Progression of Normal Flow Low Gradient "Severe" Aortic Stenosis With Preserved Left Ventricular Ejection Fraction

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Normal-flow low-gradient severe aortic stenosis (NF-LG-SAS), defined by an aortic valve area (AVA) <1 cm^2, mean pressure gradient (MPG) <40 mm Hg and indexed stroke volume ≥35 ml/m^2, is the most prevalent form of low-gradient aortic stenosis (AS) with preserved ejection fraction (PEF). However, the true severity of AS in these patients is controversial. The aim of this Doppler echocardiographic study was to investigate changes over time in the hemodynamic severity of patients with NF-LG-SAS with PEF. We retrospectively identified 96 patients who had 2 Doppler echocardiographic examinations without an intervening event. After a median follow-up of 25 (interquartile range 15 to 52) months, progression was observed, with increased transaortic MPG (from 28 [25 to 33] to 39 [34 to 50] mm Hg; p<0.001), peak aortic jet velocity (from 3.46 [3.20 to 3.64] to 4.01 [3.70 to 4.39] m/s; p<0.001), and decreased AVA (from 0.87 [0.82 to 0.94] to 0.72 [0.62 to 0.81] cm^2; p<0.001). Median annual rates of progression were 4.3 (1.7 to 8.1) mm Hg/year, 0.25 (0.08 to 0.44) m/s/year, and −0.05 (−0.10 to −0.02) cm^2/year, respectively. There was no significant change in left ventricular ejection fraction over time (p = 0.74). At follow-up, 46 patients (48%) acquired the features of classical high-gradient severe AS (MPG ≥40 mm Hg). This study shows that most patients with NF-LG-SAS with PEF exhibit significant hemodynamic progression of AS severity without EF impairment. These findings suggest that NF-LG-SAS with PEF is an "intermediate" stage between moderate AS and classical high-gradient severe AS requiring close monitoring. **(Am J Cardiol 2020;128:151−158)**

Normal-flow, low-gradient "severe" aortic stenosis (NF-LG-SAS) is the most prevalent form of low-gradient aortic stenosis (AS),[1] with preserved left ventricular ejection fraction (LVEF).[2,3] Its management is a matter of debate, as there is uncertainty about the "true" severity of AS. Patients with NF-LG-SAS are classically elderly women, with a small body surface area (BSA), less concentric left ventricular (LV) hypertrophy and concentric remodeling, less left atrial dilatation, less impaired systolic longitudinal function, and larger aortic valve area (AVA) than other forms of severe AS.[3−5] The outcome of this entity is a subject of debate. Indeed, several studies suggest that these patients have "true" severe AS and that aortic valve replacement (AVR) should be performed when symptoms appear,[6−13] whereas others have considered this entity to be in the majority of cases a moderate form of AS.[4,14−18] Given the paucity of data on the evolution of hemodynamic parameters over time in NF-LG-SAS with preserved LVEF, we studied the evolution of echocardiography Doppler parameters over time in these patients. We hypothesized that this entity represents an "intermediate" stage between moderate AS and high gradient severe AS (HG-SAS) with preserved LVEF, tending to evolve toward the classic pattern of HG-SAS with preserved LVEF.

Methods

We retrospectively identified all cases of NF-LG-SAS with preserved LVEF diagnosed from 2005 to 2015 at the echocardiography laboratories of three academic centers (Amiens, Lille, and Brussels). Inclusion criteria were (1) the presence of NF-LG "severe" AS with preserved LVEF diagnosed by transthoracic echocardiography based on the following criteria: AVA <1 cm^2, mean pressure gradient (MPG) <40 mm Hg, indexed stroke volume ≥35 ml/m^2, and LVEF ≥50% and (2) availability of a second follow-up Doppler echocardiographic examination at least 6 months

