Romanian Journal of Cardiology | Vol. 26, No. 3, 2016

ORIGINAL ARTICLE

Clinical and echocardiographic characteristics of the flow-gradient patterns in patients with severe aortic stenosis and preserved left ventricular ejection fraction

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Abstract: Aims – We studied the clinical and echocardiographic characteristics of patients (pts) with severe aortic stenosis (AS) and preserved left ventricular ejection fraction (LVEF), according to the flow-gradient classification. **Methods and results –** We enrolled 165 pts (66±11 years, 95 men) with aortic valve area (AVA) <1 cm² (indexed AVA <0.6 cm²/m²) and preserved LVEF (62±6%). Patients were stratified by LV stroke volume index (<35 mL/m² [low flow, LF] and ≥35 mL/m² [normal flow, NF]) and mean aortic gradient (<40 mmHg [low gradient, LG] and ≥40 mmHg [high gradient, HG]) into 4 groups: NF/HG, NF/LG, LF/HG, and LF/LG. LV global longitudinal strain (GLS) was measured in 133 pts. Paradoxical LF/LG AS was present in 4 pts (2.4%). Most pts with LG severe AS had a normal flow (18.2%). Compared to NF/HG (121 pts, 73.3%), NF/LG pts had a lower NYHA class and serum BNP, larger AVAs, lower LV mass index, relative wall thickness and smaller LV volumes when compared to NF/HG pts. Worse parameters of LV longitudinal and diastolic function were found in NF/HG pts compared to NF/LG pts: lower GLS (p<0.001), larger left atrial volumes (p=0.03) and higher E/e' ratios (p=0.009). **Conclusion –** We found a low prevalence of paradoxical LF/LG severe AS in pts with severe AS and preserved LVEF. According to the proposed criteria, most pts with LG severe AS have a normal transvalvular flow. These pts have a better clinical and echocardiographic profile when compared to pts with NF/HG severe AS.

Keywords: aortic stenosis, echocardiography, left ventricular function, global longitudinal strain

Rezumat: Obiectiv – Am studiat caracteristicile clinice și ecocardiografice ale pacienților cu stenoză aortică (SA) strânsă și fracție de ejecție ventriculară stângă (FEVS) păstrată (≥50%), clasificați în funcție de gradientul și fluxul transvalvular în patru grupe, conform noii clasificări. **Metode și rezultate –** Am înrolat 165 de pacienți consecutivi (66±11 ani, 95 bărbați) cu aria valvei aortice (AVA) <1 cm² (AVA indexată <0,6 cm²/m²) și FEVS păstrată (62±6%). Pacienții au fost clasificați în funcție de volumul bătaie indexat (<35 ml/m² [flux transvalvular scăzut] versus ≥35 ml/m² [flux normal]) și gradientul transvalvular mediu (<40 mmHg [gradient scăzut] versus ≥40 mmHg [gradient crescut]) în patru grupuri. Toți pacienții au fost evaluați complet clinic și ecocardiografic. Evaluarea deformării globale longitudinale VS (global longitudinal strain, GLS) a fost disponibilă la 133 de pacienți. Doar 4 dintre cei 163 de pacienți (2,4%) au fost diagnosticați cu SA cu flux paradoxal scăzut și gradient scăzut, în timp ce majoritatea pacienților cu gradient scăzut au avut un flux normal (18,2% din lotul studiat). Comparativ cu pacienții cu SA cu flux normal și gradient crescut (121 pacienți, 73,3% din lotul studiat) pacienții cu flux normal și gradient scăzut au avut o clasă NYHA mai mică și o valoare mai mică a peptidului natriuretic tip B, AVA indexată mai mare, masă VS indexată mai mică și volume VS mai mici comparativ cu pacienții cu flux transvalvular normal și gradient crescut. Deși FEVS a fost similară (p=0,6), pacienții cu flux normal și gradient crescut au avut un grad mai avansat de disfuncție longitudinală și diastolică VS: deformare longitudinală mai redusă (p<0,001), volume atriale stângi indexate mai mari (p=0,03) și un raport E/e' mai mare (p=0,009) comparativ cu cei cu gradient transvalvular scăzut. **Concluzii –** În lotul studiat am găsit o prevalență redusă a SA cu flux scăzut paradoxal și gradient scăzut. Conform criteriilor propuse în noua clasificare a pacienților cu SA strânsă și FEVS păstrată cei mai mulți dintre pacienții cu gradient scăzut au un flux transvalvular normal. Acești pacienți sunt mai puțin simptomatici și au caracteristici ecocardiografice care exprimă o funcție VS mai bună comparativ cu pacienții cu flux transvalvular normal și gradient crescut.

