International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Severe aortic stenosis patients with preserved ejection fraction according to flow and gradient classification: Prevalence and outcomes☆

Ariana González Gómez *,[1], Covadonga Fernández-Golfín [1], Juan Manuel Monteagudo [1], Carlos Izurieta [1], Rocío Hinojar [1], Ana García [1], Eduardo Casas [1], José Julio Jiménez-Nacher [1], José Luis Moya [1], Soledad Ruiz [1], José Luis Zamorano [1]

Department of Cardiology, Ramón y Cajal University Hospital, CIBERCV, Madrid, Spain

ARTICLE INFO

Article history:
Received 12 October 2016
Received in revised form 13 June 2017
Accepted 15 June 2017
Available online xxxx

Keywords:
Severe aortic stenosis
Low flow/low gradient
Preserved left ventricular ejection fraction
Echocardiography

ABSTRACT

Background: Clinicians often encounter patients with apparently discordant echocardiographic findings, severe aortic stenosis (SAS) defined by aortic valve area (AVA) despite a low mean gradient. A new classification according to flow state and pressure gradient has been proposed. We sought to assess the prevalence, characteristics and outcomes of patients with asymptomatic SAS with preserved left-ventricular ejection fraction (LVEF) according to flow and gradient.

Methods and results: In total 442 patients with SAS (AVAi < 0.6 cm2/m2) and LVEF ≥ 50% (mean age 80 + 11 years, 54,5% female) were included. Patients were classified according to flow state (≥ or <35 ml/m^2) and mean pressure gradient (≥ or <40 mm Hg): Low Flow/Low Gradient (LF/LG): 21.3%(n = 94); Normal Flow/Low Gradient (NF/LG): 32.1%(n = 142); Low Flow/High Gradient (LF/HG): 6.8%(n = 30); Normal Flow/High Gradient (NF/HG): 39,8%(n = 176). Mean follow-up time was 20.5 months (SD = 10.3). Primary combined endpoint was cardiovascular mortality and hospital admission for SAS related symptom, secondary endpoint was aortic valve replacement (AVR), comparing HG group to LF/LG group. During follow-up 17 (18%) of LF/LG patients and 21 (10.2%) of HG patients met the primary endpoint. A lower free of event survival (cardiovascular mortality and hospital admission) was observed in patients with LF/LG AS (Breslow, p = 0.002). Significant differences were noted between groups with a lower AVR free survival in the LF/LG group compared to HG groups (Breslow, p = 0.002).

Conclusions: Our study confirms the high prevalence and worse prognosis of LF/LG SAS. Clinicians must be aware of this entity to ensure appropriate patient management.

1. Introduction

Aortic stenosis (AS) is a serious health condition associated with poor outcomes and increasing prevalence due to population ageing [1]. The most important parameters to determine AS severity are aortic valve area (AVA) and transvalvular pressure gradient, and their accurate measurement is essential for the patient's diagnosis and management.

The European Society of Cardiology defines severe aortic stenosis (SAS) as an AVA of <1 cm^2 (<0.6 cm^2/m^2) or a mean aortic valve Doppler gradient of ≥40 mm Hg in the context of normal cardiac output [2,3]. The presence of patients with SAS on the basis of AVA but with low gradients (LG) has been classically related to low transvalvular flow (LF) associated with low left ventricular ejection fraction (LVEF). However, during echocardiographic studies we encounter an important proportion of patients with SAS on the basis of AVA, but who have LG (mean gradient < 40 mm Hg), despite preserved LVEF (i.e., ≥50%). Some of these patients with apparent inconsistency in AS grading, may be due to measurement errors in Doppler parameters or AVA [4], but recently, the condition known as paradoxical LF/LG SAS with the presence of SAS in the context of LF (i.e., reduced stroke volume) and LG with preserved LVEF, has been recognized and included in guidelines. This has led to a change in the way of classifying AS [5,2,3].

However, clinicians sometimes still feel reluctant in considering this new entity, moreover when the management and prognosis of this group of patients is unclear.

