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Outcome of Paradoxical Low-flow Low-gradient Severe AS Following TAVI: Paradoxical vs. Parallel to Outcome of High Gradient AS

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Abstract

Background: Transcatheter aortic valve implantation (TAVI) is already a proven choice of treatment for patients with severe aortic stenosis (AS). There is few data of the real world regarding the echocardiographic and clinical outcome of patients with paradoxical low-flow low-gradient aortic stenosis (PLFLG) after TAVI procedure.

Objectives: In this study we aimed to compare the echocardiographic and clinical outcome in a group of patients with PLFLGAS after TAVI with a group of high-gradient aortic stenosis (HGAS), both groups with preserved left ventricle ejection fraction (LVEF).

Methods: We studied the baseline echocardiographic parameters and clinical data of 178 patients with severe AS and preserved LVEF before TAVI and after one year of follow up. All data were obtained from the clinical file and the workstation in the echo-lab of our hospital. Patients with low ejection fraction and incomplete data were excluded. Patients were divided into two groups as following: Group I PLFLGAS n=32 (18%); Group II: HGAS n=146 (82%).

Results: Baseline characteristics in both groups were similar. Mean age was group I: 82±5.4 and II: 83±5.9yrs. LVEF I: 61±6.8% and II: 64±8.2%. Mean gradient I: 29±5.2mmHg and II53±12.8mmHg (p=<0.001). Global longitudinal strain (GLS) I: -15.1±2.5% and II: -16.3±4.1%. Valvulo-arterial impedance (Zva) I: 5.7±0.9 and II 5.3±13 (p= 0.07). At one year no statistically significant differences were found between groups. LVEF I: 64±8.3% and II: 65±7.9%. Mean gradient I: 7.2±3.7mmHg and II: 8.3±3.9mmHg. GLS: -17.85%±3.8% and II: -17.5±5.5%. NYHA class: Group I: 2 and II: 1 (p=0.037). Regarding NYHA class there were no significant differences at baseline and at follow up, patients in-group I showed better NYHA class I.

Conclusion: In this real world sample, the clinical and echocardiographic outcome of patients with PLFLGAS is similar to that of patients with HGAS. There is lack of information regarding the specific cause of low flow-low gradient in these patients, but apparently and at least in this series has no impact on the outcome.

Keywords: Aortic stenosis; High-gradient aortic stenosis; Paradoxical low-flow fow-gradient sortic stenosis; Transcatheter aortic valve implantation

Abbreviations: TAVI: Transcatheter Aortic valve Implantation; PLFLGAS: Paradoxical Low-Flow low-gradient Aortic Stenosis; HGAS: High-Gradient Aortic Stenosis; LVEF: Left Ventricle Ejection Fraction; GLS: Global Longitudinal Strain; SVI: Stroke Volume Index; Zva: Valvulo-Arterial Impedance; NYHA: New York Heart Association; CCSA: Canadian Cardiovascular Society Grading of Angina Pectoris

Introduction

The progressive aging of the population in developed countries and the widespread of preventive screening programs of patients with cardiovascular risks result in an increasing number of patients diagnosed with significant aortic stenosis who are candidate for transcatheter aortic valve implantation. In recent years, in clinically suitable patients for TAVI the role of cardiovascular imaging is critical in the assessment of candidates for TAVI, providing both anatomic and hemodynamic information. These modalities of cardiac imaging assist in choosing the best interventional approaches and the prosthetic valve type and its accurate sizing. According to the current ESC and ACC/AHA guidelines, severe AS is defined by an AVA of <1cm^2 (<0.6 cm^2/m^2), a peak transvalvular velocity of 4 m/s, a mean aortic valve gradient of >40 mmHg.