Cuvinte cheie: stenoză aortică, ecocardiografie, funcția ventriculului stâng, deformare globală longitudinală

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INTRODUCTION

Calcific aortic valve stenosis (AS) is presently the most common valvular heart disease and a significant health problem[1]. In the absence of other indications for heart surgery, only patients with severe AS have an indication of aortic valve replacement[2,3]. Therefore, an accurate grading of AS is mandatory for each patient. The currently used echocardiographic severity criteria are based on the measurement of peak transvalvular velocity, mean gradient and calculation of aortic valve area (AVA) by continuity equation. Conditions that reflect the discordance in currently used AS severity criteria are increasingly important in clinical practice. The most frequent discordant AS grading pattern is low gradient (LG) severe AS with preserved left ventricular ejection fraction (LVEF), these patients presenting with an indexed AVA ≤0.6 cm^2/m^2, a mean aortic gradient <40 mm Hg and an LVEF >50%. Patients with a low transvalvular flow (defined by a stroke volume index (SVi) <35 ml/m^2) are classified as having a paradoxical low flow (LF) low gradient severe AS[4]. Discordant echocardiographic grading of AS severity in a patient with normal transvalvular flow may be related to multiple factors, such as measurement errors[5], small body size, reduced arterial compliance[6,7], or discordance between AVA and mean aortic gradient cutpoints used for the definition of severe AS[8]. Minners et al. have showed that from a hemodynamic standpoint a mean aortic gradient of 40 mmHg does not correspond to an AVA of 1.0 cm^2, but rather to an AVA of 0.8 cm^2.[8] Therefore, some authors have proposed changing the criteria currently used to define severe AS, namely lowering the AVA cutpoint from 1 to 0.8 cm^2.[9]

The prognosis and management of patients with LG severe AS is not clear so far. In order to better characterize this subset of AS patients, we studied the clinical and echocardiographic characteristics of patients with severe AS and preserved LVEF, according to the recently proposed flow-gradient classification[4].

METHODS

We prospectively enrolled 165 consecutive patients with severe AS (AVA <1 cm^2, indexed AVA <0.6 cm^2/m^2) and preserved LVEF (>50%) who were referred to our echo lab. We excluded patients with atrial fibrillation, more than mild aortic or mitral regurgitation, mitral stenosis/prosthesis, and patients with coronary artery disease (by history, echocardiography, or coronary angiography). All patients gave their informed consent to participate in the study, the protocol of which was approved by our local Ethics Committee. All patients were subject to a comprehensive echocardiography (2D, conventional and tissue Doppler, 2D strain using speckle tracking echocardiography). Images were obtained using a commercially available cardiac ultrasound machine (Vivid 7 Dimension and Vivid E9, GE Healthcare, Horten, Norway) equipped with a 4S probe. Standard views and techniques were used according to the American Society of Echocardiography/European Association of Echocardiography recommendations[10]. Left ventricular volumes and LVEF were measured using the modified Simpson's rule