In this study we aim to 1) document the prevalence of patients with SAS and preserved LVEF (PLVEF) in our center according to gradient and flow state 2) compare their clinical and echocardiographic characteristics 3) assess cardiovascular mortality and hospital admission for SAS related symptoms (syncope, angina or dyspnea) as well as aortic valve replacement (AVR) in paradoxical LF/LG SAS compared to high gradient (HG) SAS.

☆ No conflicts of interest.

* Corresponding author at: Department of Cardiology, Ramón y Cajal University Hospital, Spain.
E-mail address: arianaglz@hotmail.com (A. González Gómez).

[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ijcard.2017.06.064
0167-5273/

2. Methods

2.1. Patient selection

The echocardiograms and clinical reports of patients with SAS defined as AVAi < 0.6 cm^2/m^2 with PLVEF (≥50%) by TTE were included. These had been performed during real every day practice at the echo-laboratory of Ramón y Cajal University Hospital, a tertiary hospital providing care to a population of 530.000 people.

The first TTE performed from July 2012 to June 2015 meeting criteria for SAS diagnosis was included and follow-up was performed thereafter.

Patients with other valvulopathies graded more than mild, prosthetic valves, complex congenital heart disease, hypertrophic cardiomyopathy, supravalvular or subvalvular AS and LVEF < 50%; were excluded. Patients where free of SAS related symptoms at the time of inclusion.

The study group consisted of 442 patients, they were classified in 4 groups according to their mean pressure Doppler gradient (< or ≥40 mm Hg) and SV (< or ≥35 ml/m^2) as LF/LG, LF/HG, Normal flow (NF)/LG and NF/HG. Follow-up was performed until patients presented symptoms related to SAS, underwent AVR or died.

2.2. Echocardiography

Comprehensive 2-dimensional and Doppler echocardiographic studies were performed on commercially available ultrasound equipment in accordance with the European Association and American Society of Echocardiography Guidelines [4,6].

Peak aortic velocity was recorded using continuous-wave Doppler in several acoustic windows; and the velocity-time integral (VTI) was measured. Left ventricular outflow tract (LVOT) VTI was measured using pulsed-wave Doppler by placing the sample volume just below the region of flow convergence apically from the aortic valve in the apical 5-chamber view. LVOT diameter was measured in the parasternal long-axis view in mid-systole as indicated by the current guidelines [4].

AVA was calculated using the continuity equation and indexed for body surface area. SV was calculated by multiplying the LVOT area by the outflow tract VTI. For atrial fibrillation, 5 cardiac cycles were averaged.

LVEF was calculated using Simpson's biplane method, and when not available, Teichholz's method was used. LA volume was calculated using biplane-area length method. Peak early mitral inflow filling (E-wave) was calculated using pulsed-wave (PW) Doppler performed in the apical 4 chamber view. PW tissue Doppler imaging (DTI) was performed in the apical views to acquire mitral annular septal and lateral velocities. Average e´ velocity obtained from the septal and lateral sides of the mitral annulus and was used for the prediction of LV filling pressures.

2.3. Clinical outcomes

Clinical data was obtained from hospital medical, cardiovascular surgery and interventional cardiology records. A primary combined endpoint of cardiovascular mortality and hospital admission for SAS related symptoms (syncope, angina or dyspnea) was defined. Aortic valve replacement (AVR) was considered as secondary endpoint, comparing LF/LG with HG groups.

2.4. Statistical analysis

Baseline characteristics are expressed as mean and standard deviation for continuous variables, and frequencies and percentages for categorical ones. Chi-square test and one-way analysis of variance were used for comparison between groups for categorical and quantitative variables respectively. Bonferroni adjustment was used for multiple comparisons. The probability of AVR or overall event survival (cardiovascular mortality and hospital admission) was calculated using the Kaplan-Meier's plot and the difference between the Kaplan-Meier's curves was tested by generalized Wilcoxon test. $p < 0.05$ was considered significant. Logistic regression analysis was performed to assess the determinants of the LF/LG group and HG groups. The impact of being in the LF/LG SAS group on the primary and secondary endpoints was assessed using Cox regression analysis. The results are presented as HR with corresponding 95% CI.

