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Left atrial function and remodelling in aortic stenosis

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Aims The present study sought to determine the relationship between left atrial (LA) volume (structural changes) and LA function as assessed by strain rate imaging in patients with aortic stenosis (AS).

Methods and results The study consisted of a total of 64 consecutive patients with severe AS (<1 cm^2) and 20 healthy control subjects. The phasic LA volumes and function (tissue Doppler-derived strain) were assessed in all patients. As compared with healthy controls, all strain-derived parameters of LA function were reduced in patients with AS. Conversely, only indexed LA passive volume (increased) (7.6 ± 3.8 vs. 10.5 ± 5.1 ml/m^2, $P = 0.02$) and LA active fraction (decreased) (43 ± 6.7 vs. $31 \pm 13.3\%$, $P < 0.001$) (volume-based parameters) were significantly different between AS and controls. In AS, LA volume-derived function parameters were poorly correlated with LA strain parameters. In fact, by multivariable analysis, no LA phasic strain parameters emerged as independently associated with LA phasic volume parameters.

Conclusions In AS, changes in LA function did not parallel changes in LA size. Furthermore, the increase in LA volume does not necessarily reflect the presence of intrinsic LA dysfunction.

Keywords Left atrial phasic volume • Left atrial function • Strain • Strain rate • Aortic stenosis • Atrial function • Tissue Doppler imaging

Introduction

In aortic stenosis (AS), the chronically increased afterload is accompanied by several structural and functional changes as progressive left atrial (LA) enlargement and dysfunction.[1] In this situation, LA size may serve as a surrogate marker of chronic diastolic function and left ventricular (LV) filling pressure, whereas LA dysfunction may unmask the presence of an atrial myopathic disease process.[2,3] In severe AS, both LA dilatation and dysfunction have been shown to adversely affect the outcome. Assessing the relationship between LA size and function is thus of clinical importance. LA function has three components: reservoir, conduit and active functions. Reservoir function occurs during LV systole, the conduit function results from the blood transiting from the pulmonary veins into the LV during early diastole and finally, the active contractile function arrives in late diastole to increase LV filling.[4–6] LA function has been initially described by volumetric method in several diseases. In the recent years, tissue Doppler-derived strain imaging has also been recognized to adequately assess regional and global LA function in normal subjects and in increased afterload states such as hypertension and hypertrophic cardiomyopathy. In AS, whether LA structural changes are accompanied by changes in LA function have not yet been examined. The present study sought to (i) describe the impact of AS on LA size and (ii) assess the relationship between LA volume (structural changes) and LA function as assessed by strain rate imaging.

Methods

Population

Between April 2008 and February 2010, LA volumes and function were prospectively evaluated in 64 consecutive patients with AS (aortic valve area <1 cm^2) and in 20 healthy control subjects. None of the patients had concomitant significant valvular disease, chronic atrial fibrillation or a pacemaker dependant rhythm. Calcific degenerative AS was observed in 47 patients (73%), bicuspid valve was found in 16 patients (25%) and 1 patient (1.5%) had typical rheumatic

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involvement with commissural leaflet fusion. No history of coronary artery disease, cerebrovascular disease, valvular abnormalities or diabetes was found in control subjects. Three subjects of the control group had a well-controlled hypertension.

Echocardiographic measurements

Echocardiographic examinations were performed by using Vivid 7 ultrasound system (General Electric Healthcare, Little Chalfont, UK) equipped with a 3.5 MHz variable frequency harmonic-phased array transducer. Measurements of LV dimensions and LV mass were performed by M-mode as recommended by the European Association of Echocardiography. LV end-diastolic and end-systolic volumes and ejection fraction were measured by the bi-apical Simpson method. Continuous-wave Doppler was used to measure the aortic transvalvular maximal velocities; peak and mean gradients were calculated using the simplified Bernoulli equation. Aortic valve area was calculated using the standard continuity equation.[7,8] For each measurement, at least three cardiac cycles were averaged. The LV diastolic function was evaluated by the analysis of the mitral inflow velocities (E and A waves). By using pulsed wave tissue Doppler, peak velocities during systolic (Sa) early (Ea) and late (Aa) diastole obtained at the level of septal, lateral, inferior and anterior mitral annulus were measured separately and then averaged. The E/A and E/Ea ratios were then calculated.