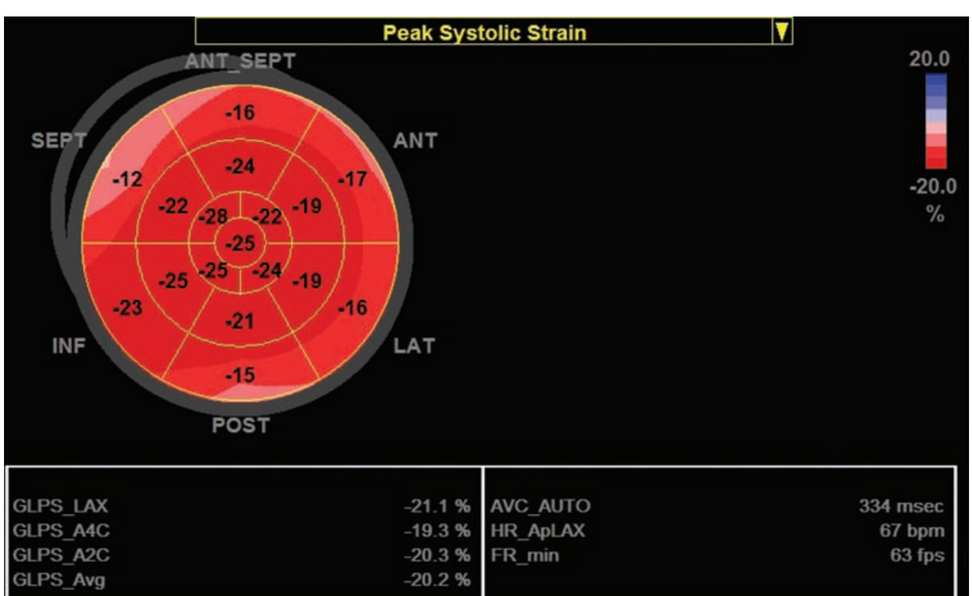

Figure 1. The illustration of LV longitudinal deformation measured off-line in 17 segments using a 2D strain software in a patient with severe aortic stenosis. Global longitudinal strain is within normal range in this patient (-20%).

from apical four- and two-chamber views and were normalized to body surface area (BSA). LV mass was calculated by the equation of Devereux[11] and indexed to BSA. The degree of calcification of the aortic valve was assessed using the classification proposed by Rosenhek et al.: 1, no calcification; 2, mildly calcified (small isolated spots); 3, moderately calcified (multiple larger spots); and 4, heavily calcified (extensive thickening and calcification of all cusps)[12].

Continuous-wave Doppler was used to measure the aortic transvalvular maximal velocities; peak and mean gradients were calculated using the simplified Bernoulli equation. LV stroke volume was calculated using pulsed wave Doppler as follows: LV outflow tract area×LV outflow tract velocity-time integral (measured by PW Doppler). Aortic valve area was calculated using the continuity equation[13]. Peak systolic (S) and peak early diastolic (e') mitral annular velocities were obtained by pulse-wave tissue Doppler imaging from the apical four-chamber view using both the septal and the lateral sites. The average e' was used to calculate the ratio of peak early-diastolic transmitral flow velocity E/e' in order to estimate LV filling pressures[14]. Global longitudinal LV strain was measured by speckle tracking echocardiography in a 17 segments model (Figure 1) using 2D images acquired with a frame rate between 50-70 fps in the apical views centered on the LV. This was feasible in 133 pts with an adequate acoustic window.

STATISTICAL ANALYSIS

Patients were stratified according to LV stroke volume index (<35 ml/m^2 [LF] vs ≥35 ml/m^2 [NF]) and aortic gradient (<40 mm Hg [LG]vs ≥40 mm Hg [high gradient, HG]) into 4 groups according to the flow-gradient classification4: group 1, LF/HG; group 2, LF/LG; group 3, NF/LG; or group 4, NF/HG. Data are reported as mean±SD or number (percentage). Skewed data such as BNP serum values were logarithmically transformed and logBNP values were used in comparative analyses. Student t tests were used to compare continuous variables, and Pearson χ^2 or Fisher exact tests were used to compare categorical variables between groups.

RESULTS

A total of 165 patients (66±11 yrs, 57.6% male) were included in our study. Baseline characteristics of patients in the whole cohort are presented in Table 1. The mean AVA was 0.7±0.2 cm^2, AVAi 0.4±0.1 cm^2/m^2, mean aortic gradient 58.2±20.3 mm Hg, and peak transvalvular velocity 4.8±0.8 m/s. Low gradient AS was present

Table 1. Baseline characteristics of patients in the whole cohort

	Whole cohort (n=165)
Age, y	66±11
Female sex, n (%)	70 (42)
Body mass index, kg/m^2	27±4
Body surface area, m^2	1.8±0.2
Comorbidities	
Hypertension, (%)	120 (73)
Diabetes mellitus, (%)	28 (17)
Dyslipidemia, (%)	76 (46)
Symptoms	
Any symptoms, n (%)	138 (84)
Dyspnea, n (%)	128 (78)
Angina, n (%)	91 (55)
Syncope, n (%)	40 (24)
NYHA class	1.9±0.7

Table 2. Clinical characteristics of patients with normal flow high gradient compared to normal flow low gradient severe aortic stenosis

