Prognostic value of diastolic function parameters in significant aortic regurgitation: the role of the left atrial strain

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Abstract
Background  The management of patients with asymptomatic significant aortic regurgitation (sAR) is often challenging and appropriate timing of aortic valve surgery remains controversial. Prognostic value of diastolic parameters has been demonstrated in several cardiac diseases. The aim of this study was to analyze the prognostic significance of the diastolic function evaluated by echocardiography, in asymptomatic patients with sAR.

Methods  A total of 126 patients with asymptomatic sAR evaluated in the Heart Valve Clinic were retrospective included. Conventional echocardiographic systolic and diastolic function parameters were assessed. Left atrial (LA) auto-strain analysis was performed in a sub-group of 57 patients. A combined end-point of hospital admission due to heart failure, cardiovascular mortality, or aortic valve surgery was defined.

Results  During a median follow-up of 34.1 (interquartile range 16.5–48.1) months, 25 (19.8%) patients reached the combined end-point. Univariate analysis showed that LV volumes, LV ejection fraction (LVEF), LV-GLS, E wave, E/e’ ratio, LA volume and LA reservoir strain (LASr) were significant predictors of events. Multivariate analysis that tested all classical echocardiographic variables statistically significant in the univariate model showed that LVEDV (HR = 1.02; 95% CI 1.01–1.03; \(p\) < 0.001) and E/e’ ratio (HR = 1.12; 95% CI 1.03–1.23; \(p\) = 0.01) were significant predictors of events. Kaplan–Meier curve, stratified by median value of LASr, showed that lower LASr values (less than median of 34%) were associated with higher rates of events (\(p\) = 0.013).

Conclusion  In this population of asymptomatic patients with sAR and normal LV systolic function, baseline diastolic parameters were prognostic markers of cardiovascular events; among them, LASr played a significant predictor role.

Keywords  Echocardiography · Aortic regurgitation · Diastolic function · Strain
Abbreviations

AUC   Area under the curve
LA  Left atrial
LASct  Left atrial strain contractile
LASr  Left atrial strain reservoir
LAScd  Left atrial strain conduit
LV  Left ventricle
LVEF  Left ventricle ejection fraction
LV-GLS  Left ventricular global longitudinal strain
sAR  Significant aortic regurgitation
SD  Standard deviation
SPAP  Systolic pulmonary artery pressure
TTE  Transthoracic echocardiography
TR  Tricuspid regurgitation

Introduction

The management of patients with asymptomatic significant aortic regurgitation (sAR) is often challenging and appropriate timing of aortic valve surgery remains controversial.

According to the latest guidelines, among patients with sAR, surgery is formally recommended when it causes symptoms, severe LV dilation (end-systolic diameter > 50 mm), left ventricular ejection fraction (LVEF) ≤ 50% or if there is a concomitant indication for cardiac surgery (i.e., significant enlargement of ascending aorta) [1].

There are no strong indicators to recommend early surgery in patients with sAR. However, delaying the time for the intervention could bring potential negative consequences, such as the risk of permanent LV dysfunction, heart failure or sudden cardiac death [2]. In this context, the identification of markers that are early altered in the natural history of the sAR, could be useful to improve the management of these asymptomatic patients.

The prognostic value of diastolic parameters has been demonstrated in several cardiac diseases. In particular, left atrial (LA) function has been shown to be an important determinant of morbi-mortality. More specifically, LA strain is a promising tool for the detection of subclinical cardiac dysfunction [3].

The purpose of this study was to analyze the prognostic significance of diastolic function parameters by echocardiography, included LA strain, in asymptomatic patients with sAR and to evaluate whether these parameters could help to identify patients at high risk of adverse events that could benefit from early cardiac surgery.

Methods

From February 2013 to November 2019, consecutive asymptomatic patients with chronic sAR evaluated in the Heart Valve Clinic were retrospective included.

Exclusion criteria included patients who already met criteria for cardiac surgery at the time of the inclusion (presence of symptoms, LV dilation or dysfunction, indication for other cardiac surgery), other concomitant significant valve disease (more than mild degree evaluated with echocardiography), LV dysfunction, the presence of atrial fibrillation or pacemaker rhythm.