Left atrial volumes

The following LA volumes were measured: (i) maximal LA volume or Vol_{max}, in ventricular systole just before mitral valve opening; (ii) minimal LA volume or Vol_{min}, after mitral valve closure and (iii) Vol_p, just before the 'P' wave on ECG (*Figure 1*). All volumes were calculated from the apical four- and two-chamber views using the Simpson biplane method of discs. Special attention was paid to start/end tracing at the mitral annulus and avoid pulmonary veins and auricle in the tracings. LA stroke volume (LASV) was estimated as the difference between Vol_{max} and Vol_{min}. The LA ejection fraction (LAEF) was calculated as $(LASV/Vol_{max}) \times 100$. Total LA volume is a composite of three distinct phases of the LA function: the passive emptying volume, the conduit volume and the active emptying volume. LA passive emptying volume $= Vol_{max} - Vol_p$; LA passive emptying fraction = LA passive emptying volume/Vol_{max}. LA active volume $= Vol_p - Vol_{min}$; LA active fraction = LA active volume/Vol_p. Finally, LA conduit volume = LV stroke volume − LASV. All volumes were indexed for body surface area.[9]

Left atrial function: strain and strain rate analysis

Colour-tissue Doppler imaging was performed in the apical four- and two-chamber views with a narrow sector width at high frame rate (≥150 /s). Careful attention was paid to align the atrial wall to the Doppler beam. A sample volume of 10 × 2 mm was placed from mid- to superior LA wall and tracked frame by frame to maintain its position within the LA walls. For each measurement, at least two end-expiratory cardiac cycles were averaged. Off-line peak strain and strain rate were obtained at the level of septal, lateral, anterior and inferior LA walls and then averaged to obtain global LA longitudinal function. The myocardial strain profiles (St) were calculated by integrating the strain rate over time and compensating for drift over the cardiac cycle. As active atrial contraction occurs in diastole, the strain curves were gated in diastole by moving the gating marker to the end of the T wave on the ECG. For strain rate, the global peak systolic (SrS), early diastolic (SrE) and late diastolic (SrA) strain rate were measured (*Figure 1*). During LV systole, LA acts as a reservoir, collecting blood from the pulmonary veins while mitral valve is closed, and so LA enlarges. Passive stretching of the LA walls, during LV systole leads to LA longitudinal lengthening, which is recorded as a positive strain rate (SrS) value. During early diastole, LA acts as a conduit for emptying (SrE) and as a booster pump during atrial contraction (PSt and SrA) in late diastole.[4,6]

The inter- and intra-observers variability for LA strain parameters were previously reported by our group.[4]

Statistical analysis

Continuous variables are expressed as mean ± SD, unless otherwise specified. Differences in continuous variables between groups were assessed by Student *t*-test. Categorical variables were analysed by the χ^2 test or Fisher exact test, as appropriate. Linear regression analysis was applied to evaluate the correlation between variables. To determine cofactors associated with parameters of LA function, a stepwise multiple linear regression was performed. All variables that were statistically significant univariately were entered in the model. The selection of variables included in the multivariate model was performed with a special care. To avoid colinearity among a subset of several variables measuring the same phenomenon, we entered in the multivariate models the variable that had the strongest association with univariate analysis. Data were analysed using Statistica Software (version 7).

Results

Characteristics of the population

Demographic and echocardiographic characteristics of the patients are described in *Table 1*. As compared with healthy controls, patients with AS were significantly older, had a higher prevalence of coronary risk factors, and received more frequently an antihypertensive treatment. Symptoms were reported by 20 patients (31%) in the group of AS patients. Despite similar LV diameters and ejection fraction, peak mitral Sa velocity as assessed by tissue Doppler imaging was significantly reduced in patients with AS compared with controls. The LV diastolic function was also altered in AS. The mitral E velocity was increased while the Ea and Aa were decreased. Consequently, E/Ea was significantly higher in patients with AS.