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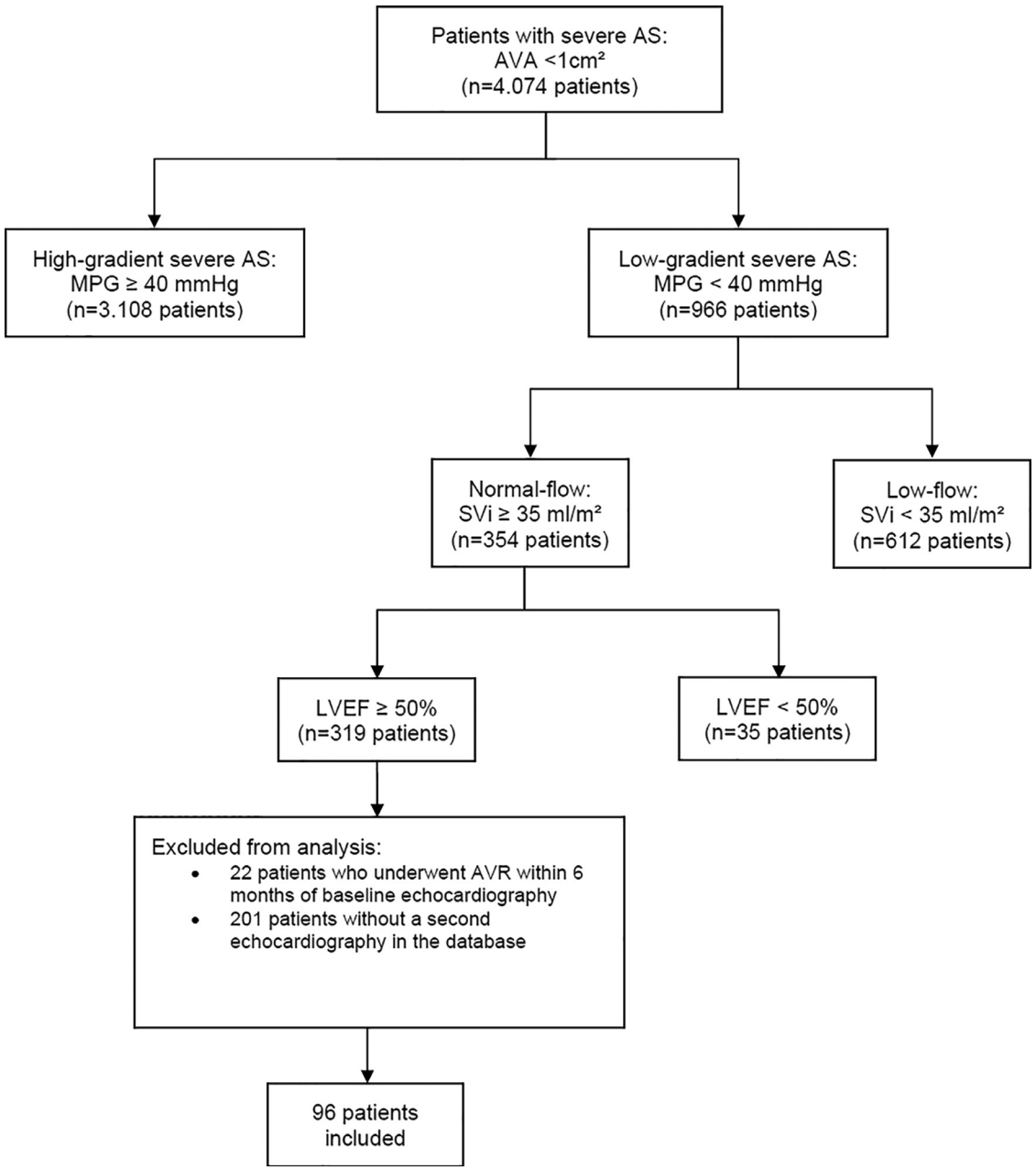

Figure 1. Flow chart of the study. AS = aortic stenosis; AVA = aortic valve area; AVR = aortic valve replacement; LVEF = left ventricular ejection fraction; MPG = mean pressure gradient; SVI = stroke volume index.

after baseline echocardiography (Figure 1). We excluded (1) patients with more than mild aortic and/or mitral regurgitation; (2) patients with prosthetic valves, congenital heart disease (with the exception of bicuspid aortic valves), supravalvular or subvalvular AS, or dynamic LV outflow tract obstruction; (3) patients experiencing AVR between the 2 examinations; and (4) patients who did not provide authorization to be included in the study. The second echocardiography was performed when scheduled during the patient's follow-up or when requested by the patient's referring cardiologist. When several follow-up echocardiograms were performed, we used the last one available for analysis. Rapid progression of AS was defined as an increase of peak aortic jet velocity ≥0.3 m/s/year.[19]

Baseline clinical and demographic characteristics, including cardiovascular risk factors, the presence of symptoms according to New York Heart Association (NYHA) class, co-morbidity status, and the presence of coronary artery disease (defined by the presence of a documented history of acute coronary syndrome, coronary artery disease previously confirmed by coronary angiography, or history of coronary revascularization), were retrospectively recorded from medical charts. The Charlson co-morbidity index was calculated for each patient. We obtained institutional review board authorizations before conducting the study. The study was conducted in accordance with institutional policies, national legal requirements, and the revised Declaration of

Helsinki. Given the retrospective nature of the study inform consent was waived.

