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Echocardiographic findings on aortic stenosis: an observational, prospective, and multi-center registry

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Abstract

Background: The aim of this aortic stenosis registry was to investigate the changes of routine echocardiographic indices and strain in patients with moderate-to-severe aortic stenosis over a 6-month follow-up period.

Methods: Our aortic stenosis registry is observational, prospective, multicenter registry of nine countries, with 197 patients with aortic valve area less than 1.5 cm^2. The enrolment took place from January to August 2017. We excluded patients with uncontrolled atrial arrhythmias, pulmonary hypertension or cardiomyopathies, as well as those with hemodynamically significant valvular disease other than aortic stenosis. We included patients who did not require intervention and who had a complete follow-up study.

Results: In patients with preserved ejection fraction, left ventricular mass has significantly increased between baseline and follow-up studies (218 ± 34 grams vs 253 ± 29 grams, p = 0.02). However, when indexed to body surface area, there was no significant difference. Left ventricular global longitudinal strain significantly decreased (-19.7 ± -4.8 vs (-16.4 vs -3.8, p = 0.01). Left atrial volume was significantly higher at follow-up (p = 0.035). Right ventricular basal diameter and mid-cavity diameter were greater at the follow-up (p = 0.04 and p = 0.035, respectively). Patients with low-flow low-gradient aortic stenosis had significantly lower global longitudinal strain (-12.3% ± -3.9% vs -19.7% ± -4.8%, p = 0.01).

Conclusion: Left atrial dilatation is one of the first changes to take place in low-flow low-gradient aortic stenosis patients even when left ventricular dimensions and function remains intact. Global longitudinal strain is an important determinant of left ventricular systolic and diastolic dysfunction and right ventricular function is an important parameter of aortic stenosis assessment. Accordingly, our registry has further shed the light on these indices role as multisite follow-up of aortic stenosis.

Keywords

aortic stenosis; echocardiography; left ventricle; volumes; right ventricle; low flow low gradient; strain

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Introduction

Important debates related to aortic stenosis (AS) types are running, and as a result earlier detection, appropriate management decision, and better clinical outcomes are crucial. In addition, more interesting thoughts arise when treatment strategy must be determined in individuals with low-flow low-gradient aortic stenosis (LFLG AS).[1] Speckle tracking echocardiography (STE) and tissue Doppler imaging (TDI) can predict regional systolic left ventricle (LV) dysfunction before global functional measures occurs, for example, LV ejection fraction (LVEF).[2]

The aim of this multicenter AS Registry was to investigate the changes of routine echocardiographic indices and strain in patients with moderate-to-severe AS over a 6-month follow-up period.

Methods

Study design

Our AS registry is observational, prospective, multicenter registry of nine countries, with 197 patients with aortic valve area less than 1.5 cm^2. The assessment was performed by the respective cardiologist in each center who had greater than 5 years of clinical experience and has been certified according to European Association of Cardiovascular Imaging.

Echocardiographic measurements

We employed the same protocol for echocardiographic assessment across institutions, according to the latest guidelines:[3] 2D-guided linear measurements for LV diameter, biplane disk summation for volume calculation, and the sum of 17 wall longitudinal strain for the global value. We also performed inter- and intra-observer variability between the observers who performed the measurements.

For the assessment of LV diastolic dysfunction, we employed the assessment of LV filling pressures.[2] Furthermore, we distributed patients according to the ESC/EACTS Guidelines for the management of valvular heart disease:[1] LFLG AS was defined according to the flow status, mean pressure gradient and aortic valve area: the flow status was defined as the stroke volume index ($\leqslant 35$ mL/m^2 for low flow and > 35 mL/m^2 for normal flow).

LV mass was calculated from interventricular septum, posterior wall, and left ventricular end-diastolic diameter.[3]

Assessment of aortic stenosis

We followed the most recent ESC/EACTS guidelines for valvular heart disease,[1] employing stress echocardiography in those cases where we needed a firm diagnosis of the degree of aortic stenosis. We employed velocity time integral from aortic and LV outflow tract velocities and the continuity equation in order to calculate the aortic valve area. We calculated LV outflow tract area according to the current recommendations.[4]

Demographics

We calculated body surface area according to the DuBois formula[5] for the indexing of our echocardiographic values. Patients' clinical presentation as per symptomatology was described according to New York Heart Association (NYHA) association functional class. Furthermore, we recorded the time from the timepoint they were initially diagnosed until the time they were recruited into the registry.