Left atrial volumes and function

LA phasic volumes and function are depicted in *Table 2*. When compared with controls, maximal, minimal, and pre '*P*' volumes were all significantly increased in patients with AS; 68% ($n = 42$) of them presented even a severe LA dilatation (indexed LA volume ≥40 ml/m^2). To note, LA enlargement was more pronounced ($P = 0.01$) in symptomatic patients with AS (*Figure 2*). LASV was also significantly increased ($P < 0.001$) while LAEF was more reduced in patients with AS ($P < 0.001$). With regard to LA phasic parameters, LA passive volume was higher while LA active fraction was lower in the AS group. Conversely, LA passive fraction was similar in both groups. After adjustment for age, differences between AS and control groups remained similar, except for LAEF (*Table 2*).

In patients with AS and severe LA dilatation, LA passive and active volumes were significantly increased while LA conduit

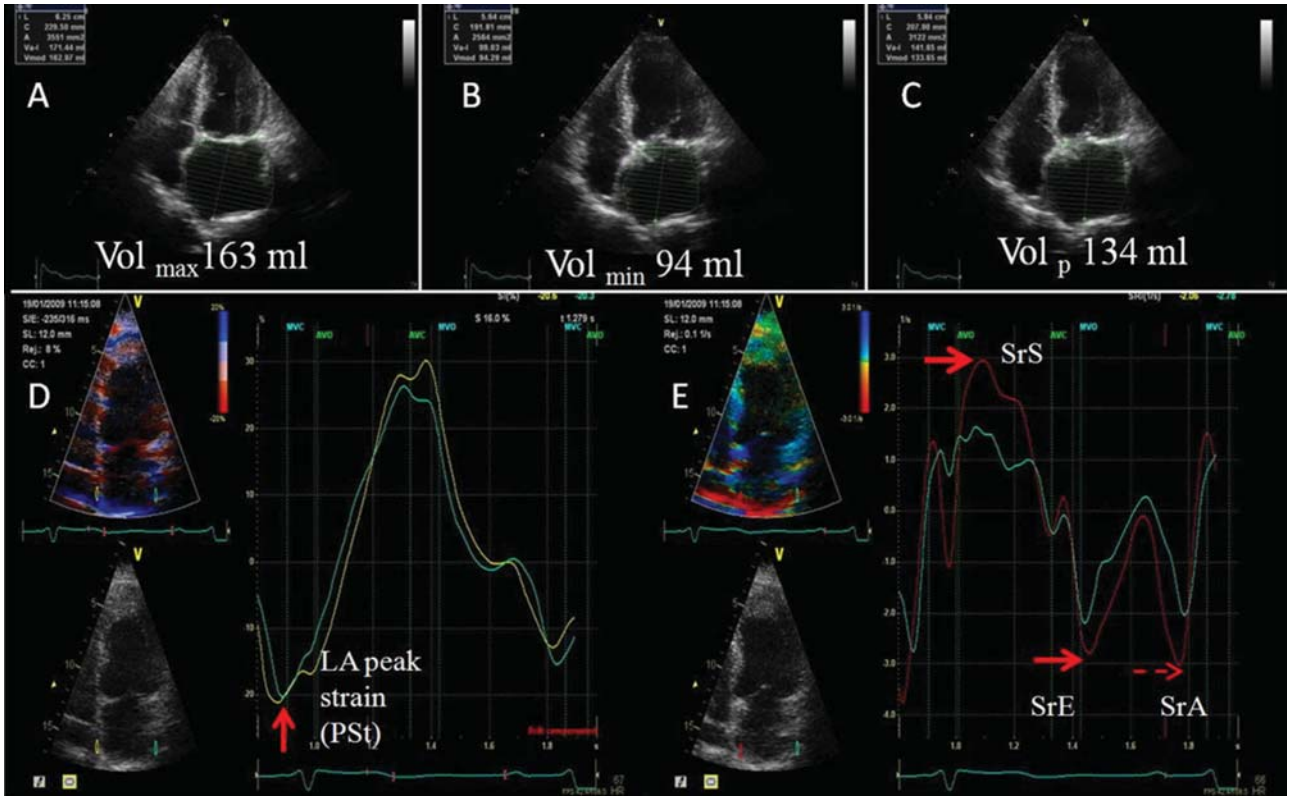

Figure 1 Examples of measurement of left atrial volumes and tissue Doppler strain imaging in a four-chamber view in a patient with aortic stenosis. (*A*) Left atrial vol_{max}, (*B*) left atrialvol_{p}, (*C*) left atrial vol_{min}, (*D*) left atrial peak strain curves in septal and lateral left atrial walls, and (*E*) left atrial strain rate curves in septal and left atrial lateral walls.

volume was significantly reduced compared with controls (*Figure 3*). Finally, regarding strain parameters, patients with AS had a significant reduction of all strain and strain rate values compared with the control group.