Blood pressure and heart rate were measured for all patients at the time of echocardiography. LV outflow tract (LVOT) diameter was measured in a zoomed cine loop of the parasternal long-axis view in early systole at the level of aortic cusp insertion. Aortic flow was systematically recorded using continuous wave Doppler from several views (apical 5-chamber, right parasternal, suprasternal, and epigastric).[20] The view identifying the highest velocities was used to determine peak aortic jet velocity and calculate the aortic velocity-time integral (VTI) and MPG (using the simplified Bernoulli equation). Three consecutive measurements for patients in sinus rhythm or 5 consecutives measurements for patients in atrial fibrillation (AF) in this view were systematically averaged. The LVOT VTI was recorded using pulsed-wave Doppler from the apical 5-chamber view, with the sample volume positioned approximately 5 mm proximal to the aortic valve.[18] The alignment of both pulsed and continuous wave Doppler was optimized to be parallel with aortic flow. Effective AVA was calculated using the continuity equation: π x (LVOT area / 2)^2 $\times$ (LVOT VTI) / (Aortic VTI). Stroke volume was calculated by multiplying the LV outflow tract area with the LV outflow tract VTI and was indexed to BSA. The degree of calcification of the aortic valve was assessed during echocardiography.[21] LVEF and ventricular volumes were calculated using the Simpson biplane method. LV wall thickness and dimensions were measured, when possible, from M-mode imaging or by default from 2-dimensional images obtained in the parasternal long-axis view using the leading-edge methodology. LV mass was estimated by the formula on the basis of linear measurements and indexed to BSA. LV hypertrophy was defined as a LV mass index >115 g m^{-2} in men and >95 g m^{-2} in women and patients were classified according to 4 patterns of LV geometry: normal; LV concentric remodeling; eccentric LV hypertrophy; and concentric LV hypertrophy.[22] Systolic pulmonary artery pressure was recorded from the maximum peak tricuspid regurgitation velocity in any view using the simplified Bernoulli equation.

Statistical analysis was performed using SPSS version 25 (IBM, Armonk, NY). Categorical variables were summarized as counts and frequency percentages. Because of skewed distribution, continuous variables were expressed as medians and interquartile ranges. For comparison between baseline and follow up, categorical variables were compared using the Pearson chi-square test and continuous variables by matched-pair analysis using the paired *t* test (for normally distributed variables) or paired samples Wilcoxon test (for non-normally distributed variables). Annualized progression was calculated as the difference between the last measurement and the first measurement divided by the duration of follow-up. Univariate and multivariate linear regression were performed to identify factors associated with annualized progression of Vmax. All covariates associated with Vmax increase in univariate analysis ($p < 0.10$) were entered in the model for multivariable analysis. The limit of statistical significance was $p < 0.05$.

Table 1
Baseline demographic and clinical characteristics of the study patients (n = 96)

Variable	Study population
Age (years)	79 (74-84)
Men	36 (38%)
Body mass index (kg/m^2)	26 (23-29)
Body surface area (m^2)	1.74 (1.56-1.88)
Heart rate (beats/minute)	70 (61-79)
Systolic blood pressure (mm Hg)	140 (129-150)
Diastolic blood pressure (mm Hg)	75 (70-80)
Hypertension	74 (77%)
Diabetes mellitus	21 (22%)
Coronary artery disease	35 (37%)
Prior myocardial infarction	14 (15%)
Prior atrial fibrillation	25 (26%)
Charlson comorbidity index	3 (1-4)
Euroscore II	2.01 (1.24-3.94)
NYHA class	
I-II	79 (83%)
III-IV	16 (17%)

NYHA = New York Heart Association.

Continuous variables are expressed as medians (25th and 75th percentiles) and categorical variables as counts and percentages.

Results

The baseline demographic and clinical characteristics of the 96 patients are presented in Table 1. The median age was 79 years, with a predominance of women (62%). More than 75% of the study population had hypertension, one-quarter had diabetes mellitus, and almost 40% had coronary artery disease. The Charlson co-morbidity index and Euroscore II were low at echocardiographic diagnosis, with a median of 3 and 2.01, respectively. Patients were mostly asymptomatic or pauci-symptomatic (83%) at diagnosis.

The baseline and follow-up echocardiographic parameters are displayed in Table 2. The median time between the 2 echocardiographic examinations was 25 (15 to 52) months.

At follow-up, the peak aortic jet velocity increased by 0.65 $\pm$ 0.60 m/s over baseline (Figure 2), corresponding to a median annual rate of progression of 0.25 (0.08 to 0.44) m/s/year (mean 0.34 m/s/year). Overall, 80 patients (84%) showed an increase in peak aortic jet velocity at follow-up. In this group, the median annual progression rate was 0.32 (0.14 to 0.47) m/s/year (mean 0.42 m/s/year). The increase in Vmax between baseline and follow-up was $\geq$0.3 m/s in 43 patients (44.8%).

