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Impact of estimated left atrial volume on prognosis in patients with asymptomatic mild to moderate aortic valve stenosis

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ABSTRACT

Background: The prognostic impact of increased left atrial (LA) volume in mild-to-moderate aortic valve stenosis (AS) is unclear. We investigated the association of estimated LA volume with prognosis in a large prospective study of patients with asymptomatic mild-to-moderate AS.

Methods: The association of estimated LA volume with major cardiovascular events (MACE, combined cardiovascular death, heart failure hospitalization and non-hemorrhagic stroke) was assessed in 1534 patients with initially mild-to moderate asymptomatic AS, participating in the Simvastatin Ezetimibe in Aortic Stenosis study for a median of 4.3 years. LA volume was estimated from LA diameter applying a validated nonlinear equation and indexed to body height in meters squared (eLAVI). An enlarged eLAVI was identified by using sex-specific cut-offs (>19 ml/height^2 in men and >17 ml/height^2 in women).

Results: Patients with enlarged eLAVI were older, more obese, and had higher systolic blood pressure and left ventricular (LV) mass index (all $p < 0.001$). During follow-up, incident MACE occurred in 137 patients, more often in patients with enlarged eLAVI (20% vs. 7.7%, $p < 0.001$). Using aortic valve replacement as a competing risk event, enlarged eLAVI at baseline predicted increased hazard rate (HR) of MACE (HR 2.21 [95% confidence interval 1.37–3.55], $p = 0.001$) independent of significant associations with presence of LV hypertrophy, older age, higher peak aortic jet velocity, serum creatinine and lower LV ejection fraction and stroke volume.

Conclusions: Presence of enlarged eLAVI was independently associated with increased risk of MACE in patients with mild-to moderate asymptomatic AS.

1. Introduction

Aortic valve stenosis (AS) is the most common heart disease requiring valve replacement in the Western world [1]. Hemodynamically, AS is characterized by pressure overload, causing left ventricular (LV) hypertrophy, afterload mismatch, and diastolic dysfunction due to both impaired relaxation and increased myocardial stiffness [2]. Consequently, the left atrial (LA) chamber will be exposed to increased LV filling pressure, causing increased LA wall tension and stretch and subsequent LA enlargement. Thus, LA volume reflects the duration and severity of diastolic dysfunction [3]. In fact, in severe AS, as the pressure overload increases, LA dilation is more pronounced [4,5]. Accordingly, LA volume has been linked to worse prognosis in severe AS [6]. In contrast, in a subset of patients with mild-to-moderate asymptomatic AS participating in the Simvastatin-Ezetimibe in AS (SEAS) study, larger LA volume assessed by Simpson's monoplane method, was not predictive of incident cardiovascular (CV) events [7]. However, the use of this method for assessment LA volume has been discouraged by current guidelines [8].

Recently, we proposed a method to estimate biplane LA volume from antero-posterior diameter, not as a substitute of direct LA volume measurement, but simply to provide a surrogate of biplane LA volume when direct measurement is not available [9]. Thus, the

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present study aimed to provide further insight in the association of LA volume with prognosis in the SEAS study, using estimated LA volume.

2. Methods

2.1. Population

This study is a post-hoc analysis within the prospective SEAS study [10]. In short, SEAS was a multicenter, double-blinded, randomized, placebo-controlled study to evaluate the effect of combined simvastatin 40 mg and ezetimibe 10 mg daily on disease progression and outcome in 1873 patients ≥45 year of age with mild to moderate AS (thickened aortic valve cusps and a peak jet velocity ≥ 2.5 and ≤4.0 m/s). Patients with other significant valvular heart disease, severe or predominant aortic regurgitation, known CV disease, diabetes mellitus, renal insufficiency or left ventricular (LV) ejection fraction <40% were excluded [11]. For the present analysis patients with atrial fibrillation at baseline (n = 177), grade 3 mitral regurgitation (n = 14) or without echocardiographic assessment of both LA diameter and LV mass (n = 148), were also excluded. Thus, the present study population consisted of 1534 AS patients. The SEAS study was approved by regional ethics committees in all participating countries. All patients gave written informed consent to participate in the SEAS study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

2.2. Echocardiography

Echocardiographic images were stored on videotapes, compact discs, or magnetic optical discs and forwarded for blinded interpretation at the SEAS Echocardiography Core laboratory, Bergen, Norway, as previous published [12–14]. Grading of AS and LV structure and function were assessed according to guidelines [8,12,13,15]. LA antero-posterior diameter was measured from the 2D parasternal long axis view at frame preceding mitral valve opening, orthogonal to the aortic root at the level of the sinus of Valsalva [8]. LA volume was estimated from the LA diameter using a nonlinear equation, validated with an elliptical model: LA volume = 2.323 (LA diameter$^{2.071}$) [9]. In our study we indexed LA volume for height, to avoid the well-known influence of obesity or body composition on body surface area [9]. Sex-specific cutoff value for definition of left atrial dilatation in general European population was used (i.e >19 ml/height^2 in men and >17 ml/height^2 in women) [16].

