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Differential left ventricular remodelling and longitudinal function distinguishes low flow from normal-flow preserved ejection fraction low-gradient severe aortic stenosis

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Aims

There is uncertainty in identifying patients with severe aortic stenosis (AS) with preserved left ventricular (LV) ejection fraction, low flow, and low gradients (LFLG). Prior studies propose that these patients demonstrate significant concentric remodelling and decreased survival, while others suggest that they have features and survival similar to moderate AS.

Methods and results

We compared the clinical characteristics, echocardiographic features, and overall survival of LFLG AS patients ($n = 38$) to those with normal-flow, low-gradient (NFLG) severe AS ($n = 75$) and moderate AS ($n = 70$). Low-flow, low-gradient patients had the lowest end-diastolic volume index (43 vs. 54 vs. 54 mL/m², $P < 0.001$), highest relative wall thickness (RWT) (60 vs. 49 vs. 48%, $P < 0.001$), and lowest septal mitral annular displacement (1.0 vs. 1.5 vs. 1.5 cm, $P < 0.001$). New York Heart Association (NYHA) class III/IV symptoms were the most frequent in the LFLG group (29 vs. 11 vs. 3%, $P < 0.001$). Survival at 3 years was significantly lower in LFLG compared with NFLG ($P = 0.006$) and moderate AS ($P = 0.002$), but not different between NFLG and moderate AS ($P = 0.49$). Higher NYHA classification (HR 1.77, 95% CI 1.22–2.57), RWT > 50% (HR 3.28, 95% CI 1.33–8.1), and septal displacement < 1.1 cm (HR 3.93, 95% CI 1.96–7.82) but not low flow were independent predictors of survival in Cox proportional hazards analysis.

Conclusion

Preserved ejection fraction, LFLG AS patients exhibit marked concentric remodelling and impaired longitudinal functional—features that predict their poor long-term survival. Normal-flow, low-gradient AS patients have outcomes similar to moderate AS.

Keywords

Aortic stenosis • Echocardiography • Remodelling • Haemodynamics

Introduction

Patients with severe aortic stenosis (AS) with preserved left ventricular (LV) ejection fraction (EF), low flow, and low gradient (LFLG), commonly known as ‘paradoxical low-flow AS’, may be difficult to identify. These individuals have LVEF in the normal range and aortic valve area (AVA) of <1.0 cm², but the mean gradient (MG) is in the mild to moderate range. The latter has

been attributed to a low-flow state defined as a stroke volume index (SVi) of <35 mL/m².¹ However, the calculated SVi can be variable depending on the formula used and can fall very close to the 35 mL/m² cut-off making the diagnosis of paradoxical low flow challenging. Associated with this haemodynamic profile is thought to be a unique cluster of features including small cavity size and significant concentric remodelling.^{1,2} Moreover, these patients have evidence of subclinical ventricular

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dysfunction^{3–5} and decreased long-term survival without valve replacement.^{1,6,7}

However, other authors have reported that low-gradient, severe AS is, in fact, largely due to inconsistent grading or inaccurate measurements.^{8,9} Additionally, other data suggest that AS patients with an AVA <1.0 cm² but a MG <40 mmHg do not have excessive hypertrophy to pressure load and have outcomes similar to moderate AS.¹⁰ This conclusion may relate to the observation that many patients with low gradients and an AVA <1.0 cm² also have normal flow⁹ and, therefore, may not carry the dismal prognosis of the ‘paradoxical, low-flow’ group. We hypothesized that when low-gradient AS patients are further sub-categorized by transvalvular flow, LFLG patients demonstrate a distinct pattern of maladaptive concentric remodelling and impaired longitudinal function secondary to pressure load which should be used to correctly distinguish them from normal-flow, low-gradient (NFLG) severe AS and moderate AS.

Methods

Patient population

A retrospective search of our echocardiographic database was performed from January through December 2008 for patients with severe AS (AVA ≤ 1.0 cm²) and normal LV systolic function (LVEF ≥ 55%) and wall motion (Figure 1). Four hundred and seventy-four patients were identified. Those with greater than mild aortic regurgitation, mitral stenosis, and mitral regurgitation (n = 170), an intracavitary gradient (n = 13), and technically difficult studies (n = 35) were excluded. From the remaining 256 patients, 143 patients with high-gradient AS (AVA < 1.0 cm² and MG > 40 mmHg) were excluded from the final analysis. The remaining 113 were further subdivided