At follow-up, MPG showed a 13 $\pm$ 11 mm Hg mean increase compared to baseline (Figure 2), corresponding to a median annual rate of progression of 4.3 (1.7 to 8.1) mm Hg/year (mean 6 mm Hg/year). Overall, we observed an increase in MPG in 84 patients (88%), a decrease in 6 (6%), and it remained unchanged in 6 (6%). The increase in MPG between baseline and follow-up was $\geq$4 mm Hg/year in 55 patients (57.3%).

At follow-up, the reduction in AVA was -0.16 ± 0.16 cm^2 (Figure 2), reflecting a median annual progression rate of -0.05 (-0.10 to -0.02) cm^2/year (mean -0.06 cm^2/year). A decrease in AVA was observed in 80 patients (83%) at follow-up. In this group, the median annual

Table 2
Baseline and follow-up echocardiographic parameters of the study population (n = 96)

Variable	Baseline	Follow-up	p value
Aortic valve area (cm^2)	0.87 (0.82-0.94)	0.72 (0.62-0.81)	**<0.001**
Indexed aortic valve area (cm^2/m^2)	0.51 (0.46-0.54)	0.42 (0.37-0.47)	**<0.001**
Peak aortic jet velocity (m/s)	3.46 (3.20-3.64)	4.01 (3.70-4.39)	**<0.001**
Transaortic mean pressure gradient (mmHg)	28 (25-33)	39 (34-50)	**<0.001**
Aortic valve velocity time integral (cm)	79 (70-90)	94 (84-111)	**<0.001**
Dimensionless index	0.27 (0.24-0.29)	0.23 (0.18-0.26)	**<0.001**
LV outflow tract diameter (mm)	20 (19-22)	20 (19-22)	0.95
LV outflow tract velocity time integral (cm)	23 (20-25)	21 (18-24)	**0.003**
Stroke volume (ml)	72 (64-83)	66 (58-79)	**0.006**
Indexed stroke volume (ml/m^2)	41.2 (37.8-46.7)	38.8 (34.0-45.4)	**0.002**
Cardiac output (ml/min)	5.11 (4.14-5.82)	4.70 (4.03-5.50)	0.07
Cardiac index ($ml/min/m^2$)	2.90 (2.60-3.32)	2.77 (2.35-3.33)	0.16
Heart rate (/min)	70 (61-79)	71 (63-82)	0.56
LV end-diastolic diameter (mm)	46 (41-51)	45 (41-51)	0.39
LV end-systolic diameter (mm)	28 (23-32)	30 (23-34)	0.14
LV end-diastolic septum thickness (mm)	11 (10-13)	13 (11-15)	**0.001**
Indexed LV end-diastolic volume (ml/m^2)	62 (51-78)	57 (48-72)	0.14
Indexed LV end-systolic volume (ml/m^2)	21 (16-28)	20 (14-27)	0.33
LV ejection fraction (%)	65 (61-71)	65 (57-71)	0.74
Index LV mass (g/m^2)	138 (106-176)	147 (115-182)	0.39
LV geometry			
Normal	8 (9%)	5 (6%)	0.29
Concentric remodeling*	8 (9%)	12 (14%)	0.23
Eccentric LV hypertrophy	24 (27%)	9 (10%)	**0.004**
Concentric LV hypertrophy	50 (55%)	63 (70%)	**0.025**
Valvulo-arterial impedance (mm $Hg/ml/m^2$)	3.95 (3.45-4.47)	4.37 (3.91-5.25)	**<0.001**
sPAP (mm Hg)	31 (25-40)	36 (27-44)	**0.04**
LA area (cm^2)	23 (20-27)	27 (21-32)	**0.02**
E/e' ratio	13.1 (10.0-16.3)	12.0 (9.35-17.0)†	0.85

LA = left atrial; LV = left ventricular; sPAP = systolic pulmonary artery pressure.
Continuous variables are expressed as medians (25th and 75th percentiles), and categorical variables as counts and percentages.
* Concentric remodeling was defined by a relative wall thickness index >0.42 in the absence of left ventricular hypertrophy (indexed LV mass <115 g/m^2 in men and <95 g/m^2 in women).
† Available for 68 patients.
Bold p values: $p < 0.05$.

reduction in AVA was −0.07 (−0.11 to −0.03) cm^2/year (mean −0.09 cm^2/year). The indexed AVA also showed a significant decrease at follow-up relative to baseline (p <0.001).