Inclusion/exclusion criteria

The enrolment took place from January to August 2017. Initially we recruited a total of 438 patients. We excluded patients with uncontrolled atrial arrhythmias or cardiomyopathies, as well as those with hemodynamically significant valvular disease other than AS. We also excluded patients with intracardiac shunts, lung disease, pre-capillary pulmonary hypertension, tricuspid regurgitation. We included patients who did not require intervention and who had a complete follow-up study.

Study subgroups

All subjects underwent two comprehensive echocardiographic studies: first baseline study at diagnosis, and the second was a follow-up study after 6 months. According to baseline findings, patients were divided into two subgroups:[1]

1. AS with preserved EF: those patients were subsequently divided into moderate vs severe AS
2. LFLG AS

Ethics approval

The study was approved by the local ethics committee of each institution and the subjects gave written informed consent. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Statistical analysis

The power of the study was calculated by the statistical service, Imperial College of Science, Technology and Medicine. The study was conducted as a prospective registry. Data were expressed as mean value ±

Table 1. Normal gradient aortic stenosis: Baseline and 6-month follow-up echocardiographic indices: Comparison of groups.[AQ: 2]

Value	Baseline	Follow-up	Difference	Comparison of groups
LVEF ((mean ± SD, %)	55 ± 10	52.3 ± 6.8	6.2 ± 3.9	0.24
LVEDD (mean ± SD, mm)	48 ± 6.8	46.9 ± 7.2	2.3 ± 1.4	0.89
LVESD (mean ± SD, mm)	28 ± 9	31 ± 4.2	4.2 ± 2	0.74
LV mass/indexed (mean ± SD, grams)	159.6 ± 12.8	170.9 ± 16.5 1,162,122,222,228.928.9	24 ± 8	0.06
Global longitudinal strain (mean ± SD %)	−19.7 ± 4.8	−16.4 ± 3.8	−6.2 ± 2	0.01
IVS (mean ± SD, mm)	13 ± 1.1	12.8 ± 0.9	1.1 ± 0.5	0.65
LVPW (mean ± SD, mm)	11 ± 0.58	10.6 ± 0.7	0.9 ± 0.2	0.53
LAVi (mean ± SD, mL/m^2)	68 ± 25.1	81 ± 18.4	24 ± 11	0.035
E wave (mean ± SD, mm/sec)	67.2 ± 27.7	69.5 ± 25.4	12.3 ± 4	0.87
A wave (mean ± SD, mm/sec)	75 ± 18.9	79 ± 15.4	2.1 ± 0.9	0.56
DT (mean ± SD, msec)	200 ± 80.2	214 ± 56.4	21 ± 10	0.67
TDI S wave—septal (mean ± SD, mm/sec)	5.6 ± 2.6	6.2 ± 3.4	1.5 ± 0.3	0.32
TDI S wave—lateral (mean ± SD, mm/sec)	6 ± 3.1	6.5 ± 2.5	1.2 ± 0.5	0.35
RV diameter—PLAX (mean ± SD, mm)	38 ± 6.9	42 ± 4.3	4 ± 1.4	0.67
RV diameter—basal (mean ± SD, mm)	42 ± 7.6	48 ± 5.3	7 ± 1.4	0.04
V, focused basal (mean ± SD, mm)				
RV_diameter—mid-cavity (mean ± SD, mm)	36 ± 9.4	42 ± 8.7	6.8 ± 1.2	0.035
RVSP (mean ± SD, mmHg)	48 ± 14.7	56 ± 16.8	15 ± 4.8	0.04
TAPSE (mean ± SD, mm)	20 ± 8.2	18 ± 4.5	4 ± 1.2	0.67
TDI RV S wave (mean ± SD, mm/sec)	12 ± 2.9	10.8 ± 2.4	3.2 ± 1	0.18
RV IVRT (mean ± SD, msec)	77.8 ± 33.1	85.9 ± 21.5	14.5 ± 5.6	0.08

LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LV: left ventricular; IVS: interventricular septum; LVPW: left ventricular posterior wall; LAVi: left atrial volume indexed; DT: deceleration time; TDI: tissue Doppler imaging; RV: right ventricle; PLAX: parasternal long axis view; A4C. apical four chamber view; RVSP: right ventricular systolic pressure; TAPSE: tricuspid annular plane systolic excursion; IVRT: isovolumic relaxation time.

standard deviation for normally distributed values and median ± interquartile change when variables were non-normally distributed. Normal distribution of each variable was assessed using the Kolmogorov–Smirnov test and for comparison between three groups we used analysis of variance (ANOVA) test with Bonferroni correction for normally distributed variables. For the non-normally distributed variables, comparison of groups was performed with Kruskal–Wallis test and the cut-off value for significance was adjusted for multiple comparison to the value of 0.01. Analysis was performed with SPSS 13.0 and Medcalc software. A p value of < 0.05 was statistically significant.

The person who performed the statistical analysis (SA) was different to the person who performed and analyzed the echocardiographic exam (rest of the group) and therefore the statistical analysis was blinded to the collection of echocardiographic data.

Results

Demographics

One hundred ninety-seven patients were recruited to the registry (mean age 72.6 ± 11.9 years old): 79 patients with moderate AS (65.8 ± 5.7 years old), 60 patients with LFLG AS (75.3 ± 9.3 years old) and 58 patients with normal flow normal gradient AS (71.5 ± 6.7 years old). Mean BSA was 1.82 ± 0.3 m^2 at baseline and 1.85 ± 0.28 m^2 at follow-up.

Sixty-seven percent of patients were in sinus rhythm on presentation, non-smoker (73%), without chronic obstructive pulmonary disease (79%), and non-diabetic (71%). The majority were also hypertensive (68.5%), hypercholesterolemic (80.7%), and with a background of a positive family history of coronary artery or valvular disease (54.8%). Most patients were on a statin (75.6%), b-blocker (84.7%), loop diuretics (72.5%), while there was an equal distribution between warfarin and aspirin intake.

Most of the patients (122 patients, 62%) were in New York Heart Association class 2 (NYHA II), and they had a well-controlled blood pressure on medicines. Furthermore, they did not have anemia (hemoglobin: 14.8 ± 2.1 g/dL). NT-BNP was raised (986 ± 364.2 pg/mL at baseline and 1052 ± 280.5 pg/mL at follow-up, p = 0.87). Finally, the duration of disease was 2.96 ± 1.8 years.

All 60 patients with LFLG AS had previously documented ischemic heart disease with the majority (49 patients had a previous STEMI) (28 patients had previous coronary bypass surgery and 32 patients had

Table 2. Aortic specific echocardiographic indices: baseline and 6-month follow-up measurements and their comparison.

Value (N = 197 patients: 118 patients with severe AS, 79 with moderate AS)	Baseline	Follow-up	Comparison of groups
Peak aortic velocity (mean ± SD, m/sec)	4.34 ± 2.1	4.5 ± 1.9	0.12
MPG (mean ± SD, mmHg)	42.5 ± 16.3	46.8 ± 15.2	0.45
PPG (mean ± SD, mmHg)	66 ± 24.8	72 ± 21.6	0.09
LVOT diameter (mean ± SD, mm)	22 ± 2.1	21.9 ± 1.9	0.9
LVOT VTI (mean ± SD, cm)	28 ± 5.6	29.2 ± 6.2	0.78
Aortic VTI (mean ± SD, cm)	99.6 ± 24.5	112 ± 23.8	0.63
Aortic valve area (mean ± SD, cm^2)	0.97 ± 0.21	0.86 ± 0.19	0.48

MPG: mean pressure gradient; PPG: peak pressure gradient; LVOT: left ventricular outflow tract; VTI: velocity time integral.

previous stents). [AQ: 1]All of them did not have any residual ischemic heart disease.