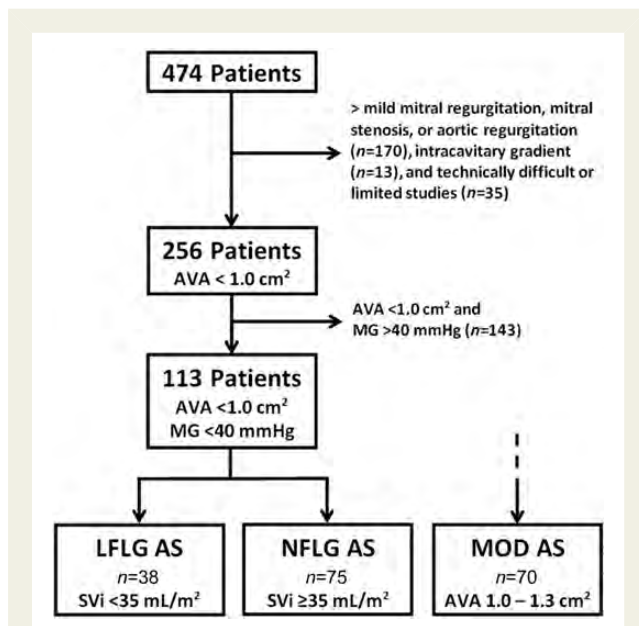


Figure 1 Description of patient population. AS, aortic stenosis; AVA, aortic valve area; LFLG, low-flow, low-gradient; MG, mean gradient; MOD, moderate; NFLG, normal-flow, low-gradient; SVi, stroke volume index.

by the Doppler-derived SVi into two groups: (i) LFLG (SVi < 35 mL/m²) and (ii) NFLG (SVi ≥ 35 mL/m²).

Both of these groups were compared with a third group of seventy patients with moderate AS (AVA 1.0–1.3 cm²) and normal LVEF. Moderate AS patients were consecutively selected and met the same exclusion criteria as the severe AS groups. Baseline demographics and history of cardiovascular risk factors and disease were collected from all patients. Symptoms were evaluated for each patient according to the New York Heart Association (NYHA) classification by review of medical records at the time of the index echocardiogram.

Stroke volume and aortic stenosis severity

The Doppler-derived SVi was calculated as follows:

$$SVi = \frac{LVOT\ CSA \times VTI}{BSA}$$

where LVOT CSA is the LV outflow tract cross-sectional area calculated from the LV outflow tract diameter and VTI is the velocity-time integral of the LV outflow tract pulsed-wave Doppler flow profile. The LV outflow tract diameter was measured twice in each patient in a standardized method as per guidelines¹¹ with care taken to prevent measurement underestimation. The transvalvular flow rate was calculated as the Doppler SVi divided by the systolic ejection period. The stroke volume index was also calculated according to the volumetric methods as the end-diastolic minus the end-systolic volume index. Cardiac output was calculated as the product of heart rate and volumetric SVi and indexed to body surface area. Aortic stenosis severity was evaluated by calculating the continuity-equation derived AVA, AVA index, mean transaortic gradient, peak transaortic velocity, and dimensionless velocity index. The energy loss index, which accounts for the distal recovered pressure gradient, and the aortic valve resistance were calculated as previously recommended.¹¹

Left ventricular geometry

Left ventricular wall thickness and internal dimensions were measured in the parasternal long-axis view. Relative wall thickness (RWT), an index of concentric remodelling, was calculated as follows:

$$RWT = \frac{200 \times PWT}{LV\ EDD}$$

where PWT is the posterior wall thickness and EDD is the end-diastolic dimension. Left ventricular volumes were measured at end-diastole and end-systole using the biplane Simpson's method. The left ventricular mass was calculated as recommended by Devereux *et al.*¹² The LV mass to end-diastolic volume ratio was also calculated as a secondary index of concentric remodelling. Concentric remodelling is defined as an increased LV wall thickness or mass with cavity size reduction. Left ventricular volumes and mass were indexed to body surface area.

Left ventricular systolic and diastolic function

Left ventricular EF was calculated using the biplane Simpson's method, while endocardial and mid-wall fractional shortening were calculated according to the recommended formulas.¹³ Longitudinal systolic function was assessed by measuring the pulsed tissue Doppler-derived systolic septal and lateral mitral annular peak velocity (S') and displacement.¹⁴ Filters and gains were adjusted to optimize the quality of the profile. Displacement was calculated by integrating the annular velocity profile over time. Left ventricular diastolic function was assessed by measuring diastolic mitral inflow and annular

velocities, pulmonary arterial systolic pressure, and left atrial volume. Tissue Doppler data were present in 173 of 183 (95%) and pulmonary arterial systolic pressure could be estimated in 147 of 183 (80%) patients. Left atrial volume was measured according to the biplane area-length method and indexed to body surface area.¹³

Survival analysis

Death from any cause was determined at 3 years from the time of the index echocardiogram in each patient. Individuals were censored from the survival analysis if they underwent aortic valve replacement before 3 years. Survival data were complete for all patients and were obtained from the Social Security death index.

