (n = 98)	Controls (n = 121)	P-value
Age (years)	35.0 ± 11.9	43.9 ± 13.8	<0.001
Sex (female, %)	58 (59.2)	67 (55.4)	0.529
BMI (kg/m ²)	25.3 ± 3.8	24.3 ± 3.2	0.047
BSA (m ²)	1.93 ± 0.21	1.87 ± 0.19	
Systolic blood pressure (mmHg)	128 ± 15.7	125 ± 13.9	0.104
Diastolic blood pressure (mmHg)	80 ± 11	80 ± 8	0.386
Heart rate (b.p.m.)	76 ± 14	62 ± 9	<0.001
QRS duration (ms)	104 ± 19	95 ± 8	<0.001
Hypertension (n, %)	11 (11.2)	0 (0)	<0.001
NYHA class I	97 (99)	121 (100)	1.000
Aortic valve stenosis location (n, %)			
None	13 (13.4)		
Subvalvular	14 (14.4)		
Valvular	69 (71.2)		
Supravalvular	1 (1)		
Bicuspid aortic valve (n, %)			
Initial repair	79 (88.8)		
Age at initial intervention (years)	19.3 ± 14.6		
No initial repair (n, %)	32 (32.7)		
Surgical (n, %)	60 (61.2)		
Percutaneous (n, %)	6 (6.1)		
Aortic re-intervention (n, %)	31 (31.6)		
NT-proBNP (pmol/L)	9.3 (5.2–18.3)		
Left ventricle dimensions			
LV end-diastolic dimension (mm/m ²)	25.9 ± 3.0	24.5 ± 2.7	<0.001
LV end-systolic dimension (mm/m ²)	16.2 ± 2.7	15.1 ± 2.3	0.002
LV end-diastolic volume (mL/m ²)	61 ± 14	63 ± 10	0.412
LV end-systolic volume (mL/m ²)	25 ± 7	25 ± 6	0.687
LV mass/BSA (g/m ²)	89 ± 21	62 ± 12	<0.001
Left ventricle systolic function			
LV ejection fraction (%)	59.0 ± 5.3	60.5 ± 4.8	0.024
LV-GLS (%)	-16.0 ± 2.6	-20.7 ± 2.0	<0.001
LV diastolic functions			
E-wave (m/s)	84 ± 21	70 ± 16	<0.001
A-wave (m/s)	60.0 ± 0.2	49.2 ± 0.2	<0.001
E/A-ratio	1.53 ± .62	1.57 ± 0.66	0.678
e' wave (cm/s)	8.4 ± 2.3	9.6 ± 2.5	0.002
E/e' ratio	10.9 ± 5.2	7.6 ± 1.8	<0.001
Aortic valve			
Aortic jet velocity (m/s)	2.7 ± 1.1	1.1 ± 0.2	<0.001
Aortic jet velocity ≥4.0 m/s	15 (15.3)	0 (0)	
Aortic regurgitation			
None/mild	69 (75)	121 (100)	<0.001
Moderate	21 (23)		
Severe	2 (2)		
Mitral valve			
Mitral valve regurgitation			
None or mild	98 (100)	121 (100)	<0.001
Moderate or more	0 (0)	0 (0)	

BMI, body mass index; BSA, body surface area; LV, left ventricle, LV-GLS, LV global longitudinal strain; NYHA, New York Class Association.

curve (AUC) for the primary outcome, since meta-analysis data are not available and there is wide variability between studies that reported this parameter with regard to reference range. The Kaplan–Meier method and log-rank tests were used to determine if impaired LAS-cd or LASR-cd is associated with event-free survival.

The association of baseline characteristics, LAS, and volume variables with outcomes was assessed using Cox proportional hazard models. Variables that showed *P*-values < 0.10 in the univariable analyses were included in subsequent multivariable analyses. Age and sex were included in all multivariable models. The number of events per variable was ensured to be >10. The final multivariable model included age, sex, *E/e'*, and BMI.