LV hypertrophy was defined using the prognostically validated cutoff values LV mass index ≥46.7 g/m$^{2.7}$ in women and ≥49.2 g/m$^{2.7}$ in men [17–19].

2.3. End-points

All end-points were adjudicated by an independent end-point classification committee whose members were unaware of study group assignments [10,11]. For the present analysis we targeted CV events associated with LA enlargement defining a post hoc composite end-point of major CV events (MACE, combined CV death, heart failure hospitalization and non-hemorrhagic stroke).

2.4. Statistical analysis

Statistical analysis was performed using IBM SPSS version 22.0 (IBM Corporation, Armonk, NY). Data are presented as mean ± SD for continuous variables and as percentages for categorical variables. Comparison between groups was performed by paired and unpaired *t*-test when appropriate, and χ^2 test. Survival curves of normal versus enlarged eLAVI were analyzed using a Kaplan-Meier plot and log rank test. The effect of enlarged eLAVI on incident MACE was identified by Cox regression analysis in both univariate and multivariate models and presented as hazard ratio (HR) and 95% confidence intervals (CI). Cox regression was run using aortic valve replacement (AVR) preceding MACE, as a competing risk event. The multivariate model was based upon significant variables in univariate analysis. Twenty-four patients experienced more than one end-point, and were censored at the time of the first event. To test whether eLAVI had an incremental prognostic value we performed ROC curve analysis. We compared in ROC curve analysis the area under the curve of the hazard from the Cox model with and without eLAVI in the model by DeLong's test. Two-tailed $p < 0.05$ was considered as statistically significant.

3. Results

3.1. Characteristics of patients with enlarged eLAVI

Patients with enlarged eLAVI were older, had higher systolic blood pressure, higher LV mass index and included higher proportion of women, obese and hypertensive patients (all $p < 0.001$) (Table 1). There was no difference in prevalence of enlarged eLAVI between randomized study treatment groups (48 vs. 52%, $p = 0.587$) and between patients who did receive an AVR before development of MACE (2.4 vs 6.9%, $p = 0.455$).

3.2. Enlarged eLAVI and outcome

During a median follow-up of 4.3 years, a total of 137 patients experienced a MACE, including 46 heart failure hospitalizations, 46 non-hemorrhagic strokes and 69 CV deaths. Patients with enlarged eLAVI had higher incidences of combined MACE as well as CV death, heart failure hospitalization and non-hemorrhagic stroke compared to those with normal eLAVI (all $p < 0.02$) (Fig. 1). Kaplan-Meier plot showed that patients with enlarged eLAVI were at increased risk for MACE ($p < 0.001$) (Fig. 2). In univariate Cox analyses, enlarged eLAVI predicted higher hazard rates of composite MACE (Table 2). In adjusted Cox analysis, enlarged eLAVI was associated with higher hazard rate of MACE (HR 2.21 [95% CI 1.37–3.55], $p = 0.001$), independent of significant associations with presence of LV hypertrophy, older age, and higher peak aortic jet velocity and serum creatinine and lower LV ejection fraction and stroke volume (all $p < 0.05$) (Table 2). ROC analysis demonstrated that area under the curve including eLAVI was 0.615 (SE = 0.035; 95% CI = 0.587-0.641) whereas without eLAVI was 0.631 (SE = 0.034; 95% CI = 0.603-0.657), resulting in no significant differences between areas ($p = 0.14$).

4. Discussion

The present study demonstrates that enlarged LAVI estimated by recently published equation predicts higher hazard rate of MACE, including heart failure hospitalizations, CV death and non-hemorrhagic stroke in patients with asymptomatic, mild to moderate AS, independently of well-known prognostic indicators including age, LV hypertrophy, LV stroke volume and AS severity [17,18,20].

Previous studies have mostly aimed to test the prognostic role of LA size in patients with severe AS. In the study of Lancellotti et al. [6], larger LA size assessed by monoplane LA area in 163 patients with moderate to severe AS was associated with increased hazard rate for new-onset symptoms, death and aortic valve replacement during 2 years follow-up. However, referral for AVR was the most frequent

Table 1
Characteristics of patients with and without eLAVI enlargement at baseline.