	NF/LG (n=30)	NF/HG (n=121)	p value
Age, y	68±10	65±11	0.1
Female sex, n (%)	51 (43.2)	13 (43.1)	0.9
Body mass index, kg/m^2	27±4	27±4	0.9
Body surface area, m^2	1.8±0.2	1.8±0.2	0.6
Comorbidities			
Hypertension, n (%)	22 (73)	87 (72)	0.8
Diabetes mellitus, n (%)	6 (20)	16 (11)	0.2
Dyslipidemia, n (%)	11 (36)	62 (51)	0.3
Symptoms			
Any symptoms, n (%)	20 (66)	105 (87)	0.01
Dyspnea, n (%)	20 (66)	97 (80)	0.1
Angina, n (%)	9 (30)	74 (61)	0.002
Syncope, n (%)	3 (10)	31(26)	0.06
NYHA class	1.8±0.6	2.0±0.7	0.04

Table 3. Echocardiographic parameters of LV function in patients with normal flow high gradient compared to normal flow low gradient severe aortic stenosis

	NF/LG (n=30)	NF/HG (n=121)	p value
LVEDVi (ml/m^2)	41±14	54±16	<0.001
LVESVi (ml/m^2)	16±6	21±8	0.002
LVSVi (ml/m^2)	43±4	47±7	0.001
LV mass (g/m^2)	132±26	160±43	0.001
LVEF (%)	61.5±5.7	62.1±6.1	0.6
LVFS (%)	42±7	39±8	0.05
S septal (cm/s)	5.9±1.2	5.3±1.4	0.04
S lateral (cm/s)	6.9±1.5	6.3±1.6	0.05
GLS (%)	-16.9±2.7	-14.2±3.5	<0.001
LAVi (ml/m^2)	42±17	50±16	0.02
E/A ratio	1.0±0.4	0.9±0.5	0.3
EDT (ms)	213±52	226±60	0.3
e' (cm/s)	7.0±1.9	5.4±1.9	<0.001
E/e' ratio	11.8±4.5	15.1±6.5	0.02

Abbreviations: LVEDVi = left ventricular end-diastolic volume indexed to BSA; LVESVi = left ventricular end-systolic volume indexed to BSA; LVSVi = left ventricular stroke volume indexed to BSA; LAVi = left atrial volume indexed to BSA; LVFS = left ventricular fractional shortening; LVEF = left ventricular ejection fraction; EDT = E-wave deceleration time; S septal = peak systolic mitral annular velocity at the septal site, S lateral = peak systolic mitral annular velocity at the lateral site

in 34 pts (21%) of our study group. Paradoxical LF/LG severe AS was present in 4 pts (mean age 67±5 yrs, three female patients, all of them symptomatic), while most patients with LG severe AS had a normal transvalvular flow (30 pts, 18.2%). The majority of pts were classified as NF/HG (121 pts, 73.3%), while 10 pts (6% of the study group) had LF/HG AS. Most patients were symptomatic (84%). However, compared to NF/HG patients, those having NF/LG were less symptomatic, with a lower prevalence of angina and syncope and a lower NYHA class.

The clinical characteristics of these two groups are shown in Table 2. The serum BNP values were available in 76 patients - range 11-4059 pg/ml, median value 207 pg/ml (86-334). Patients with NF/HG had significantly higher BNP values compared to NF/LG patients (p=0.03).

ECHOCARDIOGRAPHIC CHARACTERISTICS

Both AVA and indexed AVA were higher in patients included in the NF/LG group when compared to patients with NF/HG-AS (0.86±0.10 cm^2 vs. 0.69±0.16 cm^2, p<0.001 and 0.47±0.06 cm^2/m^2 vs. 0.38±0.08 cm^2/m^2, p<0.001). There was a trend toward a higher level of calcification of the aortic valve in patients with NF/HG-AS compared to patients in the NF/LG group (p=0.06). Blood pressure values at the time of the echocardiographic examination were not different between groups. Valvulo-arterial impedance was lower in patients with NF/LG-AS compared to NF/HG pts (3.9±0.6 vs. 4.3±0.8 mmHg/ml/m^2, p=0.03). Patients with NF/LG-AS also had a lower LV stroke volume index (43±4 vs. 47±7 ml/m^2, p=0.001) and smaller LV outflow tract diameters (20.4±1.6 vs. 21.2±2.1 mm, p=0.04).