Correlations between left atrial phasic volumes and function in controls and aortic stenosis patients

Left atrial passive volume and fraction

In controls LA passive volume strongly correlated with age, peak Ea velocity, indexed LA vol_{max} and LAEF. Similarly, LA passive fraction had a good correlation with age, peak Ea velocity and LAEF in controls. In AS, LA passive volume was correlated with indexed LA vol_{max} and Doppler annular peak Sa velocities and inversely correlated with global LA PSt ($r = -0.29$, $P < 0.05$). LA passive fraction was modestly correlated with LV systolic function parameters (LVEF and peak systolic velocity), peak Ea velocity, E/Ea ratio and LAEF in patients with severe AS. By multivariable regression, after adjustment for age, both LA vol_{max} ($P < 0.001$) and Doppler annular peak systolic velocity ($P = 0.002$) emerged as independently associated with LA passive volume in AS ($R^2 = 0.37$). To note, no parameter was independently associated with LA passive fraction (Table 3).

Left atrial conduit volume

In controls, LA conduit volume was only correlated with indexed LA vol_{max}. In AS, LA conduit volume was correlated with aortic valve area, LV ejection fraction, Doppler annular peak Sa velocity, peak Ea velocity, peak Aa velocity, global LA SrS. There was also a significant negative correlation between indexed LA vol_{max} and LA conduit volume in these patients. By multivariable analysis, after adjustment for age, LV ejection fraction, peak Ea velocity, peak Aa velocity and E/Ea ratio, both aortic valve area ($P < 0.0001$) and indexed LA vol_{max} ($P < 0.0001$) were independently associated with LA conduit volume in AS ($R^2 = 0.62$).

Left atrial active volume and fraction

In controls, LA active volume correlated with indexed LA vol_{max}, global LA PSt and global LA SrA. LA active fraction was greatly correlated with LAEF, global LA PSt and global LA SrA. In AS, LA active fraction was correlated with LV ejection fraction, Doppler annular peak Sa velocity, peak Aa velocity and LAEF. A negative correlation was found between LA active fraction and mitral E wave velocity and indexed LA vol_{max}. LA active volume was not correlated with global LA Pst and global LA SrA. There was a modest negative correlation between LA active fraction and global PSt and LA SrA. By multivariable analysis, after adjustment for LV ejection fraction, mitral E wave velocity and indexed LA vol_{max}, peak Aa velocity was the sole parameter independently

Table 1 Demographic, clinical and echocardiographic characteristics

Variables	Controls ($n = 20$)	AS patients($n = 64$)	*P*-value
Demographic data			
Age (years)	54.9 ± 7.9	71.4 ± 13.0	<0.001
Male [*n* (%)]	10 (50)	37 (58)	NS
Heart rate (bpm)	75 ± 12	71 ± 11	NS
Body surface area (m^2)	1.83 ± 0.22	1.79 ± 0.18	NS
Body mass index (kg/m^2)	25.7 ± 3.4	25.6 ± 3.5	NS
Systolic blood pressure (mmHg)	135 ± 20	141 ± 25	NS
Diastolic blood pressure (mmHg)	78 ± 11	74 ± 12	NS
Clinical data			
Coronary artery disease [*n* (%)]	0	23 (37)	<0.001
Hypertension [*n* (%)]	3 (15)	45 (63)	<0.001
Diabetes [*n* (%)]	0	17 (27)	<0.001
Dyslipidemia (*n* (%)]	6 (20)	36 (57)	<0.05
Smoking [*n* (%)]	4 (20)	11 (17)	NS
Medication			
ACE inhibitors [*n* (%)]	2 (10)	21 (33)	<0.05
Angiotensin receptor blocker [*n* (%)]	1 (5)	11 (17)	<0.05
Calcium channel blocker [*n* (%)]	0	9 (14)	<0.001
β-Blockers [*n* (%)]	1 (5)	31 (49)	<0.001
Diuretics [*n* (%)]	2 (10)	29 (46)	<0.01
LV systolic parameters			
LV end-diastolic diameter (mm)	45.1 ± 5.6	48.1 ± 8.4	NS
LV ejection fraction (%)	64.4 ± 6.5	62 ± 13	NS
Peak mitral Sa velocity (cm/s)	9.5 ± 2.2	6.1 ± 1.6	<0.001
LV diastolic parameters			
Peak mitral E velocity (cm/s)	71.4 ± 17.4	94.9 ± 31.5	<0.01
Peak mitral A velocity (cm/s)	78.2 ± 20.9	89.5 ± 31.4	NS
E/A ratio	0.96 ± 0.28	1.2 ± 0.61	NS
Mitral E deceleration time (ms)	180 ± 47	225 ± 91	<0.05
Peak Ea velocity (cm/s)	11.2 ± 2.6	6.8 ± 2	<0.001
Peak Aa velocity (cm/s)	12.5 ± 1.6	8.9 ± 2.6	<0.001
E/Ea ratio	7.8 ± 3.1	19.1 ± 13.1	<0.001