Patients with aortic stenosis, and preserved LVEF

LV mass indexed to body surface area did not have any significant difference between baseline and follow-up.

LV global longitudinal strain (GLS) significantly decreased (-19.7% ± -4.8% vs -16.4% vs -3.8%, p = 0.01) (Table 1). Left atrial volume was significantly higher at follow-up (p = 0.035). Right ventricular (RV) basal diameter and mid-cavity diameter were greater at the follow-up (p = 0.04 and p = 0.035, respectively).

RV systolic pressures were also statistically higher at the follow-up when compared with the baseline values (p = 0.04). AS quantification parameters did not show any statistical difference (Table 2).

Patients with LFLG AS

When compared with patients with preserved LVEF, patients with LFLG AS showed no statistically significant changes between the baseline and 6-month follow-up (Table 3).

Comparison of two sub-groups

Patients with LFLG AS had significantly lower GLS (-12.3% ± -3.9% vs -19.7% ± -4.8%, p = 0.01). Furthermore, there was a significant difference in LV diastolic dysfunction indices. RV systolic pressure was greater, and tricuspid annular plane systolic excursion was lower, in LFLG AS patients (p = 0.02 and p = 0.025, respectively). AS-specific indices were significantly different between the two sub-groups with LFLG AS being more severe in degree (Table 4).

Comparison: moderate versus severe aortic stenosis with normal EF

LV mass was significantly increased from baseline to follow-up (127.8 ± 12.5 grams vs 217.9 ± 34.3 grams, p = 0.04). The rest of echocardiographic indices remained the same throughout follow-up. In addition to this analysis, we separated the groups of moderate versus severe AS and we compared the groups in 6 months. A few moderate AS patients demonstrated slow progress of the disease (Table 5) but there was no statistical difference between the groups in 6 months.

Interobserver reproducibility

Two observers with more than 5 years of experience measured 50 random patients and were blinded to their pathology. Table 6 describes the interobserver variability between the observers.

Discussion

The role of diastolic dysfunction

Our study demonstrated that the echocardiographic differences and the natural history of aortic stenosis with preserved EF as well as LFLG AS. As demonstrated by Herrmann S and colleagues in a similar study with a smaller sample size of patients,[6] LFLG AS is a systemic disease with valvular, vascular, and myocardial components, resulting in a slower progression of transvalvular gradient, but worse clinical outcome. The diastolic dysfunction component is quite prominent in our study as demonstrated by diastolic assessment. We concluded that during the follow-up of AS, when LVEF is preserved, LA dilates due to high atrial pressure; and most importantly LV GLS decreases.

Our results indicate that LA enlargement matches the progressive LV stiffening and diastolic dysfunction in patients with asymptomatic AS, and this agrees with the findings of Christensen et al.[7] who studied 92 patients with asymptomatic AS with cardiac magnetic resonance, and they concluded that LA dilation is associated with LV remodeling and provides prognostic information. Due to the limited follow-up, the progress of diastolic dysfunction reflected as LA dilatation while LV dimensions and LV filling pressures (E, E') remained unchanged. As it is well documented in the literature, LA size reflects

Table 3. Low-flow low-gradient AS.

