Left atrial volume index in patients with asymptomatic severe aortic stenosis

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Abstract  Background: The proper timing for aortic valve surgery in the asymptomatic patient with severe aortic stenosis (AS) remains challenging. The aim of this study was to determine the left atrial volume index (LAVI) in asymptomatic patients with severe AS in comparison to symptomatic severe AS patients and its relation to the degree of left ventricular (LV) hypertrophy and tissue Doppler measures of LV diastolic function.

Methods: Thirty-four patients with severe AS and preserved LV function, divided into two groups were studied. Group I comprised 17 patients with symptomatic severe AS, and Group II comprised 17 patients with asymptomatic severe AS. Echocardiographic assessment of LV dimension, function, and calculation of LV mass were done. LA volume index was obtained by the biplane Simpson method. Transmitral E, A diastolic velocities, deceleration time (DT) and E/A ratio were measured. Peak S’, early (E’0) and late (A’) diastolic velocities of the lateral mitral annulus were measured by tissue Doppler imaging.

Results: LAVI was significantly higher in symptomatic compared to asymptomatic patients with severe AS (p < 0.0001). LAVI with a cutoff point of 39.5 ml/m² was a predictor of symptoms in patients with severe AS yielded an area under the curve of 0.958, P < 0.0001, with a sensitivity of 94% and specificity of 89%. LAVI had a significant positive correlation with left ventricular mass (p < 0.014), right ventricular systolic pressure (RVSP) (p < 0.009), mitral peak E (p < 0.025), and E/E’ (p < 0.008). Multiple linear regression analysis revealed that LV mass (p < 0.0001) and E/E’ (p < 0.0001) were the independent predictors of increased LAVI in severe AS.

Conclusion: Left atrial volume index can predict symptoms in patients with asymptomatic severe AS. Left ventricular mass and E/E’ were the independent predictors of increased LAVI.

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1. Introduction

Aortic stenosis (AS) is currently the most predominant valvular pathology in older adults. The disease continuum is mostly asymptomatic until the restriction on forward flow overcomes the compensatory mechanisms. The classic symptoms of severe
AS include angina, syncope, and dyspnea, all of which remains the major demarcation point in the disease’s course. The current guidelines recommend aortic valve replacement for severe AS in symptomatic or asymptomatic patients when there is impairment of left ventricular (LV) function, defined as an ejection fraction < 50%. Reduction in LV ejection fraction occurs late in the natural history of AS and most patients with severe AS have a normal LV ejection fraction even when symptoms are present. Conversely, LV hypertrophy and abnormal non-invasive measures of LV diastolic function are common in these patients.

The proper timing for aortic valve surgery in the asymptomatic patient with severe AS remains challenging. Challenges routinely encountered in the evaluation of AS in the older population are related to the difficulty in recognition of symptoms due to age-associated decrease in activity, symptom attribution to other conditions that are common in the elderly, complexity of associated multiple co-morbidities and variations in individual functional capacity.

The left atrial (LA) size is a recognized marker of increased left ventricular (LV) filling pressure and is increased in patients with severe AS and is relatively independent of loading condition so that in the absence of mitral valve disease or atrial fibrillation, LA size reflects the duration or the history of the disease.

Although M-mode LA dimension is easy to acquire, its validity has recently been challenged. Because the LA is an asymmetrical cavity, LA size is more accurately reflected by a measurement of volume rather than area or linear dimension. Furthermore, LA dilatation might not be evenly distributed in all planes, and measurement of antero-posterior dimension is likely to be insensitive to changes in LA size.

2. Aim of the work

The aim of this study was to determine the left atrial volume index (LAVI) in asymptomatic patients with severe AS in comparison to symptomatic severe AS patients and its relation to the degree of LV hypertrophy and tissue Doppler measures of LV diastolic function.

3. Patients and methods

3.1. Study population

The present study comprised 34 patients (mean age 61.2 ± 11.9 years) referred to our echocardiography laboratory between April 2010 and July 2012. The selected patients met the following inclusion criteria: (1) severe aortic stenosis, defined as an AV area of ≤1.0 cm² using the continuity equation, mean gradient ≥40 mmHg, and peak velocity ≥4.0 m/s; and (2) Normal left ventricular systolic function, defined as a LV ejection fraction of ≥50%. Degenerative calcific AS was observed in 28 patients (82.3%), and bicuspid aortic valve was the cause of AS in the remaining 6 patients (17.6%). None of the patients were rheumatic. Informed consent was taken from all patients.