Statistical analysis

Variables are expressed as mean \pm standard deviation. Continuous variables were compared with the one-way analysis of variance test with *post hoc* comparisons made with the Scheffe test. Categorical variables were compared with the Chi-square test. A *P*-value < 0.05 was considered statistically significant. Kaplan–Meier analysis was performed to depict overall survival between the three groups and by risk factors with differences in survival assessed with the log-rank test. Cox proportional hazards regression analysis was used to determine independent predictors of survival. Only unique variables with a *P*-value < 0.10 in univariable analysis were entered into the final multivariable model. A single candidate variable was selected from each of several domains (clinical, LV geometry, transvalvular flow, and

longitudinal function parameters) to avoid co-linearity and then entered into the final model. Curve fitting was performed with Graphpad Prism, version 5.0 (Graphpad Software, San Diego, CA, USA). All other analyses were performed with SPSS, version 18.0 (SPSS, Inc., Chicago, IL, USA).

Results

Among all severe AS patients with normal LVEF ($n = 256$), there were 38 LFLG (15%) and 75 NFLG (29%) patients. The remaining patients (56%) had high gradient, severe AS and were thus excluded from the final analysis. Baseline characteristics are depicted in *Table 1*. Low-flow, low-gradient patients were overall older with a trend for more females compared with the NFLG and moderate AS groups. Despite having gradients < 40 mmHg, a higher proportion of LFLG patients had a documented history of congestive heart failure with NYHA class III or IV symptoms being nearly 3 and 10 times more common than in NFLG and moderate AS patients, respectively (*Table 1*).

Stroke volume and aortic stenosis severity

Both Doppler and volumetric-derived transvalvular flow indices were lowest in the LFLG group but similar between NFLG and

Table 1 Baseline characteristics and symptoms

	LFLG (n = 38)	NFLG (n = 75)	Moderate (n = 70)	P-value
Age (years)	82.4 \pm 9.6 ^{*†}	76.0 \pm 9.8	76.9 \pm 8.8	0.002
Female, n (%)	26 (68)	39 (52)	32 (46)	0.08
Height (cm)	162.2 \pm 10.0 [†]	165.5 \pm 9.8	167.5 \pm 10.6	0.03
BMI (g/m ²)	26.6 \pm 8.0	27.1 \pm 5.7	27.6 \pm 4.5	0.73
BSA (m ²)	1.75 \pm 0.3 [†]	1.81 \pm 0.2	1.87 \pm 0.2	0.05
Standard deviations for blood pressure (mmHg) [‡]	132.1 \pm 20.7	130.7 \pm 16.2	136.6 \pm 17.7	0.13
Hypertension, n (%)	32 (84)	65 (87)	64 (91)	0.49
Dyslipidaemia, n (%)	28 (74)	68 (91)	58 (83)	0.06
Diabetes, n (%)	8 (21)	11 (15)	18 (26)	0.25
Smoking, n (%)	16 (42)	38 (51)	29 (41)	0.48
Coronary artery disease, n (%)	13 (34)	25 (33)	25 (36)	0.96
Stroke or TIA, n (%)	5 (13)	8 (11)	15 (21)	0.18
Peripheral vascular disease, n (%)	11 (29)	19 (25)	20 (29)	0.88
Atrial fibrillation, n (%)	12 (32)	11 (15)	15 (21)	0.11
Congestive heart failure, n (%)	11 (29) ^{*†}	4 (5)	7 (10)	0.001
Chronic kidney disease, n (%)	3 (8)	6 (8)	10 (14)	0.40
Symptoms				
NYHA class I, n (%)	21 (55) ^{*†}	56 (75)	59 (84)	0.004
NYHA class II, n (%)	6 (16)	11 (15)	9 (13)	0.91
NYHA class III/IV, n (%)	11 (29) ^{*†}	8 (11)	2 (3)	< 0.001

Values are expressed as mean \pm SD or n (%).

BMI, body mass index; BSA, body surface area; NYHA, New York Heart association; TIA, transient ischaemic attack.

**P* < 0.05 vs. NFLG.

[†]*P* < 0.05 vs. moderate.

[‡]Systolic blood pressure recorded at visit closest to index echocardiogram.

P-values by one-way ANOVA test for continuous variables and by Chi-square test for categorical variables.

moderate AS patients. Low-flow, low-gradient patients had the lowest AVA index, energy loss index, and highest aortic valve resistance, but a MG and peak velocity intermediate between moderate and NFLG AS (Table 2). Figure 2 depicts the relationship between AVA and MG in the entire cohort with the corresponding curve fit. For a given AVA, low-flow patients have a significantly lower MG compared with normal-flow AS patients. The vast majority of LFLG patients are below the fitted curve for the entire cohort, whereas NFLG and moderate AS groups are generally on or above this curve. This observation is consistent with a relationship between AVA and MG in LFLG AS which is distinct from NFLG and moderate AS.

Left ventricular geometry

Low-flow, low-gradient patients had the smallest LV cavity size but greatest RWVT indicating significant concentric remodelling (Table 3). The LV mass index, however, was not significantly different among the groups. The LV mass adjusted for end-diastolic volume was also highest in the LFLG group. No differences were observed between NFLG and moderate AS groups with respect to LV size, wall thickness, or mass to end-diastolic volume ratio.