Tests were considered statistically significant when two-sided *P*-values were smaller than 0.05. Statistical analysis was performed using IBM SPSS Statistics, R software, and Graphpad Prism.

Results

Study population

Ninety-eight CAS patients and 121 healthy subjects were enrolled in this study (35 ± 12 years vs. 44 ± 14 years, *P* < 0.001, 59.2% vs. 55.4% female, *P* < 0.529, respectively). *Table 1* shows the baseline characteristics of the study population. The feasibility of the LAS measurements was 75.4% in the patient group and 82.3% in the control group (*P* = 0.205). The overall feasibility was 79.1%. The acquisition frame rate for STE was 54 ± 9/s.

Left atrial volume and function

When corrected for age and sex, indexed LAV-cd was lower, and LAV-ct was higher in patients than controls [β = -0.36 mL/m², 95% confidence interval (CI): -0.63 to 0.08, *P* = 0.011 and β = 0.46 mL/m², 95% CI: 0.19–0.73, *P* < 0.001]. While LAS-cd and LASR-cd were lower in patients (β = 6.8%, 95% CI: 4.5–9.0, *P* < 0.001 and β = 0.41/s, 95% CI: 0.31–0.50, *P* < 0.001), contraction strain was higher (β = -2.0%, 95% CI: -3.7 to 0.33, *P* = 0.019), and reservoir strain and strain rate were lower (β = -4.5%, 95% CI: -7.3 to 1.7, *P* ≤ 0.001 and β = -0.24/s, 95% CI = -0.33 to 0.16, *P* < 0.001, respectively) (*Table 2* and *Figure 1*).

The results of the univariable analysis for the strain and strain rate variables are shown in [Supplementary material online, Table S1](#). In the multivariable analysis, LAS-cd and LASR-cd were significantly lower in patients compared with controls (β = 5.0%, 95% CI: 1.3–8.8, *P* < 0.009 and β = 0.39/s, 95% CI: 0.23–0.56, *P* < 0.001) when adjusted for age, sex, BMI, LV-GLS, LAVI, and *E/e'*. Left atrial strain values were not significantly different in patients with and without significant LV hypertrophy and patients with and without previous surgical intervention ([Supplementary material online, Table S2](#)).

Association of LAS and LASR with LV-GLS

Both LAS-r and LASR-r, and LAS-cd and LASR-cd, showed a weak positive correlation with LV-GLS (for LAS-r and LASR-r, *r* = 0.15, *P* = 0.032 and *r* = 0.21, *P* = 0.003; for LAS-cd and LASR-cd, *r* = 0.26, *P* < 0.001 and *r* = 0.28, *P* < 0.001, respectively), whereas there was no significant correlation between LAS-ct or LASR-ct and LV-GLS (*r* = -0.11, *P* = 0.09 and *r* = -0.1, *P* = 0.34).

Follow-up and cardiovascular outcomes

Median duration of follow-up was 9.2 (9.0–9.4) years. The primary composite outcome of any adverse cardiovascular event occurred in 48 patients [median event-free survival: 6.5 (5.9–7.3) years]. Two patients died during follow-up. One patient died in following cardiac arrest due to undocumented reasons, following intensive care unit hospitalization. The other patient died during balloon angioplasty for coronary stent restenosis in left anterior descending artery. Thirty-seven patients were hospitalized due to various different reasons. Twenty patients experienced arrhythmic complications: one atrial flutter, six atrial fibrillation, four other supraventricular tachycardias, three ventricular extrasystoles requiring treatment, two sustained ventricular tachycardias, two ventricular fibrillations treated with shock, and two atrioventricular blocks needing permanent pacemaker. Seven patients experienced thromboembolic episodes: six ischaemic cerebrovascular events and one myocardial infarction. Secondary endpoint of re-interventions occurred in 33 patients during the follow-up period [median event-free survival: 7.4 (6.8–8.1) years]. While 20 patients had surgical intervention, 13 patients had percutaneous intervention (Supplementary material online, Table S3).