Variable	Normal eLAVI n = 1398	Enlarged eLAVI (n = 145)	p
Age (years)	66 ± 10	73 ± 7	<0.0001
Women (%)	38	59	<0.0001
Obesity (%)	17	48	<0.0001
Body mass index (kg/m^2)	26.5 ± 4.1	29.7 ± 18.1	<0.0001
Systolic blood pressure (mmHg)	145 ± 20	155 ± 22	<0.0001
Diastolic blood pressure (mmHg)	82 ± 10	81 ± 8	0.100
Hypertension (%)	81	93	<0.0001
Serum creatinine (μmol/L)	93 ± 15	91 ± 18	0.185
LV ejection fraction (%)	67 ± 7	66 ± 6	0.383
LV mass index (g/m$^{2.7}$)	44.6 ± 13.7	54.5 ± 19.3	<0.0001
Septal thickness (cm)	1.1 ± 0.3	1.2 ± 0.3	0.037
Posterior wall thickness (cm)	0.9 ± 0.2	0.9 ± 0.2	0.084
LV end diastolic dimension (cm)	5.0 ± 0.6	5.1 ± 0.6	0.013
LV hypertrophy (%)	32	57	<0.0001
Peak aortic jet velocity (m/s)	3.1 ± 0.5	3.1 ± 0.5	0.636
LV stroke volume (ml)	85 ± 26	87 ± 28	0.405
E/A	0.91 ± 0.31	0.84 ± 0.26	0.008

AVR = aortic valve replacement; E/A = early peak mitral valve velocity/late peak mitral valve velocity; LAVI = left atrial volume index; LV = left ventricular; MACE major cardiovascular events.

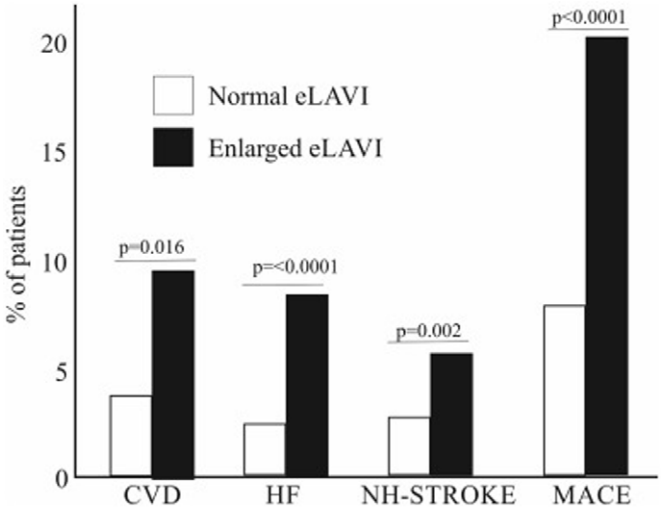

Fig. 1. Incidences of major cardiovascular events and individual cardiovascular death, heart failure hospitalization and non-hemorrhagic stroke events in patients with and without enlarged estimated left atrial volume index. CVD = cardiovascular death; eLAVI = estimated left atrial volume index; HF = heart failure hospitalization; MACE = major cardiovascular events; NH-STROKE = non hemorrhagic stroke.

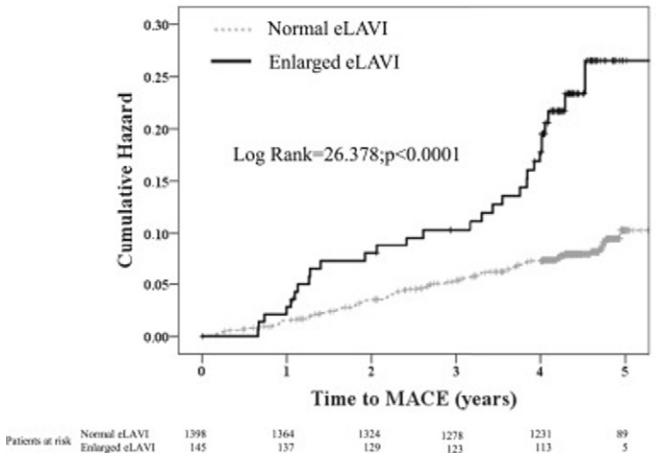

Fig. 2. Kaplan-Meier plot of incident hospitalization for cardiovascular death, heart failure, non-hemorrhagic stroke and composite major cardiovascular events in patients with enlarged and normal estimated left atrial volume index. eLAVI = estimated left atrial volume index; MACE = major cardiovascular events.

event, 77%, in that population. Similarly, Christensen et al. [5], assessed LA size by magnetic resonance imaging in 92 patients with severe AS. During 1-year follow-up, 28 patients experienced an end-point, the majority of them being AVR. In both studies, LA size was identified as an independent predictor of outcome, mostly AVR. The method used in the study by Lancellotti is now discouraged by guidelines, whereas the method used by Christensen, has limited application in routine clinical practice. In a large study in 1351 patients with asymptomatic AS, Rusinaru et al. [4] found that higher LA volume measured by modified biplane Simpson method was associated with increased all-cause mortality during 3 years follow-up in patients with severe AS, while no association with impaired outcome was found in those with moderate AS. Taken together, enlarged LAVI is well documented as a prognostic marker in severe AS.