Left ventricular function

Left ventricular EF was similar between the groups, but LFLG patients were more likely to have an EF < 60%. Indices of systolic longitudinal function, however, were most reduced in LFLG patients, while these parameters were similar in NFLG and

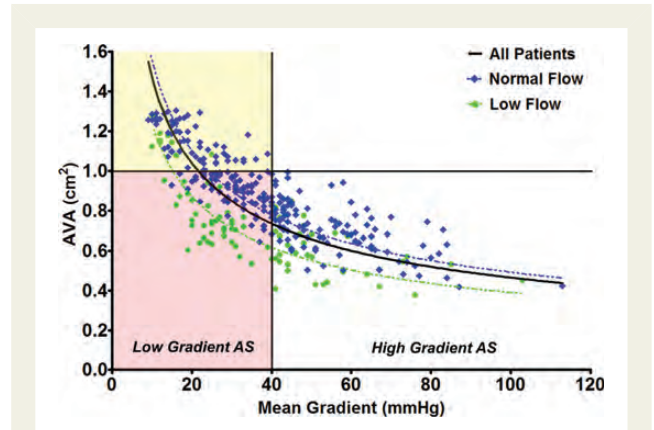


Figure 2 Relationship between mean gradient (MG) and aortic valve area (AVA) in the entire cohort including low-gradient, severe ($n = 113$, pink shade), high gradient, severe ($n = 143$), and moderate ($n = 75$, yellow shade) aortic stenosis (AS). Horizontal and vertical lines represent current cut-offs for AVA and MG for severe AS, respectively. Solid black, dashed blue, and dashed green lines represent curve fit for all, preserved EF, normal flow, and low-flow AS patients, respectively. Normal-flow (blue squares) severe and most moderate AS patients fall on or above the fitted curve for the entire cohort (solid black line) due to similar flow indices. In contrast, patients with low flow (green circles) fall predominantly below the fitted curve for all patients indicating a lower MG for a given AVA and a relationship between AVA and MG that is distinct from normal-flow AS.

Table 2 Stroke volume and aortic stenosis severity

	LFLG (n = 38)	NFLG (n = 75)	Moderate (n = 70)	P-value
Stroke volume				
Doppler stroke volume (mL)	52.9 ± 8.0* [†]	76.9 ± 10.5	76.2 ± 13.0	<0.001
Doppler stroke volume index (mL/m ²)	30.8 ± 4.1* [†]	42.8 ± 6.5	41.1 ± 7.3	<0.001
Volumetric stroke volume (mL)	50.6 ± 9.7* [†]	69.7 ± 11.0	71.7 ± 13.0	<0.001
Volumetric stroke volume index (mL/m ²)	29.4 ± 4.7* [†]	38.6 ± 5.5	38.4 ± 5.4	<0.001
Transvalvular flow (mL/s)	172.6 ± 27.4* [†]	230.5 ± 29.5	229.8 ± 39.1	<0.001
Cardiac output (L/min)	3.5 ± 0.8* [†]	4.5 ± 0.9	4.6 ± 0.9	<0.001
Cardiac index (L/min/m ²)	2.0 ± 0.4* [†]	2.5 ± 0.6	2.5 ± 0.6	<0.001
LVOT peak velocity (m/s)	0.88 ± 0.12* [†]	0.99 ± 0.15	1.0 ± 0.14	<0.001
Aortic stenosis severity				
Aortic valve area (cm ²)	0.74 ± 0.10* [†]	0.90 ± 0.08 [†]	1.15 ± 0.09	<0.001
Aortic valve area index (cm ² /m ²)	0.43 ± 0.08* [†]	0.50 ± 0.07 [†]	0.63 ± 0.10	<0.001
Energy loss index (cm ² /m ²)	0.47 ± 0.09* [†]	0.56 ± 0.09 [†]	0.73 ± 0.15	<0.001
Mean gradient (mmHg)	25.5 ± 5.7* [†]	30.4 ± 5.8 [†]	19.4 ± 7.2	<0.001
Peak velocity (m/s)	3.3 ± 0.4* [†]	3.6 ± 0.4 [†]	2.9 ± 0.5	<0.001
Aortic valve resistance (dynes*s*cm ⁻⁵)	200.8 ± 53.4* [†]	176.5 ± 31.7 [†]	110.2 ± 27.3	<0.001
Velocity index	0.27 ± 0.05 [†]	0.28 ± 0.04 [†]	0.35 ± 0.07	<0.001

Values are expressed as mean ± SD.
 LVOT, left ventricular outflow tract; VTI, velocity time integral.
 *P < 0.05 vs. NFLG.
[†]P < 0.05 vs. moderate.
 P-values by one-way ANOVA test.