At follow-up, 46 patients (48%) had acquired the features of classical HG-SAS (ie, MPG ≥40 mm Hg, AVA <1 cm^2). In these patients, the median progression of peak aortic jet velocity, MPG, and AVA was 0.32 (0.18 to 0.45) m/s/year (mean 0.39 m/s/year), 6.6 (3.0 to 9.6) mm Hg/year (mean 8 mm Hg/year), and −0.06 (−0.11 to −0.04) cm^2/year (mean −0.08 cm^2/year), respectively. Factors associated with annualized progression of Vmax are displayed in Table 3. On multivariable linear regression analysis, age <70 years, Vmax at baseline ≤3 m/s, and concentric LV hypertrophy were positively associated with annualized progression of Vmax. At follow-up, 11 patients (11%) had acquired the features of low-flow low-gradient severe AS with preserved LVEF (ie, indexed stroke volume <35 ml/m^2, MPG <40 mm Hg, AVA <1 cm^2 and LVEF ≥50%), whereas 4 (4%) had acquired those of low-flow low-gradient severe AS with reduced LVEF (LVEF between 32% and 49%).

No significant change over time were observed in terms of LV end-diastolic diameter, LV end-systolic diameter, indexed LV mass or LVEF (all p >0.14; Table 2, Figure 3). However, over time, we observed an increase in the number of patients with concentric LV hypertrophy (from 55% to 70%, p = 0.025), at the expense of less eccentric LV hypertrophy (from 27% to 10%, p = 0.004), and a significant increase in left atrial area (p = 0.02), systolic pulmonary artery pressure (p = 0.04), and valvulo-arterial impedance (p <0.001; Table 2, Figure 4). Stroke volume and stroke volume indexed to BSA both showed a significant decrease at follow-up relative to baseline (p = 0.006 and p = 0.002, respectively; Table 2, Figure 4).

After the second echocardiography, 26 patients (27%) underwent AVR (mean time: 6 ± 13 months) and 31 patients (32%) died (mean time: 14 ± 27 months).

Discussion

We demonstrate significant hemodynamic progression over time in NF-LG-SAS with preserved LVEF. Indeed, at

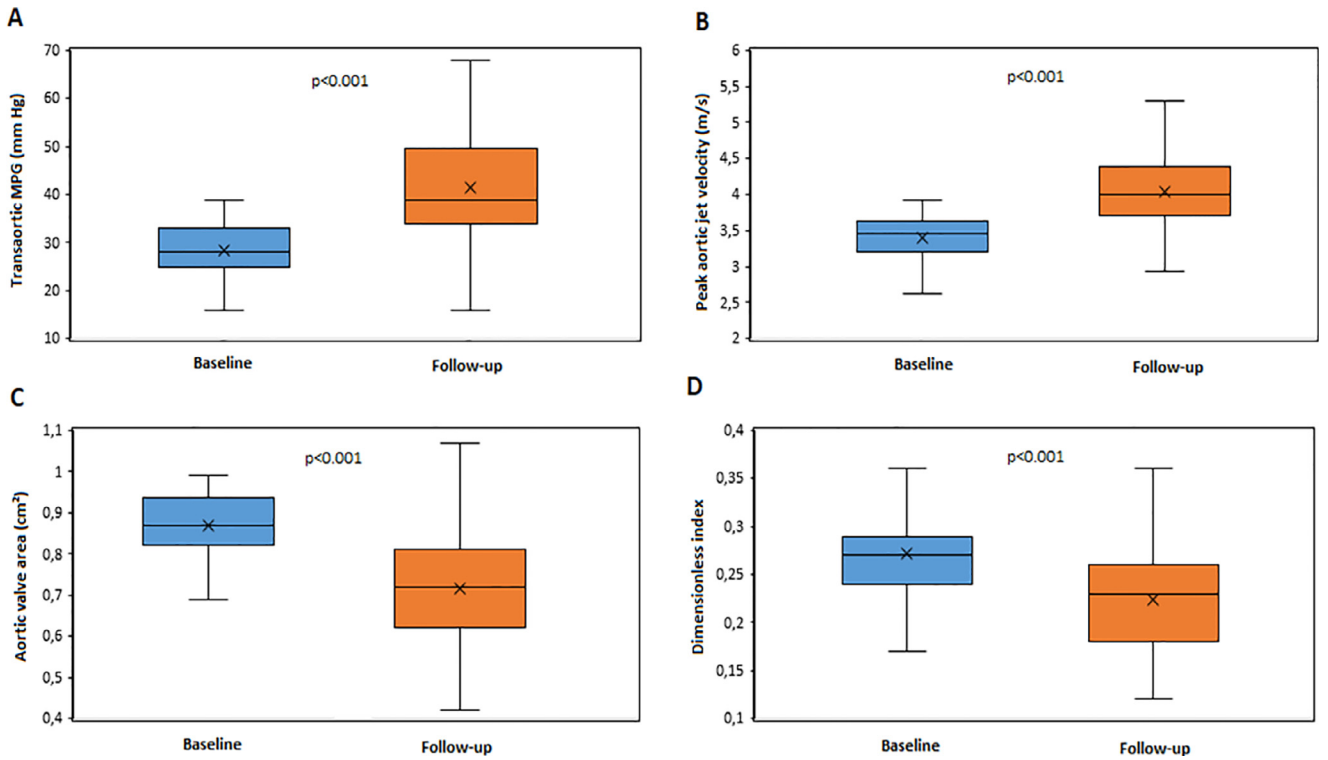

Figure 2. Changes in hemodynamic parameters of aortic stenosis severity over time: **(A)** transaortic mean pressure gradient, **(B)** peak aortic jet velocity, **(C)** aortic valve area, and **(D)** dimensionless index. Solid lines in the boxplots represent the median value and cross mark in the boxplots represent the mean value. MPG = mean pressure gradient.