The echocardiographic parameters of LV systolic and diastolic function in patients with NF/LG -AS and NF/HG-AS are presented in Table 3. Patients with NF/LG had lower indexed LV mass (p=0.002) and smaller LV volumes (p<0.004) when compared to NF/HG pts.

Although LVEF was similar between groups (62±6 vs. 61±6%, p=0.6), worse parameters of LV longitudinal and diastolic function were found in NF/HG compared to NF/LG patients. Compared to patients with NF/LG-AS, lower systolic myocardial velocities and a more impaired global longitudinal deformation were found in patients with NF/HG-AS, revealing a poorer LV systolic function. These patients had also larger indexed left atrial volumes (p=0.02) and higher E/e' ratios (p=0.03) indicating a higher degree of LV diastolic dysfunction.

DISCUSSION

In the present study, we found that most patients with low gradient severe AS have a normal transvalvular flow when classified according to the flow-gradient classification. Compared to patients with the most frequent type of severe AS (NF/HG-AS) these patients have a lower degree of LV afterload and a better LV function. This is the first study that shows worse LV longitudinal deformation in NF/HG patients with AS compared to patients with NF/LG-AS. This information adds to the previously published data indicating a better prognosis in patients with NF/LG-AS[15]. Similar to the data published by Eleid et al.[15], using the proposed cut-off value of 35 ml/m^2 for the definition of LF, we found a very low prevalence of paradoxical LF/LG -AS (<3%).

Left ventricular stroke volume is an important determinant of the transvalvular aortic gradient. It was suggested that in patients with LG severe AS, stroke volume might be decreased as a result of the small body habitus, concentric remodeling with reduced ventricular cavity size, and higher arterial impedance4. Both body surface area and body mass index are similar between different groups of AS patients in our study, although patients with NF/LG-AS have smaller LV volumes that may explain the low transvalvular gradient. In our study, patients with NF/LG-AS had larger AVA and indexed AVA compared to other groups, although the values were below the cut-off that is currently used by the guidelines to define severe AS2. Of note, LV outflow tract diameters in patients with NF/LG-AS were smaller than in NF/HG patients, and this is a key element in the AVA calculation. A study by Michelena et al.[16] showed that in patients with LV outflow tract diameters ≤2.2 cm, the majority of patients with AVA <1cm^2 have a mean gradient below 40 mm Hg. This is important for the illustration of the discordance that exists in currently used AS severity criteria. The prognosis of patients with low gradient AS and their management are still controversial[17]. Our results demonstrate that these patients have a lesser degree of LV hypertrophy, a milder impairment of LV longitudinal deformation and lower E/e' ratio suggesting lower LV filling pressures. These data suggest that patients with NF/LG AS may, in fact, have moderate AS with a milder degree of LV dysfunction. Given the lower prevalence of symptoms in this subset of patients, we suggest that a lower AVA cut-off value should be used to define severe AS.

STUDY LIMITATIONS

The observational character and the relatively small sample size, compared to that of the previously published data, are inherent limitations of the present study. However, this investigation represents the first study that shows more impaired LV longitudinal deformation in NF/HG patients with AS and preserved LVEF compared to NF/LG-AS patients, adding new data with clinical implications to the previously published research. Nevertheless, it is likely that the prevalence of LF/LG-AS patients was underestimated in our study since we have excluded patients with atrial fibrillation and/or associated mitral valve disease, although our results are similar to that reported by Eleid et al in a larger series[15].

CONCLUSION

In a relatively large number of patients with severe isolated AS and preserved LVEF, we found a very low prevalence of paradoxical low flow low gradient AS. According to the proposed flow-gradient criteria, most patients with low gradient severe AS have a normal transvalvular flow. These patients have a better clinical and echocardiographic profile when compared to patients with high gradient severe AS. These findings have potential implications for the assessment of AS severity and consequent management.

Acknowledgements: This work was supported by a grant of the Romanian Ministry of National Education, CNCS – UEFISCDI, project number PN-II-ID-PCE-2012-4-0560 (contract 21/2013) and by the Sectoral Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/159/1.5/S/132395.
We gratefully acknowledge the support of our colleagues who have referred patients for this study.

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