Table 3 Left ventricular geometry and function

	LFLG (n = 38)	NFLG (n = 75)	Moderate (n = 70)	P-value
LV geometry				
End-diastolic diameter (mm)	39.5 ± 5.3 ^{*,†}	44.2 ± 5.0	44.2 ± 4.9	<0.001
End-systolic diameter (mm)	25.2 ± 5.1	27.2 ± 4.0	27.2 ± 4.1	0.04
End-diastolic volume index (mL/m ²)	42.8 ± 6.6 ^{*,†}	54.2 ± 8.7	54.0 ± 8.3	<0.001
End-systolic volume index (mL/m ²)	13.4 ± 4.2	15.7 ± 5.3	15.6 ± 4.8	0.04
Interventricular septum (mm)	12.8 ± 1.4 ^{*,†}	12.0 ± 1.6	11.7 ± 1.7	0.003
Posterior wall thickness (mm)	11.8 ± 1.7 ^{*,†}	10.8 ± 1.3	10.5 ± 1.5	<0.001
Relative wall thickness (%)	60.4 ± 10.5 ^{*,†}	49.4 ± 8.0	48.0 ± 8.0	<0.001
LV mass index (g/m ²)	98.8 ± 23.6	100.2 ± 22.3	93.7 ± 20.6	0.19
LV mass to end-diastolic volume ratio (g/mL)	2.3 ± 0.4 ^{*,†}	1.9 ± 0.4	1.8 ± 0.4	<0.001
LV hypertrophy, n (%)	15 (40)	29 (39)	17 (24)	0.12
RWT > 50%, n (%)	34 (90) ^{*,†}	37 (49)	24 (34)	<0.001
LVOT diameter (cm)	1.9 ± 0.2 ^{*,†}	2.0 ± 0.2	2.0 ± 0.2	0.001
LV systolic function				
Ejection fraction (%)	68.9 ± 7.0	71.6 ± 6.3	71.5 ± 5.8	0.07
Ejection fraction <60%, n (%)	7 (18) ^{*,†}	4 (5)	3 (4)	0.02
Fractional shortening (%)	36.5 ± 6.1	38.4 ± 5.0	38.6 ± 4.5	0.1
Midwall fractional shortening (%)	20.8 ± 4.2 ^{*,†}	23.6 ± 3.8	22.9 ± 3.2	0.001
Septal S' (cm/s)	5.2 ± 1.2 ^{*,†}	6.3 ± 1.1 [†]	6.9 ± 1.5	<0.001
Lateral S' (cm/s)	6.8 ± 1.9 ^{*,†}	7.8 ± 1.7	8.1 ± 1.9	0.004
Septal displacement (cm)	1.0 ± 0.3 ^{*,†}	1.5 ± 0.3	1.5 ± 0.3	<0.001
Lateral displacement (cm)	1.3 ± 0.3 ^{*,†}	1.7 ± 0.4	1.7 ± 0.3	<0.001
LV diastolic function				
E velocity (cm/s)	87.9 ± 25.2	86.3 ± 21.7	82.0 ± 19.3	0.33
E/A ratio	1.1 ± 0.7	1.0 ± 0.4	0.9 ± 0.3	0.07
Septal E' (cm/s)	4.9 ± 1.8 [*]	5.8 ± 1.5	5.7 ± 1.7	0.02
Lateral E' (cm/s)	6.6 ± 2.3	7.2 ± 2.5	7.1 ± 2.1	0.37
Septal E/E'	20.9 ± 11.3 ^{*,†}	15.6 ± 5.4	15.5 ± 6.0	0.006
Lateral E/E'	14.8 ± 6.3	13.0 ± 4.9	12.6 ± 5.3	0.12
Left atrial volume index (mL/m ²)	47.1 ± 14.4 ^{*,†}	40.2 ± 10.9	38.5 ± 8.7	0.002
Pulmonary arterial systolic pressure (mmHg)	40.7 ± 9.8	38.1 ± 6.9	39.6 ± 8.4	0.33

Values are expressed as mean ± SD or n (%).

A, late diastolic transmitral inflow velocity (in reference to 'E/A'); E, early diastolic transmitral inflow velocity; E', early diastolic mitral annular velocity; LV, left ventricular; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; S', systolic mitral annular velocity.

*P < 0.05 vs. NFLG.

†P < 0.05 vs. moderate.

P-values by one-way ANOVA test for continuous variables and by Chi-square test for categorical variables.

moderate AS patients (Table 3). Diastolic function was also most abnormal in LFLG patients who demonstrated the lowest early diastolic septal mitral annular velocity, highest E/E' ratio, and highest left atrial volume index, while these parameters were similar in NFLG and moderate AS patients.