Local Ethical Committee approved the study.

Echocardiogram protocol analysis

The closest transthoracic echocardiogram (TTE) study to the first medical visit in the Heart Valve Clinic was used as baseline analysis. TTE was performed using the commercially available echo systems in the Imaging Unit, according to the standard protocol [4, 5]. Measurements were reviewed and re-performed by trained echo-cardiographers.

The severity of AR was assessed using an integrated method including a combination of several measurements (vena contracta width, pressure half-time of the AR jet, the presence of diastolic retrograde flow in aorta, and the LV size) according to the established practice guidelines [1, 6]. Aortic regurgitation was considered severe by the presence of the following criteria: the width of the vena contracta > 6 mm, pressure half-time < 200 ms, the presence of holo-diastolic retrograde flow in aorta and some degree of LV enlargement.

LV size was evaluated by its diameters from the parasternal long axis view and by its volumes from the apical four chamber view. LVEF was measured using Teicholz method and apical biplane Simpson’s method.

LV diastolic function was evaluated following the established recommendations from the American Society of Echocardiography and the European Association of Cardiovascular Imaging [7], which included the following parameters:

- Trans-mitral flow was recorded by pulsed wave Doppler echocardiography, from apical four chamber view, by placing the sample volume at the tips of the mitral leaflets. Peak E wave velocity, peak A wave velocity, E to A wave ratio (E/A) and E wave deceleration time were determined.

- Tissue Doppler imaging was performed in the apical four chamber view and pulsed wave Doppler sample volume was placed in the septal and lateral mitral annulus. The peak annular systolic wave velocities were recorded (e’ septal and e’ lateral). From these measurements, the mitral E/e’ septal and E/e’ lateral ratios were calculated, as well as the mean of both results (E/e’ ratio).

The severity of tricuspid regurgitation (TR) was assessed using an integrated method, according to the established practice guidelines [6]. The systolic pulmonary artery pressure (SPAP) was estimated using TR peak velocity and right atrial pressure, which was estimated by the inferior
vena cava diameter from long-axis sub-xiphoid view and its response to inspiration.

LA size was measured at its antero-posterior diameter from the long axis parasternal view in the end-systolic period, and by LA volume, that was measured using the biplane area length method.

In a sub-group of patients with TTE performed in the Philips stations, LA and LV auto-strain analysis was performed with an offline workstation (auto-strain TOMTEC). To measure the LA auto-strain, from the apical four chamber view focus in the LA with a minimum loop length of 2 beats, the software uses Advanced Automatic View Recognition technology to identify LA and automatic contour placement, which automatically detects and places the LA border. The software automatically provides the measurement of the average strain for the three major LA functions throughout the cardiac cycle: reservoir (LASr), conduit (LAScd) and contractile (LASct) values. The reference point for deformation analysis was at end diastole (Fig. 1). We select this point as the timing of initial length for atrial strain assessment because it is easier to identify the R wave than the P wave and to make it possible to generalize its use for all the patients independently of the basal cardiac rhythm. In the same way, for the LV-GLS, apical four, two and three chamber views were selected. The software automatically identifies each view, detects and places the LV border, and provides the measurement of the LV-GLS.

Clinical outcomes

Combined clinical end-point included hospital admission due to heart failure, cardiovascular mortality, or aortic valve surgery for having reached the indications for surgery and excluding those undergoing surgery due to aortic dilatation or dissection. Clinical data were obtained from hospital’s records.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD). Categoric variables were described as number and percentage. For comparison, 2 normally distributed variables, Student’s t test for continuous variables and chi-squared test for categorical variables were used. The analysis was adjusted for age and sex.