NS indicates non-significant; ACE, angiotensin-conversion enzyme and LV, left ventricle.

associated with LA active fraction in AS ($R^2 = 0.22$, $P = 0.02$). A similar result was observed in controls ($R^2 = 0.27$, $P = 0.003$).

Discussion

In AS, both the extent of LA remodelling and dysfunction markedly affect the clinical outcome.[4–13] From a mechanistic point, whether the decrease in LA function is an epiphenomenon of the increased LA size is unknown. The present study confirms and extends previous reports by showing that both LA structural and functional changes are common in AS.[4,14] As compared with controls, volumes are increased and function of the LA is depressed. However, although all strain-derived parameters of LA function are declined, only indexed LA passive volume (increased) and LA active fraction (decreased) (volume-based parameters) are significantly different. Furthermore, changes in LA function appear not to parallel changes in LA size in AS.

Left atrial volumes in aortic stenosis

Clinically, LA volume is most commonly expressed by the LA vol_{max}.[4–6,10] In AS, LA size increases with severity of valve stenosis and worsening diastolic dysfunction and reflects the magnitude and the chronicity of the increased LV filling pressure.[8] In asymptomatic patients with severe AS, LA size has been shown to be a powerful prognostic marker.[1,10] To note, after aortic valve replacement, LA remodelling is also associated with clinical outcome.[13] In the present study, LA vol_{max} was related to all atrial phasic volumes. However, only LA passive volume (larger) and LA active fraction (reduced) were significantly different as compared with controls. In these patients, LA may achieve a maximal degree of expansion during LV systolic period to progressively accommodate the elevated LV filling pressures. To note, LA passive volume was even larger in symptomatic patients. In these patients, the increase in LA active emptying probably represents an ultimate compensatory

Table 2 Left atrial volumes and function

Variables	Controls ($n = 20$)	AS patients ($n = 64$)	*P*-value	Age-adjusted *P*-value
Indexed LA vol_{max} (mL/m^2)	29 ± 7.3	48.2 ± 19.9	<0.001	0.003
Indexed LA vol_{min} (mL/m^2)	12.2 ± 7.5	26.8 ± 28.3	<0.001	0.01
Indexed LA vol_p (mL/m^2)	21.4 ± 6.3	37 ± 18.3	<0.001	0.02
Indexed LASV (mL/m^2)	16.9 ± 5.1	21.1 ± 8.5	<0.001	0.04
LAEF (%)	58.1 ± 7.4	47.1 ± 13.4	<0.001	NS
Phasic LA volumes and function				
Indexed LA passive vol (mL/m^2)	7.6 ± 3.8	10.5 ± 5.1	0.02	0.01
LA passive fraction (%)	26.4 ± 10.4	23.6 ± 10.6	NS	NS
Indexed LA conduit vol (mL/m^2)	45.2 ± 18.2	35.3 ± 27.4	NS	NS
Indexed LA active vol, mL/m^2)	9.2 ± 3.4	10.6 ± 5.9	NS	NS
LA active fraction (%)	43 ± 6.7	31 ± 13.3	<0.001	0.02
Strain and SR parameters				
Global LA SrS (s^{-1})	2.43 ± 0.73	1.66 ± 0.58	<0.001	0.012
Global LA SrE (s^{-1})	−2.31 ± 0.89	−1.5 ± 0.61	<0.001	0.016
Global LA SrA (s^{-1})	−3.17 ± 0.65	−2.3 ± 0.94	<0.001	0.017
Global LA PSt (%)	−21.7 ± 6.2	−14.9 ± 6.3	<0.001	0.001