Value (N = 60 patients)	Baseline	Follow-up	Comparison of groups
LVEF (mean ± SD, %)	39 ± 8.9	37.5 ± 8.2	0.64
LVEDD (mean ± SD, mm)	49 ± 6.1	46.9 ± 7.2	0.09
LVESD (mean ± SD, mm)	32 ± 11.7	31 ± 4.2	0.7
LV mass/indexed (mean ± SD, grams/m^2)	82.5 ± 10.9	83.2 ± 11	0.8
Global longitudinal strain (mean ± SD, sec)	−12.3 ± 3.9	−11.8 ± 2.9	0.5
IVS (mean ± SD, mm)	10 ± 1.5	9.8 ± 1.2	0.62
LVPW (mean ± SD, mm)	9 ± 0.85	9.1 ± 0.76	0.58
LAVi (mean ± SD, mL)	80 ± 24.2	81 ± 25.6	0.17
E wave (mean ± SD, mm/sec)	94.7 ± 15.8	93.4 ± 14.2	0.65
A wave (mean ± SD, mm/sec)	53.2 ± 11.4	49.3 ± 10.8	0.52
DT (mean ± SD, msec)	245.2 ± 45.3	252 ± 40.5	0.7
TDI S wave—septal (mean ± SD, mm/sec)	3.6 ± 2.1	3.5 ± 1.8	0.68
TDI S wave—lateral (mean ± SD, mm/sec)	7 ± 2.5	6.5 ± 2.1	0.42
RV diameter—PLAX (mean ± SD, mm)	42 ± 5.8	44 ± 2.7	0.9
RV diameter—A4C- basal (mean ± SD, mm)	44 ± 6.9	46 ± 5.8	0.48
RV diameter—A4C, mid-cavity (mean ± SD, mm)	35 ± 5.7	40 ± 6.2	0.08
RVSP (mean ± SD, mmHg)	64 ± 10.2	68 ± 9.4	0.27
TAPSE (mean ± SD, mm)	15.3 ± 2.7	14.6 ± 2.9	0.84
TDI RV—S wave (mean ± SD, mm/sec)	10.2 ± 2.2	9.4 ± 1.8	0.34
RV IVRT (mean ± SD, msec)	92.4 ± 24.1	98 ± 19.2	0.21
Peak aortic velocity (mean ± SD, m/sec)	3.2 ± 0.5	3.4 ± 0.2	0.36
MPG (mean ± SD, mmHg)	29 ± 9.6	30.2 ± 10.3	0.48
PPG (mean ± SD, mmHg)	52 ± 14.5	48 ± 12.7	0.82
LVOT diameter (mean ± SD, mm)	21 ± 1.2	21 ± 1.1	0.9
LVOT VTI (mean ± SD, cm)	18.7 ± 7.8	17.5 ± 6.5	0.78
Aortic VTI (mean ± SD, cm)	66.5 ± 21.2	72.3 ± 20.4	0.63
Aortic valve area (mean ± SD, m^2)	0.6 ± 0.12	0.54 ± 0.19	0.45

LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LV: left ventricular; IVS: interventricular septum; LVPW: left ventricular posterior wall; LAVi: left atrial volume indexed; DT: deceleration time; TDI: tissue Doppler imaging; RV: right ventricle; PLAX: parasternal long axis view; A4C: apical four chamber view; RVSP: right ventricular systolic pressure; TAPSE: tricuspid annular plane systolic excursion; IVRT: isovolumic relaxation time; MPG: mean pressure gradient; PPG: peak pressure gradient; LVOT: left ventricular outflow tract; VTI: velocity time integral.

hemodynamic burden in patients with asymptomatic severe aortic stenosis[8] and it reverses post-invasive treatment of aortic stenosis.[9]

LFLG AS

There were no significant changes in the echocardiographic indices at baseline and follow-up, in the LFLG patients. This may be related to the slow progress of the disease especially when LV dysfunction and the severity of AS are established.

A similar retrospective study[10] of 116 consecutive patients with aortic stenosis who had undergone follow-up echocardiography at a median interval of 698 days, described an annual change of aortic valve area (AVA) and MG for the entire cohort was $-0.09 \pm 0.14\,cm^2$ (decrease in AVA) and 2 ± 6 mmHg (increase in MG). **[AQ: 3]**They also concluded LG AS probably represents an intermediate stage between moderate AS and severe AS with normal EF.[10] TOPAS study stresses the importance of contractile reserve study in LFLG patients.[11]

The value of global longitudinal strain

GLS can quantify the burden of myocardial dysfunction in patients with severe AS regardless of their LVEF.[11] Subclinical myocardial dysfunction that is characterized by impaired LV GLS is often present in patients with asymptomatic severe AS and is associated with symptom development and the need for intervention.[12] As an asset to the LV and LA remodeling, our registry demonstrated that a decreased GLS might be an indicator of progression of AS severity and LV impairment in patients with preserved LVEF. LV GLS has been proved to be independently associated with all-cause mortality on multivariable Cox regression analysis (hazard ratio = 1.17, 95% confidence interval = 1.09-1.26; $p < 0.001$). Furthermore, it can allow us to risk-stratify severe AS patients and

Table 4. Comparison between normal gradient and LFLG.