Statistical analysis was performed using SPSS 19.0 (IBM, Armonk, NY, USA).

3. Results

3.1. Patient's characteristics

A total of 442 patients were included in the study (mean age 80 ± 11 years, 54.5% women). Patients were classified into four groups according to transaortic mean gradient and flow state as follows: LF/LG: 94 patients (21.3%); NF/LG: 142 patients (32.1%); LF/HG: 30 patients (6.8%); NF/HG: 176 patients (39,8%). Demographic and clinical data are summarized in Table 1. There were no significant differences among clinical variables except for atrial fibrillation, which was significantly more prevalent in LFLG group (64.2%).

Echocardiographic characteristics are shown in Table 2. All patients had SAS according to AVA, with significant differences between groups in gradient and flow. The measurement of the LVOT was significantly smaller in the LF/HG group what lead to significantly smaller mean indexed AVA in this group.

3.2. Clinical outcomes

Mean follow-up time was 20.5 ± 10.3 months. Fifty-four (12.2%) patients died during follow-up. Combined primary endpoint of cardiovascular mortality and hospital admission and secondary endpoint of AVR was compared between paradoxical LF/LG group and HG groups. The NF/LG patients group was excluded since these patients may have a non-severe AS related to discrepancies between the cut-point values of AVA and mean gradient. Eleven (7.7%) of the NF/LG patients died from non-cardiovascular cause, and only one due to heart failure during follow-up. Seventeen (18%) of LF/LG patients (cardiovascular death in 5 patients and hospital admission for SAS related symptoms in 12 patients) and 21 (10.2%) of HG patients (cardiovascular death in 7 patients and hospital admission for SAS related symptoms in 14) met the primary endpoint. A lower free of event survival (cardiovascular mortality and hospital admission) was observed in patients with LF/LG SAS group (Breslow, $p = 0.002$) by univariate analysis (Fig. 1). After 30 months a decrease in the number of patients at risk (<50 patients) due to lack of long term follow-up could explain the overlap of both curves shown in Fig. 1.

153 patients (34.6%) underwent AVR. Surgical valve replacement was performed in 115 patients (75.2%) while 38 patients underwent percutaneous valve replacement. Significant differences were noted

Table 1
Clinical characteristics of severe aortic stenosis patients.

		LFLG	NFLG	LFHG	NFHG	p*
Age (years)		82 ± 8	80 ± 10	78 ± 12	79 ± 11	0.197
Gender%	Female	52.1	54.2	56.7	55.7	0.946
Hypertension %		80.2	82.9	82.1	80.4	0.947
Diabetes %		29.6	22.8	35.7	30.4	0.389
Dyslipidemia %		42.0	48.8	53.6	51.4	0.542
Smoking %	Non-smoker	75.3	75.6	64.3	82.4	0.144
	Ex-smoker	16.0	20.3	28.6	15.5	
	Smoker	8.6	4.1	7.1	2.0	
Atrial fibrillation %		64.2	37.4	35.7	32.4	<0.001
COPD %		11.1	9.8	7.1	10.1	0.945
Creatinine mg/dl		1.08 ± 0.93	0.96 ± 0.63	1.00 ± 0.40	0.89 ± 0.65	0.182
GFR < 60%		37.8	31.0	24.1	28.7	0.424
CAD %		26.9	22.8	14.3	19.7	0.464

LF = low flow, LG = low gradient, NF = normal flow, HG = high gradient, COPD = chronic obstructive pulmonary disease, GFR = glomerular filtration ratio, CAD = coronary artery disease.

* Adjusted p value by Bonferroni post hoc test.

Please cite this article as: A. González Gómez, et al., Severe aortic stenosis patients with preserved ejection fraction according to flow and gradient classification: Prevalence and outcomes, Int J Cardiol (2017), http://dx.doi.org/10.1016/j.ijcard.2017.06.064