To evaluate diastolic parameters that could serve as early markers of cardiovascular outcome, the following Cox regression models were constructed: (a) a univariate model with all the variables of interest collected; (b) a multivariate model including parameters currently used to indicate surgery (LVEDV, LVESV and LVEF) and the most relevant conventional diastolic function parameters that were statistically associated with the composite end-point in the univariate analysis (E, E/e’ ratio and LA volume. SPAP was excluded in the analysis because its echocardiographic

![Fig. 1 Left atrial (LA) auto-strain analysis. From the apical four chamber view focus in the LA. The software automatically detects and places the LA border and provides the measurement of the average strain for the three major LA function throughout the cardiac cycle: reservoir (LASr), conduit (LAScd) and contractile (LASct) values. The reference point for deformation analysis was at end diastole.](image-url)
evaluation was only possible in 39 patients). The backward elimination method was used for selection of covariates.

Area under the receiver operating characteristic curve (AUC) was used to evaluate LASr accuracy to predict cardiovascular events. The Kaplan–Meier survival curves for patients above and below the median value of LASr, were performed to summarize the follow-up experience of the study population. LASr was the LA strain parameter used for the analysis for being the strongest LA strain parameter available with more reliable scientific evidence.

Interaction was studied.

This was a hypothesis-generating and exploratory study; therefore, no formal sample size calculation was performed in advance.

The statistical analyses were performed using SPSS software version 26.0 (SPSS Inc, Chicago, Illinois, United States) and R version 3.3.2.

Results

A total of 126 patients were included. Mean age of the patients was 70 ± 17.0 years. Among them, 25 (19.8%) had bicuspid valve, 75 (59.5%) were men, 78 (62.4%) had hypertension, 44 (35.3%) suffered from dyslipidemia and 11 (9.6%) had concomitant coronary artery disease with preserved LVEF.

During a median follow-up of 34.1 (interquartile range 16.5–48.1) months follow-up, 25 (19.8%) patients reached the combined end-point (n = 5 developed heart failure, n = 25 underwent surgery, and n = 4 died due to cardiovascular etiology). Another 3 patients that had undergone valve surgery exclusively due to aortic dilatation and another 7 patients that had died from an extra-cardiac etiology were not included in the cardiovascular event group. Clinical and echocardiographic characteristics of both groups (control and cardiovascular event group) are displayed in Table 1.

Univariate analysis showed that LV volumes, LVEF, LV-GLS, E wave, E/e’ ratio, LA volume, PSAP and LASr were significant predictors of events, whereas LA diameter and LV diastolic diameter were not. Statistical significance was maintained in the analysis adjusted for age and sex (Table 2).

Multivariate model, that tested all echocardiographic variables statistically significant in the univariate model showed that the E/e’ ratio (p < 0.01) and LVEDV (p < 0.001), were significant predictors of events (Table 2).

In a sub-group of 57 patients, LA auto-strain analysis was obtained. During the same follow-up period, 8 (14%) patients developed the combined end-point (7 patients underwent surgery, one of them developed previous heart failure and died due to cardiovascular etiology). Another 3 patients that underwent valve surgery exclusively due to aortic dilatation were excluded from the cardiovascular event group.

Area under the receiver operating characteristic (AUC) curve was used to evaluate LASr accuracy to predict cardiovascular events (AUC = 0.78 p = 0.012) (Fig. 2). Kaplan–Meier curve, stratified by median value of LASr, showed that lower LASr values (less than median of 34%) were associated with higher rates of events (p = 0.013) (Fig. 3).

Discussion

In this population of asymptomatic patients with sAR and normal LV systolic function, baseline echocardiographic diastolic function parameters were prognostic markers of cardiovascular events; among them, LASr played a significant predictor role. In addition, our results also showed that LV volumes had greater prognostic value that LV diameters in patients with asymptomatic sAR.

In accordance with current clinical practice guidelines [1], aortic valve replacement in patients with sAR should be limited to symptomatic patients or those with LV dilatation/dysfunction. However, there are possible advantages of an early surgery in valvular heart disease to prevent sudden cardiac death, persistent LV systolic dysfunction or worse perioperative and postoperative outcomes. In addition, considering the development of new percutaneous treatments less aggressive than cardiac surgery, identifying those conditions associated with a worse prognosis and who may benefit from an early intervention, seems important.