Value	Baseline LFLG (60 patients)	Baseline Normal flow (58 patients)	Comparison of groups
LVEF (mean ± SD, %)	39 ± 8.9	55 ± 9.97	0.04
LVEDD (mean ± SD, mm)	49 ± 6.1	48 ± 6.8	0.25
LVESD (mean ± SD, mm)	32 ± 11.7	28 ± 9	0.54
LV mass (mean ± SD, grams)	154.2 ± 25.8	217.9 ± 34.3	0.01
LV mass/indexed (mean ± SD, grams/m^2)	78.9 ± 12.8	109.4 ± 17.8	0.008
GLS (mean ± SD, %)	−12.3 ± 3.9	−19.7 ± 4.8	0.01
IVS (mean ± SD, mm)	10 ± 1.5	13 ± 1.1	0.04
LVPW (mean ± SD, mm)	9 ± 0.85	11 ± 0.58	0.12
LAVi (mean ± SD, mL/m^2)	80 ± 24.2	68 ± 25.1	0.06
E wave (mean ± SD, mm/sec)	94.7 ± 15.8	67.2 ± 27.7	0.02
A wave (mean ± SD, mm/sec)	53.2 ± 11.4	75 ± 18.9	0.04
DT (mean ± SD, msec)	245.2 ± 45.3	200 ± 80.2	0.04
TDI S wave—septal (mean ± SD, mm/sec)	3.6 ± 2.1	5.6 ± 2.6	0.025
TDI S wave—lateral (mean ± SD, mm/sec)	7 ± 2.5	6 ± 3.1	0.23
RV diameter—PLAX (mean ± SD, mm)	42 ± 5.8	38 ± 6.9	0.21
RV diameter—A4C, basal (mean ± SD, mm)	44 ± 6.9	42 ± 7.6	0.45
RV diameter—A4C, mid-cavity (mean ± SD, mm)	35 ± 5.7	36 ± 9.4	0.4
RVSP (mean ± SD, mmHg)	64 ± 10.2	48 ± 14.7	0.02
TAPSE (mean ± SD, mm)	15.3 ± 2.7	20 ± 8.2	0.025
TDI RV—S wave (mean ± SD, mm/sec)	10.2 ± 2.2	12 ± 2.9	0.08
RV IVRT (mean ± SD, msec)	92.4 ± 24.1	77.8 ± 33.1	0.04
Peak aortic velocity (mean ± SD, m/sec)	3.2 ± 0.5	4.4 ± 0.5	0.01
MPG (mean ± SD, mmHg)	29 ± 9.6	48 ± 5.8	0.01
PPG (mean ± SD, mmHg)	52 ± 14.5	72 ± 10.4	0.02
LVOT diameter (mean ± SD, mm)	21 ± 1.2	22 ± 1.8	0.67
LVOT VTI (mean ± SD, cm)	18.7 ± 7.8	29 ± 3.2	0.01
Aortic VTI (mean ± SD, cm)	66.5 ± 21.2	99.8 ± 21.6	0.01
Aortic valve area (mean ± SD, m^2)	0.6 ± 0.12	0.62 ± 0.14	0.9

LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LV: left ventricular; IVS: interventricular septum; LVPW: left ventricular posterior wall; LAVi: left atrial volume indexed; DT: deceleration time; TDI: tissue Doppler imaging; RV: right ventricle; PLAX: parasternal long axis view; A4C: apical four chamber view; RVSP: right ventricular systolic pressure; TAPSE: tricuspid annular plane systolic excursion; IVRT: isovolumic relaxation time; MPG: Mean pressure gradient; PPG: peak pressure gradient; LVOT: Left ventricular outflow tract; VTI: velocity time integral.

Table 5. Comparison between moderate and severe AS with normal EF (power point).