Survival analysis

Kaplan–Meier analysis demonstrated a significant difference in survival between LFLG and NFLG AS (58 vs. 79%, $P = 0.006$) and moderate AS (58 vs. 85%, $P = 0.002$) patients at 3 years (Figure 3). There was no difference in survival, however, between NFLG and moderate AS groups ($P = 0.49$). Unique predictors of survival in the Cox proportional hazards model were RWT >

50% (HR 3.28, 95% CI 1.33–8.10, $P = 0.01$), systolic septal mitral annular displacement <1.1 cm (HR 3.93, 95% CI 1.96–7.82, $P < 0.001$), chronic kidney disease (HR 4.20, 95% CI 1.84–9.62, $P = 0.001$), and higher NYHA classification (HR 1.77, 95% CI 1.22–2.57, $P = 0.003$; Table 4). Three-year survival was 65% for RWT ≥ 50% and 91% for RWT < 50%. Three-year survival was 40% for septal mitral annular displacement <1.1 cm and 86% for displacement ≥ 1.1 cm (Figure 4).

Discussion

Our study demonstrates that among patients with preserved EF, low-gradient, severe AS, there exist two distinct subgroups

based on transvalvular flow. The LFLG subgroup exhibits a unique haemodynamic profile with a lower MG for a given AVA (Figure 2). Moreover, they display pronounced concentric remodelling with small cavity size and impaired longitudinal function despite preserved EF in the setting of severe pressure load. These latter

features are maladaptive as they are associated with the reduced SVi, worse NYHA class, and poor survival at 3 years. Since the prognosis of LFLG patients has been shown to improve with aortic valve replacement,^{1,15} it is important to identify these patients correctly.

NFLG patients, on the other hand, exhibit a haemodynamic profile and pattern of myocardial adaptation to pressure load that is distinct from LFLG and similar to moderate AS. These patients have less severe concentric remodelling with larger LV cavity size, relatively preserved longitudinal function, and, therefore, normal transaortic flow suggesting less advanced disease. They are more likely to be asymptomatic compared with those with LFLG AS, and their overall survival at 3 years is better than LFLG AS and similar to moderate AS. However, in contrast to moderate AS, the mean AVA observed in these patients is significantly lower, while transaortic gradients are higher, suggesting that this group may, in fact, be in a transitional phase between moderate and severe, high-gradient AS.

To correctly distinguish these two subgroups of preserved EF, low-gradient, severe AS, indices of concentric remodelling and longitudinal function should be used in conjunction with those of transvalvular flow. In Cox proportional hazards analysis, pronounced LV concentric remodelling and depressed longitudinal systolic function but not low-flow were, in fact, independently predictive of all-cause death at 3 years in low-gradient AS patients.

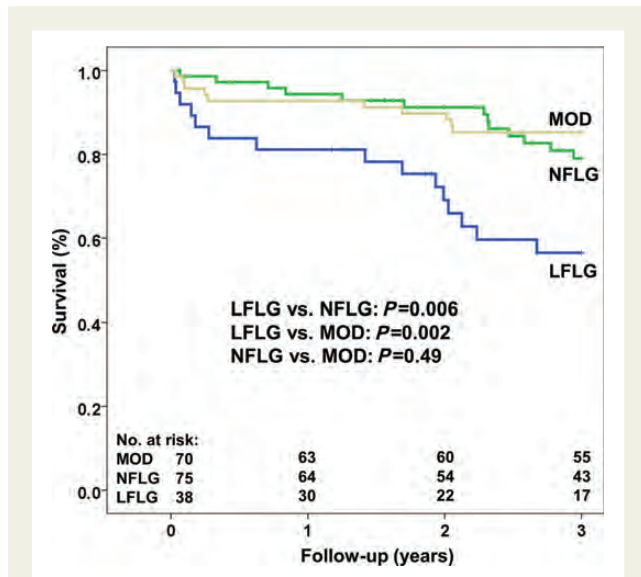


Figure 3 The Kaplan–Meier survival curve for low-flow, low-gradient (LFLG); normal-flow, low-gradient (NFLG); and moderate (MOD) aortic stenosis groups during the 3-year follow-up period. Hash marks indicate censoring times.