The evaluation of diastolic function and left ventricular filling pressures is very important in the characterization and prognosis of most heart diseases, including valvular diseases. Echocardiography is the technique of choice for its evaluation. The latest diastolic function guidelines [7] recommend routine evaluation of mitral flow, calculation of mitral annulus velocities by tissue Doppler, LA volume and SPAP, for the analysis of diastolic function.

Previous studies have analyzed the role of the diastolic function in sAR undergoing aortic valve replacement. Ma et al. described that LV diastolic dysfunction, analyzed by the integration of 2 echocardiographic parameters (LA volume index and E/e’ ratio) is highly prevalent in patients undergoing aortic valve replacement and might improve after surgery [8]. In a similar way, Cayli et al. [9] reported that diastolic function is a reliable parameter in predicting outcomes in patients with sAR and LV dysfunction. They found that preoperative diastolic dysfunction had an adverse impact on the recovery of the cardiac function after surgery and justified this finding due to the correlation of the myocardial fibrosis and worse diastolic function. Kim et al.
also found that preoperative E/e’ ratio was correlated with postoperative improvement of LVEF [10].

To the best of our knowledge, this study is the first to evaluate the clinical relevance of baseline diastolic function parameters in patients with asymptomatic sAR. In our sample, E wave, E/e’ ratio, SPAP and LA size and function have significant prognostic value in these patients. Among the analyzed diastolic function parameters, we found that LASr played a significant predictor role in outcomes, stronger than LA diameter. In patients with sAR, the volume and pressure overload promote LV dilatation and eccentric hypertrophy; in this context, LA function estimated by strain can be reduced even in the absence of LA dilatation, mainly due to interstitial fibrosis, and reflects LV filling pressure. In fact, LA volume has been

![Table 1 Baseline patient characteristics according to the occurrence of the composite outcome during follow-up](image)

Values are expressed as mean±standard deviation for continuous variables and No. (%) for categorical variables

CV cardiovascular, BMI Body mass index, BNP B-type natriuretic peptide, TR tricuspid regurgitation, SPAP Systolic pulmonary artery pressure, LVEDD left ventricular end diastolic diameter, LVESD left ventricular end systolic diameter, LVEDV left ventricular end diastolic volume, LVESV left ventricular end systolic volume, LVEF left ventricular ejection fraction, LV-GLS left ventricular global longitudinal strain, LASr left atrial strain reservoir, LAScd left atrial strain conduit

*Adjusted for age and sex

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shown to have low sensitivity in the early detection of LA dysfunction in the setting of LV diastolic dysfunction [11].

A great advantage of LASr is that a single measurement provides more information than other composite indices used to analyze diastolic function. LASr is a complex measurement that takes into account multiple functional, structural, and hemodynamic factors. These include LA internal pressure, LA stiffness, relaxation property of the atrial myocardium, LV longitudinal shortening (passive stretch of LA myocardium during ventricular systole), ventricular elastic recoil, stroke volume and pulmonary circulation. Therefore, not only atrial pressure directly influences LARr. This ability of LASr to combine all this information in a single measurement makes it a very useful clinical tool.

There are few data available on the prognosis implications of LA function in sAR. Salas Pacheco et al. [12] demonstrated that in patients with severe aortic disease (AR and aortic stenosis), LASr was the main variable associated with pulmonary hypertension, they considered that the

### Table 2
Cox Regression Analysis between echocardiographic parameters and outcome events

| Parameter                  | Univariate analysis | Multivariate analysis |
|----------------------------|---------------------|-----------------------|
| LVEDV (ml)                 | 1.01 (1.01–1.02)    | <0.001                |
| LVEF (ml)                  | 3.85 (1.44–10.33)   | 0.007                 |
| LV-GLS (%)                 | 0.95 (0.90–1.00)    | 0.053                 |
| E                          | 1.02 (1.00–1.03)    | 0.015                 |
| A                          | 1.01 (1.00–1.03)    | 0.128                 |
| E/e’ ratio                 | 1.10 (1.04–1.17)    | 0.002                 |
| TR (grade)                 | 1.63 (0.77–3.44)    | 0.200                 |
| SPAP (mmHg)                | 1.10 (1.02–1.16)    | 0.008                 |
| LA volume (ml)             | 1.02 (1.00–1.04)    | 0.013                 |
| LASr ED                    | 0.93 (0.87–0.99)    | 0.021                 |
| LV-GS (%)                  | 1.32 (1.04–1.69)    | 0.025                 |
| LA diameter (mm)           | 1.02 (0.94–1.10)    | 0.637                 |
| LVEDD (mm)                 | 1.03 (0.97–1.10)    | 0.377                 |