Value	Moderate AS (N = 79)	Follow-up of this group	Severe AS (N = 58)	Follow-up of this group	Comparison of groups (moderate/severe)	Comparison of groups (baseline)
Aortic valve area (mean ± SD, cm^2)	1.2 ± 0.16	1.04 ± 0.2	0.62 ± 0.14	0.6 ± 0.2	NS	0.02
Peak aortic velocity (mean ± SD, m/sec)	3.4 ± 0.3	3.7 ± 0.4	4.4 ± 0.5	4.6 ± 0.6	NS	0.01
MPG (mean ± SD, mmHg)	27 ± 6.5	32 ± 7.2	48 ± 5.8	52 ± 5.5	NS	0.01
PPG (mean ± SD, mmHg)	48 ± 0.9	54 ± 1.1	72 ± 10.4	76 ± 9.5	NS	0.04
LVOT diameter (mean ± SD, mm)	21.5 ± 0.3	21.2 ± 0.2	22 ± 1.8	21 ± 1.2	NS	0.9
LVOT VTI (mean ± SD, cm)	18.3 ± 5.6	19.2 ± 4.7	29 ± 3.2	32 ± 3	NS	0.02
Aortic VTI (mean ± SD, cm)	66.4 ± 18.2	68.2 ± 19.3	99.8 ± 21.6	102 ± 22.1	NS	0.02
LVEF (mean ± SD, %)	57 ± 6.7	56 ± 6.5	55 ± 9.97	54 ± 5.6	NS	0.75
LVEDD (mean ± SD, mm)	47.2 ± 5.9	45.6 ± 6	48 ± 6.8	44 ± 5.6	NS	0.52
LVESD (mean ± SD, mm)	29.5 ± 9.2	25.4 ± 8.2	28 ± 9	26 ± 7.2	NS	0.41
LV mass/indexed (mean ± SD, gm)	127.8 ± 12.5	132 ± 10.4	217.9 ± 34.3	220.5 ± 33.7	NS	0.04
Global longitudinal strain (mean ± SD, %)	−19.5 ± 2.9	−18 ± 2.5	−19.7 ± 4.8	−18.5 ± 4	NS	0.62
IVS (mean ± SD, mm)	11 ± 0.9	11 ± 0.5	13 ± 1.1	13 ± 2	NS	0.32
LVPW (mean ± SD, mm)	10 ± 0.73	10 ± 0.5	11 ± 0.58	12 ± 1.1	NS	0.5
LAVi (mean ± SD, mL/m^2)	54 ± 17.8	57 ± 16.5	68 ± 25.1	72 ± 18.2	NS	0.25

LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LV: left ventricular; IVS: interventricular septum; LVPW: left ventricular posterior wall; LAVi: left atrial volume indexed.

Table 6. Bland Altman analysis for interobserver variability.

Value (N = 50 patients)	Comparison of groups
LVEF (mean ± SD, %)	0.94
LVEDD (mean ± SD, mm)	0.88
LVESD (mean ± SD, mm)	0.85
LV mass (mean ± SD, grams)	0.8
GLS (mean ± SD, %)	0.95
IVS (mean ± SD, mm)	0.85
LVPW (mean ± SD, mm)	0.88
LAVi (mean ± SD, mL/m^2)	0.89
E wave (mean ± SD, mm/sec)	0.81
A wave (mean ± SD, mm/sec)	0.8
DT (mean ± SD, msec)	0.74
TDI S wave—septal (mean ± SD, mm/sec)	0.78
TDI S wave—lateral (mean ± SD, mm/sec)	0.8
RV diameter—PLAX (mean ± SD, mm)	0.72
RV diameter—A4C, basal (mean ± SD, mm)	0.76
RV diameter—A4C, mid-cavity (mean ± SD, mm)	0.8
RVSP (mean ± SD, mmHg)	0.92
TAPSE (mean ± SD, mm)	0.86
TDI RV—S wave (mean ± SD, mm/sec)	0.87
RV IVRT (mean ± SD, msec)	0.75
Peak aortic velocity (mean ± SD, m/sec)	0.8
MPG (mean ± SD, mmHg)	0.85
PPG (mean ± SD, mmHg)	0.87
LVOT diameter (mean ± SD, mm)	0.88
LVOT VTI (mean ± SD, cm)	0.82
Aortic VTI (mean ± SD, cm)	0.78
Aortic valve area (mean ± SD, m^2)	0.92