Prognostic role of left atrial strain and strain rate

Only LAS-cd and pLASRcd demonstrated significant discriminative ability for the primary composite and secondary outcomes (AUC = 0.44, 95% CI: 0.32–0.56, $P = 0.049$ and AUC = 0.69, 95% CI: 0.57–0.80, $P = 0.003$, respectively) (Supplementary material online, Table S4). Kaplan–Meier event-free survival curves were constructed for strata of high and low LAS-cd and LASR-cd values. Event-free median survival was 5.8 (5–6.7) vs. 7.8 (6.8–8.7) years (log-rank test $P = 0.008$) for patients with low vs. high LAS-cd for the primary outcome. For LASR-cd, AUC analysis for primary composite outcome yielded a cut-off of 0.615/s (Youden's index = 0.68, AUC = 0.63, $P = 0.015$). Kaplan–Meier analysis at this cut-off

demonstrated an event-free median survival of 5.3 (4.3–6.3) vs. 7.5 (6.7–7.3) years in patients with low vs. high LASR-cd (log-rank test $P < 0.001$), for the primary composite outcome (Figure 2A and B). Both of the parameters at the selected cut-offs were also associated with secondary outcome during follow-up (Figure 3A and B).

In univariable Cox regression analysis, LAS-cd, LASDR-cd, age, hypertension, BMI, e' , and E/e' were associated with primary composite and secondary outcomes during follow-up. In addition, BMI was associated with the primary composite outcomes, but not with the secondary outcome (Table 3). LAS-cd was not associated with the primary composite outcomes [hazard ratio (HR) = 0.31, 95% CI: 0.09–1.04, $P = 0.06$], when adjusted for age, sex, E/e' , and BMI but was associated with the secondary outcome (HR = 0.33, 95% CI: 0.11–0.99, $P = 0.049$) when adjusted for age and sex. LASR-cd was associated with the primary composite outcome (HR = 0.49, 95% CI: 0.26–0.89, $P = 0.02$) when adjusted for age, sex, E/e' , and BMI and secondary outcome (HR = 0.44, 95% CI: 0.23–0.82, $P = 0.01$) when adjusted for age and sex.

Discussion

The results of this study on patients with CAS showed in the cross-sectional analysis that LAS parameters corresponding to LA emptying are depressed when compared with healthy controls; and in the prospective study we found impaired LA passive emptying to be associated with adverse outcome.

Feasibility of the left atrial strain

Previous studies demonstrated the feasibility of LAS in healthy adults 83.3–96.7%.¹⁵ Our feasibility in the control group was close to this reference range. However, feasibility was considerably lower in patients with CAS. The lower feasibility in patients with CAS was mainly caused by poor tracking or LA foreshortening in a majority of the cases.

Table 2 Left atrium volumes, strain, and strain rate values in patients vs. controls

	Patients (n = 98)	Controls (n = 121)	P	Corrected for age and sex	
				B (95% CI)	P
Left atrium volumes					
LA maximum volume index (mL/m ²)	35 ± 12	35 ± 9	0.93	0.10 (−0.19–0.38)	0.50
LA minimum volume index (mL/m ²)	13 ± 6	13 ± 6	0.95	0.25 (−0.02–0.51)	0.07
LA conduit volume index (mL/m ²)	14 ± 6	15 ± 6	0.19	−0.36 (−0.63–0.08)	0.011
LA precontraction volume index (mL/m ²)	21 ± 9	20 ± 7	0.41	0.46 (0.19–0.73)	<0.001
Left atrial strain					
LA reservoir strain (%)	34.2 ± 11	36.3 ± 11	0.16	−4.5 (−7.3–1.7)	<0.001
LA conduit strain (%)	−18.1 ± 8.7	−23.5 ± 9.9	0.001	6.8 (4.5–9.0)	<0.001
LA contraction strain (%)	−14.9 ± 6.0	−12.8 ± 5.9	0.009	−2.0 (−3.7–0.33)	0.019
Left atrial strain rate					
LA reservoir strain rate (1/s)	1.02 ± 0.30	1.17 ± 0.33	<0.001	−0.24 (−0.33–0.16)	<0.001
LA conduit strain rate (1/s)	−0.73 ± 0.31	−1.02 ± 0.43	<0.001	0.41 (0.31–0.50)	<0.001
LA contraction strain rate (1/s)	−0.72 ± 0.26	−0.73 ± 0.29	0.80	0.01 (−0.07–0.09)	0.879

LA, left atrium; CI, confidence interval.