In contrast in non-severe AS, Dalsgaard et al. tested the association of LA volume with outcome in the SEAS study [7]. A significant association with AVR was demonstrated, while no association with more objective end-point like mortality or hospitalization for heart failure was demonstrated [7]. Of note, LA volume was assessed by monoplane area in the majority of patients in their analysis. Thus, the present analysis in the same patients adds considerable new information. First, we demonstrate the prognostic value of eLAVI based upon a simple measurement of LA anterior-posterior diameter, which in easily applicable in large patient cohorts, including historic databases from studies that did not measure LA volume. Furthermore, our study targeted objective end-points, and considered AVR as a competing risk. Thus, the present study adds new information on the importance of LA size assessment even in asymptomatic patients with mild to moderate AS, in particular to identify patients at higher risk for incident CV death, heart failure hospitalization and non-hemorrhagic stroke, independent of presence of more established risk factors in AS including age, sex, LV hypertrophy and AS severity.

As expected, enlarged eLAVI was less prevalent in the present study population than reported in severe AS, where the hemodynamic burden is higher [21]. Previous publications have identified a number of

Table 2
Predictors of incident MACE at univariate and multivariate Cox regression analysis, with AVR as competing risk event.

Predictor	MACE (n = 137)					
	Univariate analysis			Multivariate analysis		
	p	HR	95% CI	p	HR	95% CI
Age (≥65 years)	<0.0001	2.34	1.55–3.53	0.007	1.93	1.99–3.11
Men	0.284	1.21	0.85–1.72			
Randomized Treatment	0.611	1.09	0.78–1.53			
Obesity	0.069	0.70	0.48–1.03			
Body mass index (kg/m^2)	0.401	1.02	0.98–1.06			
Systolic blood pressure (mmHg)	0.398	1.00	0.99–1.01			
Diastolic blood pressure (mmHg)	0.363	0.99	0.97–1.01			
Hypertension	0.517	0.86	0.55–1.34			
Serum creatinine (μmol/L)	0.004	1.02	1.01–1.03	0.03	1.01	1.00–1.02
LV hypertrophy	<0.0001	1.91	1.37–2.68	0.031	1.53	1.04–2.26
Enlarged eLAVI	<0.0001	2.80	1.86–4.22	0.001	2.21	1.37–3.55
LV Ejection fraction (%)	0.012	0.97	0.94–0.99	0.032	0.97	0.94–0.99
Aortic peak jet velocity (m/s)	<0.0001	1.93	1.43–2.62	0.001	1.76	1.25–2.47
LV stroke volume (ml)	0.007	0.99	0.98–0.99	0.007	0.99	0.98–0.99
E/A ratio	0.035	0.48	0.24–0.95	0.790	1.09	0.58–2.04

AVR = Aortic valve replacement; eLAVI = estimated left atrial volume index; LV = left ventricular; MACE = major cardiovascular events.

covariables of LA enlargement, including older age, sex, higher systolic BP and body mass index [22,23]. In the present study, in patients with estimated eLAVI at baseline, the prevalence of obesity and hypertension were higher than in patients with normal eLAVI, confirming previous associations with LA dilatation [3,22,24].

4.1. Limitation and strength of the study

Identification of enlarged eLAVI by our method cannot take into account the potential geometric distortion of LA geometry sometimes occurring with LA dilatation, typically when dilatation occurs along the longitudinal axis [9]. Still, as demonstrated, enlarged eLAVI by our method predicted increased hazard rate of MACE, independent of well-known prognosticators in asymptomatic mild-moderate AS. Another limitation is the limited capture of LV diastolic function in accordance with modern guidelines. In fact, the echocardiographic protocol used in the SEAS study performed during 2002-8 captured only a few LV diastolic function variables. In particular, mitral annular velocities and peak tricuspid valve regurgitation velocity were not included. The association of LV diastolic function with eLAVI could therefore not be assessed in detail.

5. Conclusions

Presence of enlarged eLAVI in patients with mild-to moderate asymptomatic AS is independently associated with increased risk of MACE, in particularly CV death, heart failure hospitalization and non-hemorrhagic stroke.

Declaration of competing interest

None.

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