They were divided into two groups according to the presence or absence of symptoms (including dyspnea, angina, and syncope):

- Group I comprised 17 patients with symptomatic severe AS.
- Group II comprised 17 patients with asymptomatic severe AS.

3.2. Exclusion criteria

- Patients with clinically significant mitral valve stenosis or regurgitation or more than mild aortic regurgitation.
- Patients with LV systolic dysfunction (LVEF < 50%).
- Atrial fibrillation.
- Previous myocardial infarction.
- Diabetes mellitus.
- Renal insufficiency.
- History of stroke or peripheral vascular disease.
- Inadequate image quality.

3.3. History and clinical examination

The patients’ symptoms were obtained including the presence or absence of dyspnea according to NYHA classification, history of angina and syncope. Clinical examination was performed especially for patient’s height, weight, heart rate, and blood pressure on the day of echocardiogram. All patients were in sinus rhythm.

3.4. Echocardiography

Complete M-mode, two-dimensional and Doppler echocardiograms were performed using GE (vivid 3 pro) NORWAY, using 2.5 MHz multifrequency transducer.

Left ventricular ejection fraction was measured using a single plane measurement from the apical four-chamber view using the modified Simpson’s method.

Left ventricular mass was calculated from end-diastolic septal wall thickness (SWT, cm), LV dimension (LVDD, cm), and LV posterior wall thickness (PWT, cm), using the following equation:

\[
\text{LVmass (g)} = (0.80 \times 1.04(\text{LVDD + PWT + SWT}^{3}) - \text{LVDD}^{3}) + 0.6
\]

LV hypertrophy was considered present when LV masses indexed by body surface area were ≥104 g/m² in women and ≥116 g/m² in men.

The continuous-wave velocity examination was performed in multiple windows to obtain maximal jet velocity. The peak and mean transaortic valve gradients were calculated using the modified Bernoulli equation.

The AV area was calculated by continuity equation using the velocity–time integral of the aortic and LV outflow tract flows, and indexed by body surface area (AVA indexed [AVAII]).

Aortic valve area = \(\frac{(\text{LVOTTVI} \times \text{LVOT area})}{(\text{AVTVI})}\)

The LA volume was obtained by the biplane Simpson method in apical 2- and 4-chamber views using the built-in software of the machine. For this purpose, LA areas were manually traced at end-systole in apical four- and two-chamber views, ensuring that there was no foreshortening of the atrium. The area was...
then planimetered with the inferior LA border defined as the plane of the mitral annulus, excluding the confluence of the pulmonary veins and the LA appendage. A horizontal line is drawn across the mitral annular plane, and LA area does not include the funnel of the mitral valve leaflets (Figs. 1 and 2). The apical long-axis view was used instead of the two-chamber view if the left atrium in the latter view appeared foreshortened. Automatic volume calculation was performed using the software for the modified Simpson’s disc summation method resident in the echo machine. LA volume was indexed to body surface area and expressed as LA volume index (ml/m²).

Normal values: LA volume/BSA (ml/m²): Normal reference range: 22 ± 6 ml/m². An LAVI value ≥ 32 ml/m² is considered significantly increased and an LAVI value ≥ 40 ml/m² is considered severely increased.13,22

Left atrial anteroposterior diameter was measured in the parasternal long-axis view by M-mode using the leading edge of the posterior aortic wall to the leading edge of the posterior atrial wall, or where M-mode was not feasible, by two-dimensional echocardiography in the same view using the largest diameter during left ventricular end systole. LA diameter of 40 mm was considered as the cut-off for normal on the basis of common clinical practice.14,15

In the apical four chamber view, using a 1–2 mm sample volume, PW Doppler cursor is placed between the mitral leaflet tips during diastole. From the mitral inflow profile, the E- and A-wave velocity, E-deceleration time (DT), and E/A velocity ratio were measured.23