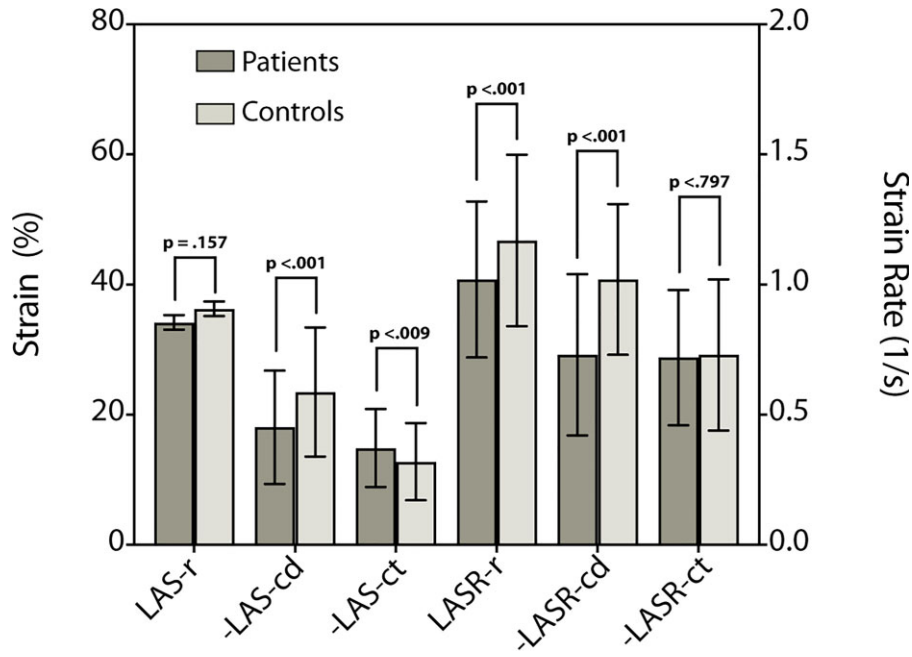


Figure 1 Strain and strain rate parameters in congenital aortic stenosis patients vs. healthy adults. LAS-r/LASR-r, left atrium reservoir strain and strain rate; LAS-cd/LASR-cd, left atrium conduit strain and strain rate; LAS-ct/LASR-ct, left atrium contraction strain and strain rate.