NS, non-significant; LA, left atrial; SV, stroke volume; LAEF, left atrial ejection fraction.

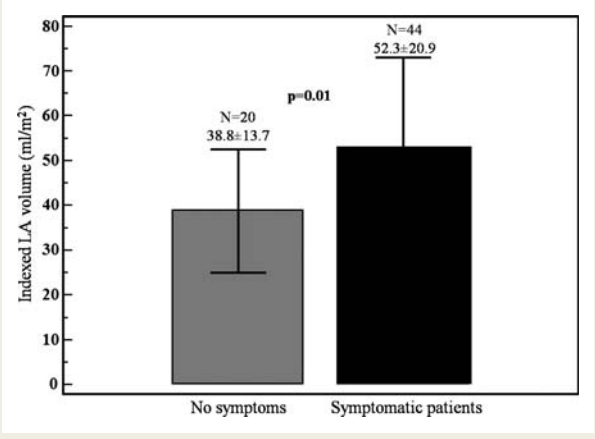

Figure 2 Indexed left atrial vol_{max} of patients with aortic stenosis according to the presence of symptoms. LA indicates left atrial.

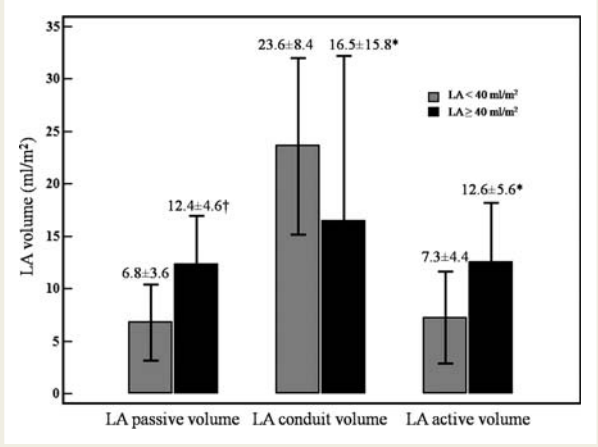

Figure 3 Left atrial phasic volumes in patients with or without severe left atrial dilatation. †$P < 0.01$, *$P < 0.05$.

mechanism to LA dilatation (Starling mechanism).[15] In other words, when cellular adaptation is exhausted, the increase in LV filling pressure may increase LA wall tension and myocyte stretch inducing myolysis, fibrosis, apoptosis and in turn LA enlargement.[1]

Left atrial function in aortic stenosis

In AS, preserved LA function helps in maintaining optimal cardiac output despite the impaired LV relaxation and reduced LV compliance. Reduction of LA active function may thus favour clinical deterioration, the occurrence of atrial fibrillation and alter the spontaneous outcome.[1,10,16] The accurate assessment of LA function is thus challenging. As for volumes, the different phases of LA function (reservoir, conduit and active contractile functions) can be adequately examined (tissue Doppler-derived strain imaging) during the cardiac cycle.[3,9] Contrary to LA phasic volumes, we found that all three components of LA function (strain and strain rate parameters) were reduced in AS, highlighting that the assessment of LA function by volumetric method or strain imaging is not equivalent. Indeed, the reduction in neither LA passive function—global LA SrS—nor in LA conduit function—global LA SrE—was related to the increase in LA passive volume or in LA conduit volume. Moreover, LA active function (global LA SrA) was moderately correlated with LA active fraction in AS. To note, this correlation was stronger in controls, suggesting that in AS the decrease in LA contraction does not purely parallel the increase in LA