Prior studies

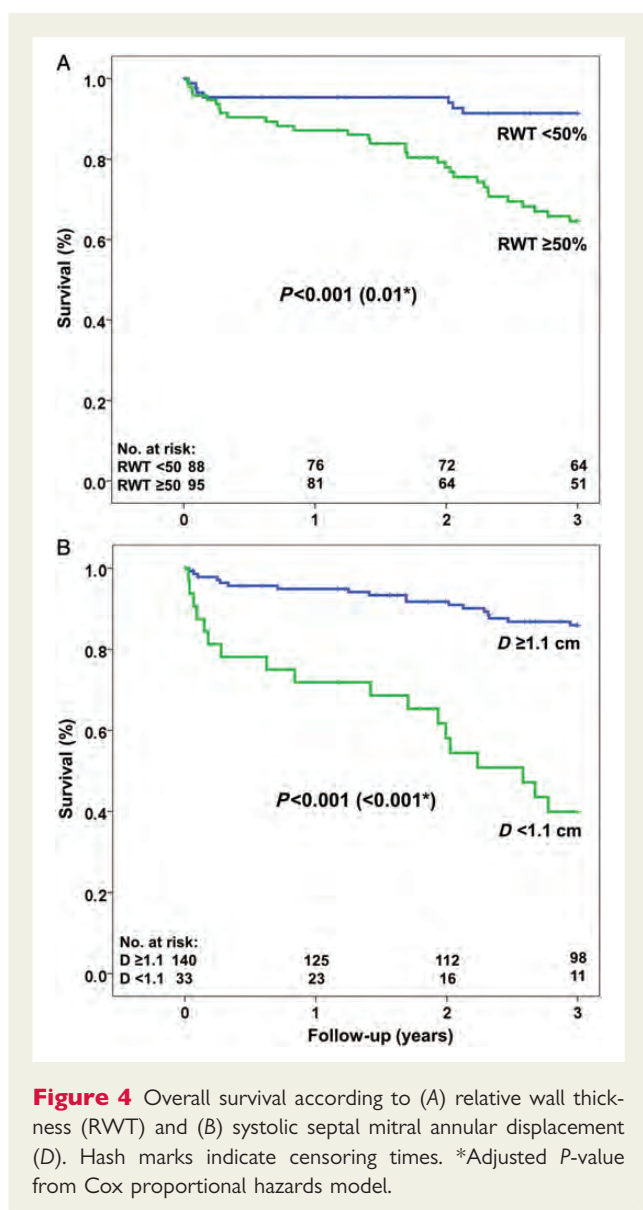
While Hachicha *et al.*¹ initially described the association of concentric remodelling, subclinical LV dysfunction, and decreased survival in a large cohort of patients with preserved EF, low-flow, severe

Table 4 The Cox proportional hazards model

	Univariable analysis			Multivariable analysis		
	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Baseline characteristics						
Age	1.07	1.03–1.12	0.001	–	–	–
CHF	3.32	1.61–6.84	0.001	–	–	–
CKD	2.84	1.30–6.20	0.009	4.20	1.84–9.62	0.001
NYHA class	2.17	1.56–3.04	<0.001	1.77	1.22–2.57	0.003
Echocardiographic variables						
RWT > 50%	4.54	2.0–10.3	<0.001	3.28	1.33–8.10	0.01
LV mass/EDV > 2 g/mL	2.79	1.44–5.40	0.002	–	–	–
LV hypertrophy	2.28	1.21–4.30	0.01	–	–	–
Doppler SVi < 35 mL/m ²	3.15	1.67–5.96	<0.001	–	–	–
MWFS < 20%	2.50	1.28–4.89	0.007	–	–	–
Septal S' < 5.5 cm/s	2.47	1.29–4.76	0.007	–	–	–
Septal D < 1.1 cm	5.88	3.05–11.3	<0.001	3.93	1.96–7.82	<0.001
PASP > 45 mmHg	2.72	1.36–5.42	0.005	–	–	–

173 of 183 (95%) patients were included in the final model. Echocardiographic variables were dichotomized according to values based in the literature or by receiver operating characteristic analysis if not previously defined.

CHF, congestive heart failure; CKD, chronic kidney disease; D, displacement; EDV, end-diastolic volume; LV, left ventricular; MWFS, mid-wall fractional shortening; PASP, pulmonary arterial systolic pressure; S', systolic mitral annular velocity; SVi, stroke volume index.



AS, they did not limit their analysis to patients with a MG <40 mmHg. Moreover, the study included patients with an EF between 50 and 55% in whom a lower gradient may not be unexpected.¹⁶ Their results appeared to be in contrast to those of Jander et al.¹⁰ who demonstrated that low-gradient, severe AS patients have less severe concentric remodelling and an overall survival similar to moderate AS. However, low-gradient AS patients in this latter study were not further stratified into separate subgroups by SVi. Moreover, discrepant values for SVi using two different formulas may have led to the inclusion of normal-flow AS patients into the low-gradient, severe AS group. Therefore, the low-gradient AS subgroups evaluated in these studies were possibly much different from each other. A more recent case-match analysis by Clavel et al.¹⁵ demonstrated that LFLG patients have a worse survival than high gradient and moderate AS but NFLG patients were excluded by design.

Discordance between AVA and MG may not, however, solely be due to a normal EF, low-flow phenomenon but rather to inherent

inconsistent cut-offs for these parameters for grading AS severity.^{8,17} This observation has also been demonstrated to occur frequently both in the echocardiography⁸ and cardiac catheterization⁹ laboratories in the setting of both reduced and preserved transaortic flow. In theoretical examinations of the Gorlin formula, a MG <40 mmHg is, in fact, expected to occur with AVA values just <1.0 cm² when transaortic flow is normal.^{18,19} These patients are represented by NFLG patients who have a higher MG for a given AVA compared with LFLG AS (Figure 2). Prior observations have demonstrated that NFLG patients exhibit preserved longitudinal strain^{3,7} and better outcomes compared with LFLG AS⁷—findings that are consistent with ours.