follow-up, we observed worsening of at least 1 parameter of AS severity quantification (MPG, peak aortic jet velocity, or AVA) in >80% of patients. Mean MPG and peak aortic jet velocity were significantly higher at follow-up than at baseline (p <0.001 both), with 48% of patients developing the hemodynamic profile of HG-SAS. Median annual rates of progression of MPG and peak aortic jet velocity were 4.3 mm Hg/year and 0.25 m/s/year, respectively, with a simultaneous annual reduction of AVA of 0.05 cm^2/year. Such hemodynamic progression was not associated with

Table 3
Factors associated with annualized progression of Vmax identified by univariate and multivariable linear regression analysis

Variable	Annualized progression of Vmax			
	Univariate analysis		Multivariable analysis	
	r	p	r	p
Age >70 years	−0.221	<0.001	−0.284	0.014
Men	−0.16	0.31	–	–
Body surface area (per 0.1 cm^2 decrease)	0.059	0.57	–	–
NYHA (3-4 vs 1-2)	0.180	0.083	0.160	NS
Hypertension	−209	0.042	−0.038	NS
Coronary artery disease	0.006	0.96	–	–
Diabetes mellitus	−0.201	0.051	−0.190	NS
Atrial fibrillation	−0.016	0.88	–	–
Charlson comorbidity index	0.014	0.89	–	–
Vmax >3 m/s	−0.234	0.022	−0.220	0.030
Stroke volume index (ml)	0.126	0.22	–	–
LV end-diastolic diameter	−0.187	0.073	−0.066	0.53
LVEF (%)	0.027	0.80	–	–
Index LV mass (g/m^2)	−0.083	0.44	–	–
Concentric LV hypertrophy	0.268	0.011	0.214	0.026
Valvulo-arterial impedance (mm Hg/ml/m^2)	−0.023	0.83	–	–
Left atrial area (cm^2)	−0.036	0.82	–	–
Systolic pulmonary artery pressure (mm Hg)	0.154	0.18	–	–

LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; NS = nonsignificant.