Table 3 Correlations (*r*) of phasic left atrial volumes and function in healthy control subjects and aortic stenosis patients

Variables	Indexed LA passive volume		LA passive fraction		Indexed LA conduit volume		Indexed LA active volume		LA active fraction	
	Controls	AS	Controls	AS	Controls	AS	Controls	AS	Controls	AS
Age	−0.58†	−0.06	−0.58†	−0.22	0.20	−0.24*	0.21	0.02	0.19	−0.24
LV systolic function										
LVEF	0.01	−0.04	0.15	0.34†	0.23	0.35*	−0.14	−0.10	0.24	0.27*
Peak Sa velocity	0.26	0.25*	0.31	0.39†	0.01	0.38*	−0.05	0.04	0.13	0.28*
LV diastolic function										
E wave velocity	0.38	0.10	0.34	−0.29*	−0.38	−0.16	−0.11	0.07	−0.09	−0.33*
A wave velocity	−0.11	0.09	−0.05	0.04	0.02	0.13	−0.03	0.07	0.20	0.08
Peak Ea velocity	0.55*	−0.03	0.55*	0.05	−0.36	0.30*	−0.17	−0.09	−0.13	0.02
Peak Aa velocity	0.24	0.10	0.37	0.38†	0.07	0.33*	−0.16	0.01	0.22	0.39*
E/Ea ratio	−0.23	0.08	−0.23	−0.26*	−0.01	−0.4*	−0.05	0.13	−0.18	−0.17
AVA	–	0.12	–	0.25*	–	0.65†	–	−0.1	–	0.10
LA parameters										
Indexed LA vol_{max}	0.5*	0.51†	−0.09	−0.37†	−0.5*	−0.48†	0.79†	0.49†	0.09	−0.38*
LAEF	0.65†	0.14	0.76†	0.63†	−0.35	0.08	−0.05	0.22	0.56*	0.85†
Strain parameters										
Global LA PSt	0.10	−0.29*	0.30	−0.26*	0.07	−0.13	−0.66†	−0.19	−0.67†	−0.25*
Global LA SrS	0.38	0.20	0.27	0.23	−0.22	0.30*	0.20	0.03	0.30	0.18
Global LA SrE	−0.21	0.06	−0.11	−0.04	0.20	−0.20	−0.1	0.13	−0.2	0.02
Global LA SrA	0.11	−0.20	−0.05	−0.20	−0.05	−0.20	−0.5*	−0.16	−0.67*	−0.29*

LVEF, left ventricular ejection fraction; AVA, aortic valve area; LA, left atrial; LAEF, left atrial ejection fraction.
*$P < 0.05$.
†$P < 0.01$.

volume. In our study, late diastolic mitral annular velocity (peak Aa velocity) but not global LA SrA emerged as an independent parameter associated with LA active fraction in both AS and controls. Furthermore, although peak Aa velocity is reduced in AS, it remains highly load dependent, which may limit its accuracy to unmask the presence of LA dysfunction. Furthermore, it rather reflects the displacement of the mitral annulus than intrinsic LA function.[1,17] Conversely, global LA SrA seems to be less affected by loading conditions. LA SrA could represent a more accurate parameter for evaluating the LA contractile function and identify the presence of an atrial myopathic disease process.

Limitations

Patients with AS generally have other comorbidities, such as hypertension or coronary artery disease, and often required multiple medications. These factors may have a confounding impact on our data. Nonetheless, this limitation does not affect the validity of the main results of this study, which is the demonstration that the increase in LA volume does not reflect the presence of intrinsic LA dysfunction.

Evaluation of LA volume by echocardiography has some limitations. Three-dimensional echocardiography and cardiac magnetic resonance imaging can certainly improve the accuracy of the assessment of LA size, but are not widely available. LA function has been examined with tissue Doppler-derived strain imaging, which is well known to be angle dependant. All care was taken to ensure that tracking was in the LA wall and measurements performed with an angle of interrogation $<30^{\circ}$.

Conclusion

The LA phasic components can be assessed by both volume and tissue Doppler-derived methods. In AS, however, LA volume-based function parameters are poorly correlated with LA strain parameters. Furthermore, the increase in LA volume does not reflect the presence of intrinsic LA dysfunction.

Conflict of interest: none declared.

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