The right ventricular systolic pressure was determined from peak TR jet velocity, using the simplified Bernoulli equation and combining this value with an estimate of the RA pressure: RVSP = 4(V)² + RA pressure.24

Peak systolic (S0) and early (E0) and late (A0) diastolic velocities of the lateral mitral annulus were measured by pulsed wave tissue Doppler imaging from the apical four-chamber view. The ratio E/E0 was calculated.25

3.5. Statistical analysis

All data were analyzed using a SPSS software package (version 17.0, SPSS Inc. Chicago, Illinois, USA). Continuous variables were expressed as mean ± SD, and categorical variables were expressed as percentage. Comparison of categorical and continuous variables was performed using Chi-square test and independent t-test, respectively. The correlation between LAVI and clinical, echocardiographic data was determined with Spearman and Pearson correlation analysis. Receiver-operating characteristics (ROC) curve was used to detect the cut-off value of LAVI that predict symptoms in patients with severe AS. The optimal cut-off point was selected as the point on the curve that had the shortest distance to the top-left corner. Multivariate regression analysis was performed to define the independent variables associated with LAVI. A P value of < 0.05 was considered statistically significant.

4. Results

Demographic data of symptomatic and asymptomatic aortic stenosis patients are summarized in Table 1, there was no difference in both groups as regards age, gender, height, weight, BSA, and BMI. Patients with asymptomatic severe AS had higher systolic blood pressure.

The echocardiographic characteristics are listed in Table 2. Symptomatic AS patients had higher peak aortic velocity (4.5 ± 0.29 vs. 4.3 ± 0.30; p < 0.009), mean aortic gradient (58.7 ± 5 vs. 50.7 ± 5.9; p = 0.0001), PWT (14.88 ± 1.21 vs. 12.58 ± 1.09; p < 0.002), and LA diameter (45.58 ± 2.82 vs. 40.70 ± 2.33; p = 0.0001), while AV area was lower in symptomatic severe AS (43.58 ± 3.83 vs. 40.70 ± 2.33; p = 0.002), and LA diameter (45.58 ± 2.82 vs. 40.70 ± 2.33; p = 0.0001), while AV area was lower in symptomatic severe AS (0.72 ± 0.09 vs. 0.82 ± 0.08, p < 0.002). There was no significant difference in LVEF, LVSD, and LVDV between symptomatic and asymptomatic severe AS.

Left atrial volume index was significantly higher in symptomatic patients with severe AS (41.94 ± 1.98 vs. 37.11 ± 2.99, p = 0.0001, Table 2, Fig. 3).

Patients with symptomatic severe AS had lower late (A0) diastolic velocities of the lateral mitral annulus (10.76 ± 1.67 vs. 12.17 ± 1.50, p < 0.015), while E/E0 was significantly higher in symptomatic severe AS (12.58 ± 1.55 vs. 9.8 ± 1.2, p < 0.0001, Table 3). No significant difference between both groups as regards mitral peak, E, A, mitral E/A ratio, deceleration time, peak systolic (S0) and early (E0) diastolic velocities of the lateral mitral annulus was found (Table 3).

The Receiver-operating characteristics curve (ROC) for left atrial volume index (LAVI) as a predictor of symptoms in patients with severe aortic stenosis showed that LAVI with a
A cutoff point of 39.5 ml/m² yielded an area under the curve (AUC) of 0.958, \( P < 0.0001 \), with a sensitivity of 94% and specificity of 89% (Fig. 4).

Left atrial volume index (LAVI) had a significant positive correlation with left ventricular mass (\( r = 0.584, \ p < 0.014 \)), RVSP (\( r = 0.611, \ p < 0.009 \)), mitral peak E (\( r = 0.542, \ p < 0.025 \)), and E/E (\( r = 0.616, \ p < 0.008 \), Fig. 5). No significant relation to other demographic and echocardiographic data was reported.

Multiple linear regression analysis with left atrial volume index (LAVI) as dependent variable revealed that left ventricular mass (\( p < 0.0001 \)) and E/E \( 0 \) (\( p < 0.0001 \)) were the independent predictors of increased LAVI in asymptomatic patients with severe AS (Table 4).