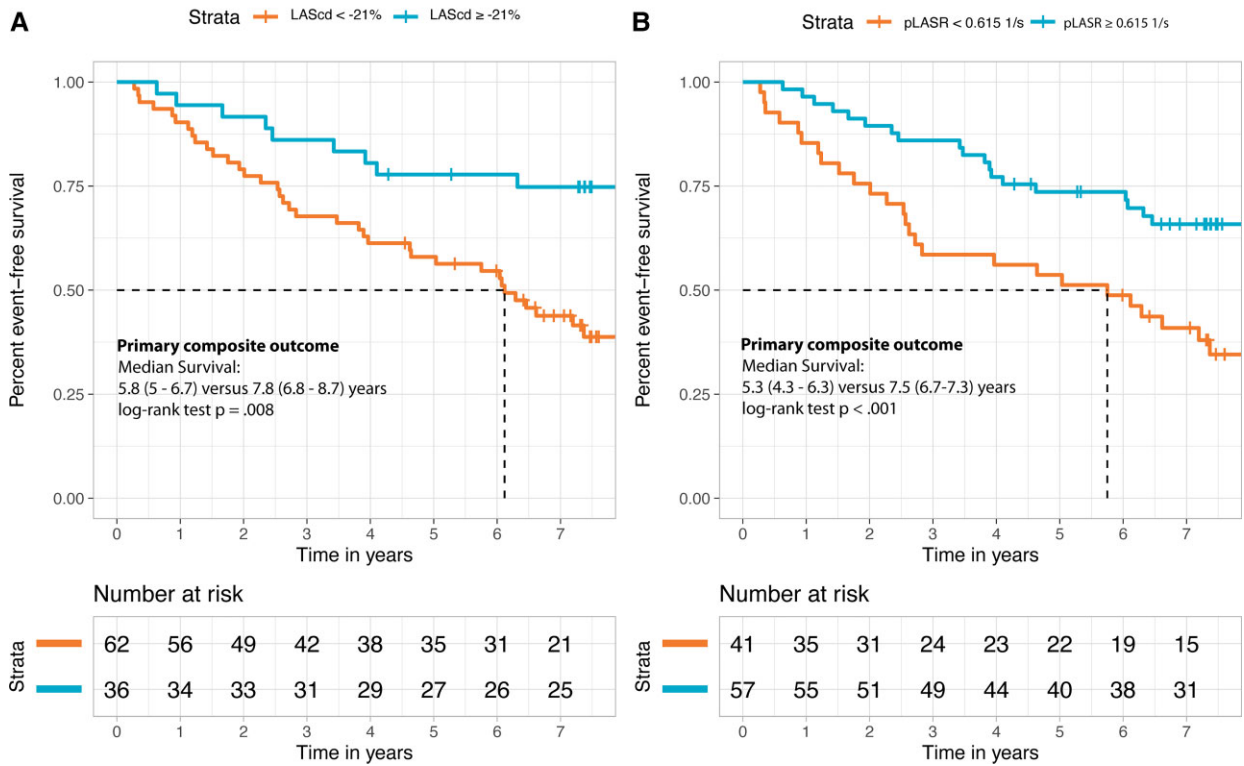


Figure 2 (A) Percent primary composite outcome-free survival in patients with depressed (<-21%) vs. preserved left atrial conduit strain and (B) patients with depressed (<0.615/s) vs. preserved left atrial conduit strain rate.