New categorization system in aortic stenosis based on stroke volume index

By categorizing preserved EF, severe AS patients by indices of both transaortic gradient and flow, our results help reconcile the aforementioned discrepancies in the literature by demonstrating that LFLG patients are distinct, while it is the NFLG AS category which is similar to moderate AS. Similarly, Lancellotti et al.⁷ have demonstrated that stratifying severe AS patients according to SVi can help distinguish the LFLG subset from NFLG AS which had the best outcomes of the various flow-gradient AS subgroups in their study. However, the divergent patterns of LV adaptation to pressure load among the groups were not emphasized in their study, and a moderate AS group was not provided for further comparison.

Despite differences in calculated transvalvular flow, distinguishing LFLG from NFLG AS may be difficult due to overlap in AS severity parameters and potential for discrepant SVi values (particularly when utilizing different formulas for flow). Correct categorization of preserved EF, low-gradient, severe AS patients is, nonetheless, important given the clinical implications of the LFLG diagnosis and more benign course of NFLG AS. Echocardiographic evaluation of increased concentric remodelling (i.e. RWT > 50%) and depressed longitudinal function should, therefore, be an essential component of the comprehensive evaluation of preserved EF, low-gradient, severe AS, since these features are the mechanistic basis of the pathological low-flow state and independent predictors of long-term survival. Direct planimetry of the AVA by three-dimensional transoesophageal echocardiography or cardiac computed tomography and longitudinal strain analysis are additional methods clinicians may use to differentiate these two subgroups.

Since NFLG AS patients have a favourable overall survival despite having an AVA <1.0 cm², our observations have important implications for grading AS severity. In addition to integrating indices of transvalvular flow when considering AS severity, our observations regarding NFLG AS (who have a mean AVA of 0.9 cm²) suggest that appropriate AVA cut-off for severe AS may, in fact, be <1.0 cm². However, some NFLG AS patients in our study underwent aortic valve replacement during the follow-up period, indicating that selected patients in this subgroup may have had progression of their valvular stenosis with the development of higher gradients, symptoms, and/or LV dysfunction. Limited prior observations also suggest that these patients may still benefit from aortic valve replacement.²⁰ Further study is

needed to understand outcomes and the benefit of valve replacement in these patients.

Longitudinal function and myocardial fibrosis

Myocardial fibrosis detected by histological analysis and by cardiac magnetic resonance imaging has been shown to be associated with reduced septal longitudinal strain and mitral ring displacement by echocardiography^{21,22} and to be an independent predictor of poor prognosis in AS patients.^{23,24} The subendocardial fibres which are responsible for long-axis function are, in particular, vulnerable to replacement fibrosis due to microvascular ischaemia and increased wall stress.^{21,22} A recent examination of preserved EF, LFLG patients by MRI and histology has demonstrated that this group exhibits extensive fibrosis in the basal septum similar to severe AS patients with depressed LVEF.²² In this study, mitral ring displacement, which was most preserved in moderate AS patients, correlated well with myocardial histological fibrosis score ($R = -0.79$, $P < 0.0001$) and valvuloarterial impedance ($R = -0.61$, $P < 0.01$)²²—parameters now known to be independent predictors of survival in patients with AS.^{1,23–25} These findings, therefore, are consistent with our observation that reduced systolic septal mitral annular displacement is an independent predictor of survival in preserved EF, low-gradient, severe AS.

Limitations

The retrospective nature of this study may introduce selection biases. However, our survival results are consistent with prior prospective observations.⁷ Although LV outflow tract measurement error may have contributed to underestimation of SVi and AVA, we confirmed Doppler-derived flow parameters in each patient by calculating flow using volumetric methods. We also observed highly significant differences between the three groups in multiple parameters of concentric remodelling, transaortic gradients, and longitudinal function that were independent of SVi determination. Lastly, since blood pressure readings at the time of the echocardiogram were not available, we were unable to calculate valvuloarterial impedance—a key parameter that should also be used to assess patients with preserved EF, low-gradient, severe AS.

Conclusion

There are two very distinct sub-categories of preserved EF, low-gradient, severe AS. Low-flow, low-gradient patients exhibit a distinct haemodynamic profile, marked concentric remodelling, impaired systolic longitudinal function, and poor survival at 3 years. Normal-flow, low-gradient patients, on the other hand, do not demonstrate these features and have a better long-term survival that is similar to moderate AS. While SVi should be used for the initial stratification of these severe AS patients, indices of LV concentric remodelling and longitudinal function provide reliable parameters that should be used to distinguish low-flow from NFLG severe AS.

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