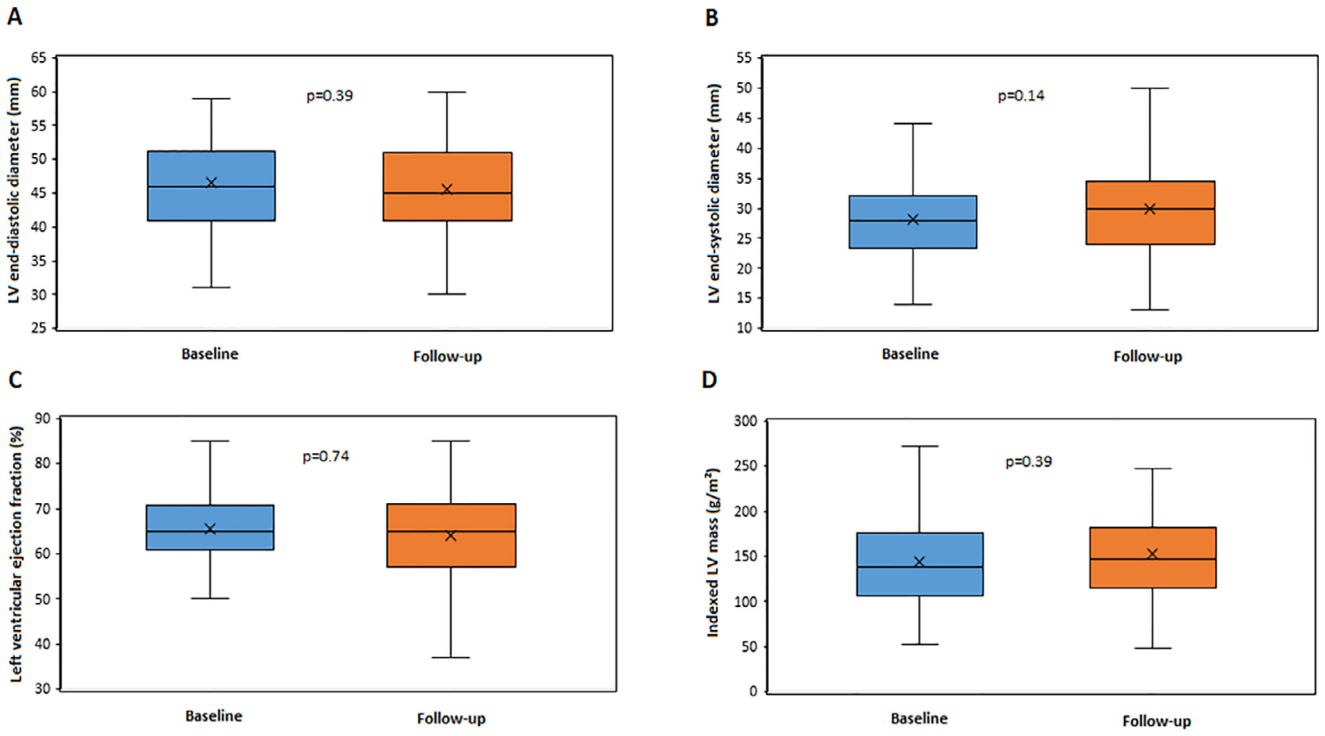

Figure 3. Changes in left ventricular (LV) end-diastolic diameter **(A)**, LV end-systolic diameter **(B)**, left ventricular ejection fraction **(C)**, and indexed LV mass **(D)** over time. Solid lines in the boxplots represent the median value and cross mark in the boxplots represent the mean value. LV = left ventricular.

significant LVEF impairment. However, we observed more LV concentric hypertrophy over time and an increase in left atrial area.

Patients with NF-LG-SAS and preserved LVEF are classically elderly, with a small BSA and less concentric LV hypertrophy, less severe left atrial dilation, and less severely impaired systolic longitudinal function than other forms of severe AS.[3,4] However, its outcome and its management are a matter of debate. Several studies have suggested a poor outcome for this form of AS.[6,7,11–13] A

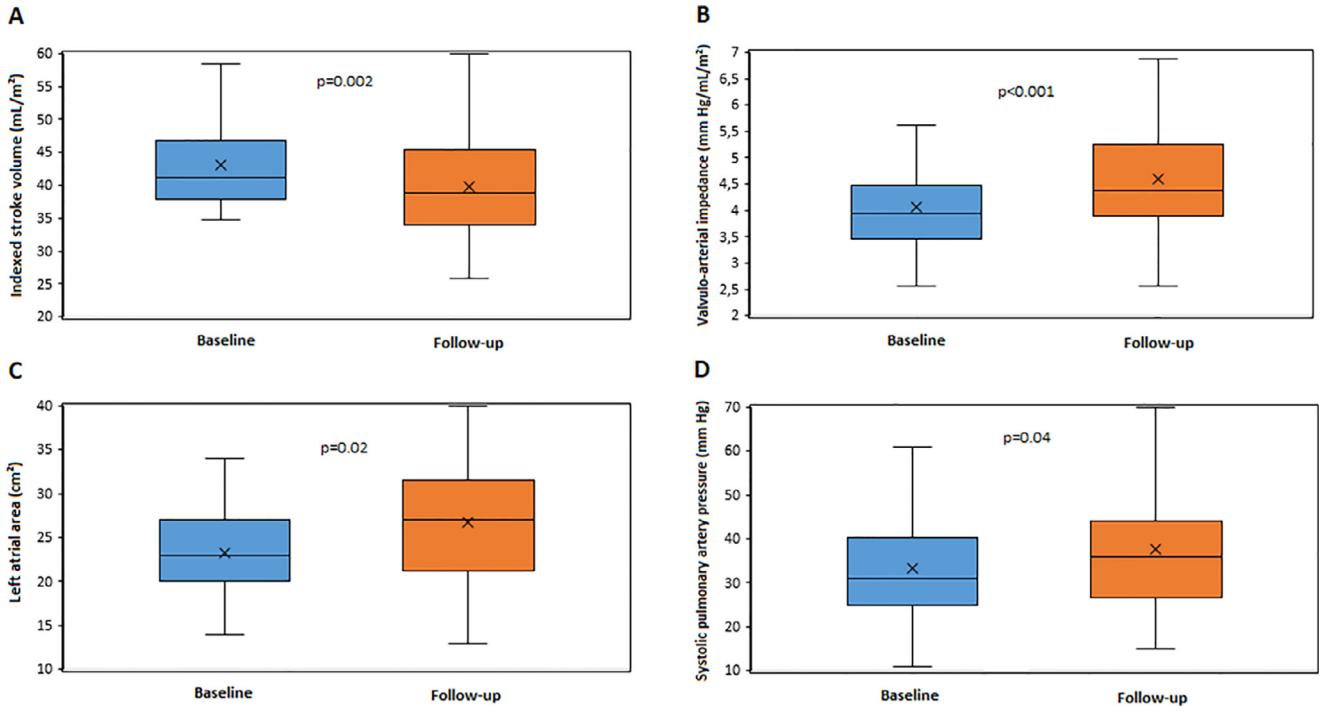

Figure 4. Changes in indexed stroke volume **(A)**, valvulo-arterial impedance **(B)**, left atrial area **(C)**, and systolic pulmonary artery pressure **(D)** over time. Solid lines in the boxplots represent the median value and cross mark in the boxplots represent the mean value.