Univariate analysis: all the echocardiographic systolic and diastolic function parameters assessed. Multivariate analysis: parameters currently used to indicate surgery (LVEDV, LVEF and LVEF) and conventional diastolic variables statistically significant in the univariate model (E, E/e’ ratio, LA volume) except SPAP because it is available only in 39 patients.

CI confidence interval, HR hazard ratio, LVEDV left ventricular end-diastolic volume, LVEF left ventricular end-systolic volume, LVEF left ventricular ejection fraction, LV-GLS left ventricular global longitudinal strain, TR tricuspid regurgitation

**Fig. 2** Receiver operating characteristic (ROC) curve used to evaluate LASr accuracy to predict cardiovascular events. Area under curve (AUC)=0.78; p=0.012 demonstrated that LASr value was accurate to predict cardiovascular events in patients with sAR

**Fig. 3** Kaplan–Meier analysis for cardiovascular events. Kaplan–Meier analysis stratified by median value of LASr (less than median of 34%) showed that lower LASr values were associated with significantly higher rates of cardiovascular events (p=0.013)
maintenance of LASr function may be one explanation for the absence of pulmonary hypertension in some patients with severe aortic disease. In isolated aortic stenosis, LA enlargement is recognized as a marker of aortic stenosis severity as well as predictor of postoperative clinical outcomes independently of mean trans-aortic gradient and LV mass [13]. Even more, LASr has been shown as an independent predictor of prognosis in patients with aortic stenosis [14].

We used automated quantification technique for the LA strain assessment, which has the potential advantages of time-saving and greater accuracy and reproducibility of the measurements [15]. Its implementation could lead to simplify these measurements, making it possible to obtain the deformation parameters in the daily clinical practice.

Finally, although the objective of the study was to analyze diastolic function in patients with sAR, an interesting finding has been that LV volumes have more prognostic value than LV diameters. This finding is in accordance with current guidelines [5] that considered the LV size and function should be routinely assessed by calculating volumes and the biplane method to assess LVEF. However, the indications for valve replacement in sAR are still based on LV diameters [1]. Previous studies described that LV long axis diameter is closely related with LV systolic and diastolic function in patients with chronic severe AR and that LV long axis function is impaired prior to deterioration of LV global systolic function in these patients, which might indicate subclinical LV dysfunction [16]. Therefore, a global assessment of the LV size and function seems necessary, beyond that provided by the determination of isolated diameters.

Although further studies, with large sample size, are required to establish cut-off points, we believe that careful assessment of diastolic function including LA strain, could be useful to identify high risk patients who could benefit from shortening follow-up periods and early aortic surgery.

Limitations

Our study was an analysis from clinical database, from single referral center with limited number of patients and cardiovascular events. Diastolic parameters are difficult to assess in valvular patients with volume overload; however, they have been analyzed in other volume overload valvulopathies, such as mitral regurgitation, with confirmed prognostic value. Due to the retrospective nature of the study, LA auto-strain was not available throughout the sample.

This was a hypothesis-generating and exploratory study; therefore, no formal sample size calculation was performed in advance. This limitation and the small number of events in the follow-up may lead to an overfitting problem in the multivariate analysis. However, all the parameters were also significant in the univariate model.

Further prospective studies with larger sample size are required to confirm and validate our findings.

Conclusion

In patients with asymptomatic sAR, baseline diastolic parameters were significant predictors of cardiovascular events in the follow-up. LASr was a significant prognostic marker. LV volumes had greater prognostic value that LV diameters in patients with asymptomatic sAR.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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