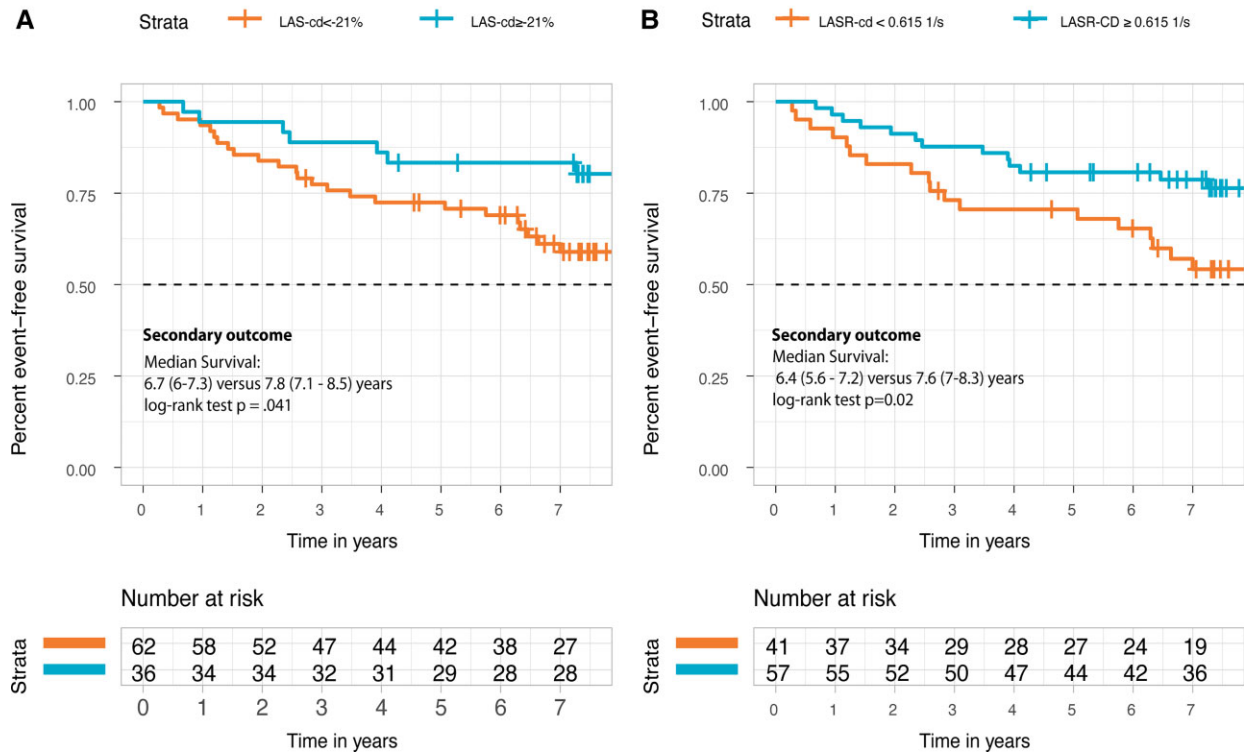


Figure 3 (A) Per cent secondary outcome-free survival in patients with depressed (< -21%) vs. preserved left atrial conduit strain and (B) patients with depressed (< 0.615/s) vs. preserved left atrial conduit strain rate.

Left atrial phasic functions

Left atrial adverse remodelling occurs in two domains: functional alterations and structural alterations. While the structural alterations manifest as changes in the volumes and dimensions, functional alterations are observed via changes in LA deformation parameters and phasic changes in volume parameters. The LAVi has been the established parameter for assessing the LA structural adverse remodelling. LAVi and LAminVi were demonstrated to be higher in patients with severe AS previously.⁹ In the current study, when corrected for age and sex, there was no difference with regard to LAVi or LAminVi between patients and controls. Of note, only 15 (15.3%) of the patients in our study had severe aortic stenosis. Additionally, the mean age of our patients was younger than the patient cohorts in the similar studies, which enrolled mainly AS patients with degenerative aetiology.^{8,10,16} A younger patient cohort with different pathophysiology (congenital vs. degenerative) and less severe disease most probably resulted in similar LA volumes.

In aortic stenosis, the proposed initial response to increased LV systolic pressures is myocardial hypertrophy to stabilize wall stress, at the expense of increased filling pressures as well as impaired early diastolic relaxation.¹⁷ Although decreased LAS-r values were reported in patients with degenerative AS, similar LAS-r and LAS-cd values but increased LAS-ct values were demonstrated in patients with valvular CAS vs. controls, previously.¹⁸ Similarly, we demonstrated a characteristic pattern of preserved LAS-r (≥24%) and decreased LAS-cd and LASR-cd, reflecting impaired passive relaxation; and

increased LAS-ct, pointing to an increased contribution of LA pump function to diastolic filling. The balance between LA active and passive emptying function might play an important role in compensating for increased filling pressures in early stages, while reservoir function becomes impaired later. Additionally, functional remodelling with an increased contribution of active emptying might reflect the adaptability of the heart to hemodynamic load.

According to these findings, we propose a three-stage LA functional impairment scale in patients with AS. In stage 1, there is no/minimal atrial functional impairment. In stage 2, functional impairment becomes evident with minimal or absent accompanying structural changes. LAS-cd and LASR-cd decrease with or without increases in measures of active emptying, such as active emptying volume, LAS-ct, and LASR-ct. Conventional Doppler-derived diastolic dysfunction measures might or might not be performed. In stage 3, LA function is impaired, and all the strain and strain rate values are decreased (Figure 4).