LVEF: left ventricular ejection fraction; SD: standard deviation; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LV: left ventricular; GLS:; IVS: interventricular septum; LVPW: left ventricular posterior wall; DT: deceleration time; TDI: tissue Doppler imaging, RV: right ventricle, PLAX: parasternal long axis view; A4C: apical four chamber view, RVSP: right ventricular systolic pressure, TAPSE: tricuspid annular plane systolic excursion, IVRT: isovolumic relaxation time; MPG: mean pressure gradient, PPG: peak pressure gradient; LVOT: left ventricular outflow tract, VTI: velocity time integral.

may influence the setting of the optimal timing of aortic valve replacement.[11,13] In our study, there was no significant difference between moderate and severe AS GLS which may be attributed to the established diastolic dysfunction but not significant difference between the groups.

The role of RV dysfunction

RV dysfunction is common in AS patients, which can be explained by the RV-LV interdependence. RV dilatation and function should be taken into consideration when deciding toward surgical or percutaneous treatment. Furthermore, it is important to detect early markers of elevated pulmonary pressures before the establishment of pulmonary hypertension.[12,14]

Characteristic	Baseline value
Male / Female (N, %)	102 (51.8%) / 95 (48.2%)
Duration of disease (mean ± SD)	2.96 ± 1.8 years
NYHA class (median)	Class II
Systolic blood pressure (mean ± SD)	126.8 ± 21.4 mmHg
Diastolic blood pressure (mean ± SD)	61.9 ± 12.5 mmHg
Weight (mean ± SD)	77.2 ± 15.5 kg
Height (mean ± SD)	165 ± 22.2 cm
Heart rate (mean ± SD)	70 ± 11.8 BPM
QRS duration (mean ± SD)	100 ± 17.9 msec.
Hemoglobin (mean ± SD)	14.8 ± 2.1 g/dl
Creatinine (mean ± SD)	1.28 ± 0.15 mg/dl
eGFR (mean ± SD)	42 ± 8.4 ml/min/m2
CRP (mean ± SD)	18 ± 2.5 mg/l
NT-proBNP (mean ± SD)	986 ± 364.2 pg/mL

Figure 1. Characteristics of registry population. **[AQ: 4]**

The slow progress of aortic stenosis

Our study is in agreement with the literature which emphasizes the slow progress of aortic stenosis. It is characterized by years to decades of slow progression followed by rapid clinical deterioration and high mortality once symptoms develop. Pelikka PA and colleagues[15] obtained long-term follow-up in 622 patients with isolated, asymptomatic AS and they concluded that most patients will develop symptoms within 5 years. Furthermore they pointed out that age, chronic renal failure, inactivity, and aortic valve velocity are independently predictive of all-cause mortality.

As a conclusion, our study provides demographic and echocardiographic insights in aortic stenosis in a large multicenter cohort. It confirms current knowledge that aortic stenosis is a slow progress valvular entity and early imaging indices will help the preservation of LV function post intervention.

Limitations

The study has a short follow-up to detect any prognostic markers and no conclusion can be made regarding longer term evolution. The blood results described at baseline were not available at the whole extent during follow-up. Despite documentation of the risk factors within demographics, there was no multiple linear regression taking place to assess the effect of confounding factors such as hypertension on the degree of aortic stenosis.

Conclusion

LA dilatation is one of the first changes to take place in LFLG AS patients even when LV dimensions and function remains intact. GLS is an important determinant of LV systolic and diastolic dysfunction and RV function is an important parameter of AS assessment.

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Declaration of Conflicting Interests

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Ethical approval[AQ: 5]

The manuscript and the material within the manuscript have not been published and are not being considered for publication elsewhere in whole or in part in any language, including publicly accessible web sites or e-print servers, except as an abstract.

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