meta-analysis even suggested that the prognosis of this entity is comparable to that of HG-SAS, reporting a 52% reduction in the relative risk of mortality when AVR was performed in this population.[6] In contrast, we and others reported that patients with NF-LG-SAS show comparable survival to that of moderate AS patients when AVR was performed during follow-up, according to guidelines and suggest that AVR performed at the stage of NF-LG AS does not improve survival.[4,14,16,18] Moreover, we recently reported that patients with HG-SAS showed significant excess mortality compared with patients with NF-LG-SAS with preserved LVEF.[18] These data suggest that most of these patients should be considered to have a moderate form of AS and should be initially treated conservatively.[18] Accordingly, Kang et al[16] reported that overall and cardiovascular mortality were not significantly different for symptomatic patients with NF-LG-SAS when a watchful observation strategy was applied compared with an early AVR strategy. Current European guidelines consider that patients with NF-LG-SAS usually only have moderate AS and should not be referred at this stage for AVR.[23,24]

Although changes in Doppler echocardiographic parameters over time in patients with low-flow low-gradient severe AS and preserved LVEF have been specifically investigated,[25,26] there are no specific data concerning the evolution over time of hemodynamic severity parameters in the NF-LG-SAS setting. These data are however essential for understanding the "true" severity of this form. Prospective studies on the rate of hemodynamic progression in AS have reported an average rate of increase in MPG of 7 mm Hg/year, with an increase in aortic jet velocity of 0.3 m/s/year, and a decrease in AVA of 0.1 cm^2/year.[27] Here, we report a comparable mean progression in patients with NF-LG-SAS and preserved LVEF (averages of 0.34 m/s/year, 6 mm Hg/year, and 0.06 cm^2/year, respectively), but with individual variations. Accordingly, Kang et al[16] reported that MPG increased significantly in patients with NF-LG-SAS at a median echocardiographic follow-up of 1.9 years when a strategy of watchful observation was applied. Here, we observed that nearly half the patients (48%) acquired the features of classical HG-SAS, with a median follow-up of 25 months. Such a high rate of progression of NF-LG-AS with preserved LVEF toward classical HG-SAS supports careful and close echocardiographic monitoring for these patients, especially when MPG is close to 40 mm Hg or Vmax to 4 m/s.

During follow-up, we also observed changes in LV geometry, with more concentric LV hypertrophy associated with an increase of LA area, suggesting evolution of the aortic valve disease. The observed significant decrease in stroke volume index may suggest an alteration of LV systolic function. However, we did not observe a significant reduction in LVEF or left ventricular volume variation.

Our study had several limitations. First, it was subject to the limitations inherent in the analysis of retrospective data. Second, there was a certain degree of selection bias, as we selected patients who had at least 1 available follow-up echocardiography and no aortic valve intervention between the 2 examinations. Third, although cardiologists with expertise in valvular heart disease performed the diagnosis and follow-up, inherent measurement errors may have led to a certain degree of misclassification of NF-LG-SAS as another form of AS. Fourth, valvular calcium scoring assessed by computed tomography, which has been identified as a predictor of AS progression was not available in our database. Fifth, left ventricular global longitudinal strain data were not available. Finally, we identified some factors associated with the hemodynamic progression of AS. Unfortunately, the aortic valve calcium scoring using computer tomography, a classic factor of progression, was not available in our database.

In conclusion, these findings strongly suggest that NF-LG-SAS with preserved LVEF generally represents an "intermediate stage" of AS between classical moderate AS and classical HG-SAS with preserved LVEF. Over time, these patients present a high risk of rapid progression to high-gradient AS, with LA and LV remodeling, without significant LVEF impairment. They should therefore be subject to close and rigorous clinical and echocardiographic monitoring and be referred for AVR when indicated, in accordance with current European guidelines.

Author Contribution

The contribution of the authors is as follows:

Design of the study: Tribouilloy.

Acquisition of data: All authors.

Analysis and interpretation of data: Chadha, Bohbot, Tribouilloy.

Drafting of the manuscript: Chadha, Bohbot, Tribouilloy;

Critical revision for important intellectual content: All authors.

Statistical analysis: Chadha, Bohbot.

Study supervision: Tribouilloy, Maréchaux, Vanoverschelde.

Disclosures

The authors have no conflicts of interest to disclose.

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