5. Discussion

Increased LA volume has been shown to be an important marker of an adverse event in various cardiac diseases.26–30 However, studies in patients with AS have been limited to the assessment of postoperative outcome.31,32

At 5 years, the probability of remaining symptom free for asymptomatic patients with severe AS was only 33%, and the probability of remaining free of cardiac events, including cardiac death or AV surgery was only 25%.33 Standard clinical and echocardiographic characteristics are imperfect in identifying patients at risk.33

Early elective AVR could represent a beneficial option in those with low comorbidities. Recently, Kang et al. 2010 reported that, compared with the conventional approach (i.e.,
wait for symptoms), early surgery in patients with asymptomatic AS and preserved LVEF was associated with better postoperative LV mass improvement, lower occurrence of postoperative LV dysfunction, and higher long-term survival. The aim of this study was to determine the left atrial volume index (LAVI) in asymptomatic patients with severe AS in comparison to symptomatic severe AS patients and its relation to the degree of LV hypertrophy and tissue Doppler measures of LV diastolic function.

The higher peak aortic velocity, mean aortic gradient, LV mass, PWT, SWT, and RVSP in symptomatic AS were expected with increased severity of long standing disease (Table 2). The significantly higher LAVI in symptomatic patients reflects chronic exposure of the LA to abnormal LV diastolic function and the resultant increased LA filling pressure. Consequently, LA pressure increases in order to maintain adequate LV filling. This causes an increase in LA wall tension, resulting in stretching and dilatation of the LA. No difference was found in pulsed wave tissue Doppler S0 that estimates global longitudinal LV contractile function (Table 3).

Our study showed no significant difference in mitral peak E, A wave, E/A ratio, and DT in both groups which reflects that the increased atrial contribution to LV filling is the same in symptomatic and asymptomatic severe AS patients, and excessive afterload rather than severity of LV diastolic function is the predominant determinant of symptoms for most patients with AS. This finding may be comparable with Abhayaratna’s description that LA volume is useful for monitoring long-term hemodynamic control, whereas Doppler and tissue Doppler assessment of instantaneous filling pressure is better suited for monitoring hemodynamic status in the short term.

Mitral annulus late diastolic velocity (A0) was lower in symptomatic patients (Table 3) and emerged as strongly associated with LA contractile function. A decrease in intrinsic LA contractile function and reduced LV compliance at end-diastole may thus contribute to the attenuated active LA emptying in AS. No difference was found in pulsed wave tissue Doppler S’ that estimates global longitudinal LV contractile function (Table 3).

In the present study, the E/E0 ratio, an estimate of LV filling pressure, was significantly increased in patients with symptomatic AS. This parameter emerged as the main determinant of LA reservoir function. This means that the elevated LV filling pressure caused by increased LA pressure may impede

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Comparative analysis of pulsed wave mitral flow and tissue Doppler imaging of the lateral mitral annulus data between asymptomatic and symptomatic AS patients.</th>
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</thead>
<tbody>
<tr>
<td>Mitral peak E (m/s)</td>
<td>0.70 ± 0.059</td>
</tr>
<tr>
<td>Mitral peak A (m/s)</td>
<td>1.16 ± 0.16</td>
</tr>
<tr>
<td>Mitral E/A ratio</td>
<td>0.82 ± 0.06</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>214.7 ± 16.02</td>
</tr>
<tr>
<td>TDI E’ (cm/s)</td>
<td>7.5 ± 0.74</td>
</tr>
<tr>
<td>TDI A’ (cm/s)</td>
<td>12.17 ± 1.50</td>
</tr>
<tr>
<td>TDI S’ (cm/s)</td>
<td>6.79 ± 0.70</td>
</tr>
<tr>
<td>E/E0</td>
<td>9.8 ± 1.2</td>
</tr>
</tbody>
</table>

TDI = tissue Doppler imaging, DT = deceleration time.
adequate LA filling in patients with AS. Kim et al. 2010 reported that the E/E\textsubscript{0} ratio, an estimate of LV filling pressure, was significantly increased in patients with AS.