Prognostic role of left atrial strain and strain rate

Risk stratification and early intervention as indicated is of paramount importance in aortic valve disease, because once the symptoms such as angina, heart failure, or syncope occur, prognosis is dismal.¹⁹ LAVi predicted cardiac adverse outcomes in the general population and in patients with asymptomatic AS.^{20,21} Additionally, previous studies

Table 3 Univariable associations of clinical and echocardiographic parameters with the outcomes

Total number of events	Primary composite outcome (n = 48)		Secondary outcome (n = 33)	
	HR (95% CI)	P	HR (95% CI)	P
Left atrial strain parameters				
LA reservoir strain (%)	0.85 (0.63–1.14)	0.27	0.81 (0.57–1.16)	0.25
LA conduit strain (%)	0.64 (0.46–0.88)	0.005	0.58 (0.40–0.84)	0.004
LA contraction (%)	1.153 (0.81–1.65)	0.43	1.14 (0.74–1.74)	0.56
LA reservoir strain rate (1/s)	0.83 (0.62–1.12)	0.22	0.89 (0.62–1.27)	0.52
LA conduit strain rate (1/s)	0.676 (0.55–0.83)	<0.001	0.64 (0.50–0.82)	<0.001
LA contraction strain rate (1/s)	0.70 (0.77–1.47)	0.70	1.03 (0.71–1.49)	0.89
Clinical assessment				
Age (years)	1.05 (1.03–1.08)	<0.001	1.04 (1.01–1.07)	0.007
Sex (male)	0.76 (0.43–1.34)	0.35	0.83 (0.41–1.65)	0.59
Hypertension	0.19 (0.09–0.40)	<0.001	4.28 (1.89–9.71)	<0.001
BMI (kg/m ²)	1.08 (1.07–1.16)	0.04	1.06 (0.98–1.16)	0.16
Systolic blood pressure (mmHg)	1.02 (1.00–1.04)	0.10	1.02 (1.00–1.04)	0.10
Diastolic blood pressure (mmHg)	1.02 (0.99–1.05)	0.19	1.01 (0.98–1.05)	0.41
Heart rate (b.p.m.)	0.99 (0.97–1.01)	0.18	0.99 (0.97–1.02)	0.49
QRS duration (ms)	1.07 (0.99–1.02)	0.46	1.00 (0.98–1.02)	0.73
Echocardiography				
LV dimensions				
LV end-diastolic volume (mm)	0.99 (0.97–1.02)	0.57	1.01 (0.98–1.03)	0.63
LV end-systolic volume (mm)	0.99 (0.95–1.03)	0.58	1.00 (0.96–1.05)	0.91
LV mass/BSA (g/m ²)	1.00 (0.99–1.01)	0.92	1.00 (0.99–1.02)	0.87
Aortic jet velocity (m/s)	1.06 (0.80–1.40)	0.69	1.23 (0.88–1.73)	0.23
LV systolic function				
LV ejection fraction (%)	1.01 (0.95–1.07)	0.69	1.03 (0.96–1.10)	0.43
LV-GLS (%)	1.09 (0.99–1.22)	0.12	1.09 (0.96–1.24)	0.20
LV Diastolic function				
LA volume index (mL/m ²)	1.01 (0.99–1.03)	0.48	1.00 (0.97–1.03)	0.87
LV E-wave (cm/s)	1.63 (0.35–7.62)	0.54	0.79 (0.13–5.02)	0.80
LV E/A-ratio (cm/s)	0.52 (0.18–1.46)	0.22	0.60 (0.17–2.07)	0.42
LV e' (cm/s)	0.71 (0.60–0.85)	<0.001	0.68 (0.56–0.83)	<0.001
LV E/e'	3.12 (1.40–6.94)	0.005	3.16 (1.39–7.20)	0.009

LA, left atrium; LV, left ventricle; GLS, global longitudinal strain; HR, hazard ratio; CI, confidence interval.

demonstrated an independent prognostic role of LAS-r in patients with AS when adjusted for conventional parameters of diastolic function.^{8,16} Decreased LAS-r at cut-offs of 17%, 19.8%, and 21% were associated with an increased occurrence of adverse events.^{8,10,16}

Left atrial maximum volume index was not associated with primary composite or secondary outcomes in univariable analysis in this study. Among conventional echocardiographic parameters of diastolic function, e' and E/e' were associated with primary composite and secondary outcomes. In contrast to previous studies on degenerative AS, LAS-r or LASR-r were not associated with outcomes in univariable analysis. Of note, LV-GLS, the parameter that is proposed to mirror changes in LA phasic functions, was also not associated with primary or secondary outcomes. LAS-cd was associated with secondary outcomes, and LASR-cd was associated with primary and secondary outcomes, even when adjusted

for E/e' in the multivariable models. These findings show that LAS-cd and LASR-cd can be used as biomarkers with prognostic value independent of conventional measures of diastolic dysfunction in patients with CAS.

Limitations

This study was not designed to demonstrate the natural progression of LA functional adverse remodelling. Longitudinal echocardiographic follow-up is needed to validate the classification of LA functional adverse remodelling proposed herein for this reason. An extrapolation of the results from this study to patients with degenerative AS might not be appropriate due to differences in pathophysiology. Finally, due to inherent intervendor variability with LAS, the results should be interpreted taking into account the specified analysis software.

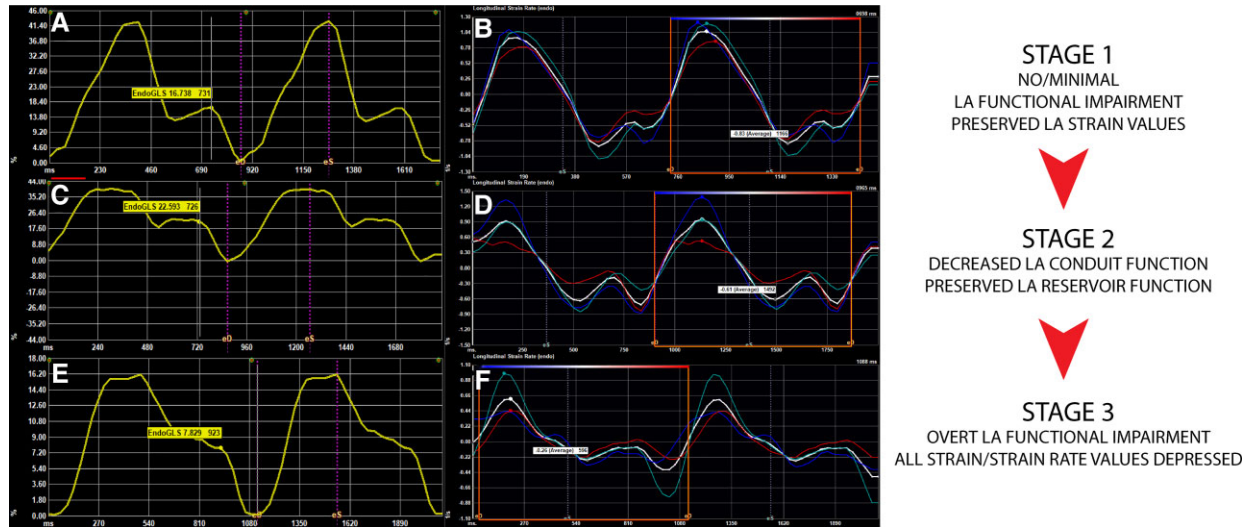


Figure 4 Left atrial strain (left panel) and strain rate (right panel) curves from congenital aortic stenosis patients at different stages of left atrial damage, (A and B). A congenital aortic stenosis patient with preserved left atrial strain and strain rate pattern, (C and D). A congenital aortic stenosis patient with depressed left atrial conduit strain and strain rate profile, (E and F). A congenital aortic stenosis patient with depressed left atrial reservoir, conduit, and contraction strain/strain rate pattern

Conclusion

A detailed evaluation of LA phasic functions with particular focus on conduit function is warranted in patients with CAS and is helpful in risk stratification.

Lead author biography



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Data availability

The data is available and permission might be sought per reasonable request.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Funding

Dr F.O.M. is the recipient of a Turkish Society of Cardiology Research Grant for the year 2019 and an European Association of Cardiovascular Imaging (EACVI) research grant for the year 2020.

Conflict of interest: None declared.

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