In a study carried by Ralph et al. 2010, there was a modest but statistically significant association between increasing severity of AS and lower E\textsubscript{0} and higher E/E\textsubscript{0} in asymptomatic patients. However, after adjusting for peak velocity in multivariate analysis there was no significant association between any measure of diastolic function at baseline or during follow-up and subsequent symptomatic deterioration.

In the current study, LAVI ≥ 39.5 mL/m\textsuperscript{2} was found to be an independent predictor of symptoms in severe AS with sensitivity of 94% and specificity of 89% (Fig. 4). Dahl et al. 2011 studied patients with preoperative severe AS and reported that event-free survival in patients with left atrial volume index of ≥ 40 mL/m\textsuperscript{2} at 1 year was 71% compared with 88% in patients with left atrial volume index less than 40 mL/m\textsuperscript{2}.

Grace et al. 2010 reported that left atrial enlargement was significantly correlated with symptom development but the association diminished after adjusting for aortic valve area and peak velocity. It was a retrospective study and they did not measure the left atrial volume.

In patients with severe AS, we found that left ventricular mass and E/E\textsubscript{0} were independent predictors for increased LA volume index (Table 4). Dahl et al. 2011 reported that preoperative left atrial dilation in severe symptomatic AS was associated with left ventricular hypertrophy and increased filling

**Figure 5** Correlation between LAVI and LV mass, right ventricular systolic pressure, E/E\textsuperscript{0}, and mitral peak E.

**Table 4** Linear regression analysis with LAVI as dependent variable.

<table>
<thead>
<tr>
<th></th>
<th>Beta</th>
<th>P</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass (g/m\textsuperscript{2})</td>
<td>0.066</td>
<td>0.001</td>
<td>0.033–0.099</td>
</tr>
<tr>
<td>RVSP (mmHg)</td>
<td>0.072</td>
<td>0.062</td>
<td>–0.004–0.147</td>
</tr>
<tr>
<td>Mitral peak E (m/s)</td>
<td>0.125</td>
<td>0.065</td>
<td>–0.008–0.258</td>
</tr>
<tr>
<td>E/E\textsuperscript{0}</td>
<td>1.27</td>
<td>0.001</td>
<td>0.860–1.695</td>
</tr>
</tbody>
</table>
pressure, and persistent abnormalities in left ventricular filling pressure and left ventricular mass index at 1 year after surgery.\textsuperscript{41}

Pellikka et al. 2005 showed that LV hypertrophy was found to be an independent predictor for the development of symptoms in a study of 622 patients with asymptomatic, but hemo-dynamically significant AS with a peak systolic velocity > 4 m/s.\textsuperscript{33} However Ralph et al. 2010 reported that neither echocardiographic LV mass nor electrocardiographic LV hypertrophy predicted symptomatic deterioration after accounting for the severity of the valve stenosis.\textsuperscript{40}

Dalsgaard et al. in 2008 studied patients with mild to moderate AS and showed that the LA volume is related not only to the AV area, but also to the LV mass, concomitant mitral regurgitation, a history of hypertension, LV end-diastolic volume, and a restrictive filling pattern.\textsuperscript{11} Same wise, Saraiva et al. in 2010 studied patients with severe aortic stenosis and LV systolic dysfunction; they showed that the LA volume and total and active LA emptying fractions displayed the strongest correlations with the right ventricular systolic pressure, irrespective of the aortic valve (AV) area or gradient.\textsuperscript{43}

Hence, increased LAVI is not just a benign compensatory mechanism but likely reflects severe consequences of pressure overload in AS with important implications for outcome. We believe that monitoring progression of AS by mean gradient and aortic valve area alone is insufficient. Therefore, LA volume needs to be a part of comprehensive echocardiographic examination and to be considered in timing of surgical treatment in patients with asymptomatic severe AS.

5.1. Study limitations

The limitations of the present study include the small sample size, and we did not take into account the effects of aging and hypertension on LA function, and lastly the absence of evaluation of the presence and extent of coronary artery disease in these patients.

6. Conclusion

Left atrial volume index can predict symptoms in patients with asymptomatic severe AS. Left ventricular mass and E/E' were independent predictors for increased LAVI.

Conflict of interest

None declared.

References