But beside the first main group (high gradient with normal ejection fraction ≥ 50%) there are two groups where the diagnosis of severe AS may be challenging and should be noted: the second group: low flow low gradient severe AS with the presence of LV systolic dysfunction. These modalities of cardiac imaging assist in choosing the best interventional approaches and the prosthetic valve type and its accurate sizing. According to the current ESC and ACC/AHA guidelines, severe AS is defined by an AVA of <1cm^2 (<0.6 cm^2/m^2), a peak transvalvular velocity of 4 m/s, a mean aortic valve gradient of >40 mmHg. But beside the first main group (high gradient with normal ejection fraction ≥ 50%) there are two groups where the diagnosis of severe AS may be challenging and should be noted: the second group: low flow low gradient severe AS with the presence of LV systolic dysfunction.

In this case, Dobutamine stress echocardiography has been shown to distinguish between true severe and pseudo-severe AS and provide useful information concern in contractile reserve. A third group consists of patients with paradoxical low flow low gradient severe AS. In this group, left ventricular (LV) ejection fraction is well preserved. Although transcatheter aortic valve implantation (TAVI) is already a proven choice of treatment for patients with severe aortic stenosis (AS), there is few data of the real world regarding the echocardiographic and clinical outcome of patients with paradoxical low-flow low-gradient aortic stenosis (PLFLG) after TAVI procedure.

Objectives

In this study, our aim was to compare the echocardiographic and clinical outcome in a group of patients with PLFLGAS after TAVI with a group of high-gradient aortic stenosis (HGAS), both groups with preserved left ventricle ejection fraction (LVEF).

Methods

For this prospective cohort study, we included only our patients who had evidence of severe AS and a preserved LVEF and were candidates for TAVI intervention after the informed consent had been provided for them and the study protocol had been approved by the ethical committee of research foundation in the hospital. These patients were subdivided into 2 groups depending on whether they had normal LV flow output (high gradient severe AS with normal ejection fraction) or paradoxical low flow output (paradoxical low flow low gradient severe AS). We studied the baseline echocardiographic parameters and clinical data of 178 patients with severe AS and preserved LVEF before TAVI and after one year of follow up. All data were obtained from the clinical file and the workstation in the echocardiography-lab (Q- lab Advanced Quantification software, Philips Ultrasound, USA) at our hospital. Patients with low LV ejection fraction and patients with normal flow-under gradient were excluded.

A. **Clinical data:** Included history of smoking, documented diagnosis of hypertension, hypercholesterolemia, diabetes, obesity, coronary heart disease and previous myocardial infarction beside symptoms (angina, heart failure, syncope) and the quality of life. These data were collected in all patients. All risk factors are described in (Table 1).

Table 1: Baseline demographic and characteristics of the patients in both groups.

Risk factors	PLFLGAS	HGAS	P value
Age (years)	82±5	83±5	0.7
Arterial hypertension	84.3%	83.9%	0.9
Hyperlipidemia	36.3%	29.5%	0.3
Diabetes	31.25%	39.16%	0.6
Coronary artery disease	23.5%	27.3%	0.4
Myocardial infarction	16.7%	15.1%	0.7
Atrial fibrillation	29.4%	31.3%	0.6
Smoking	11.1%	15.4%	0.2

B. **Echocardiographic data:** LV ejection fraction was measured with use of Simpson biplane method and 3D echo. Stroke volume was measured by pulsed wave Doppler in the LV outflow tract and was indexed for body surface area, AVA using the continuity equation and transvalvular gradients using the modified Bernoulli equation. We paid particular attention to search for the highest peak transvalvular velocity with the use of multi-window continuous- wave Doppler interrogation. 2D and 3D TTE and TEE were used to confirm the valve stenosis severity and calculate effective orifice area and aortic valve regurgitation during the intervention and the follow up studies. Values of peak global longitudinal strain (GLS) and peak segmental longitudinal strain (SLS) values obtained by Speckle-tracking echocardiography (STE) in (Q-lab Advanced Quantification software, Philips Ultrasound, USA). As a measure of global LV after load, we calculated the valvulo-arterial impedance by dividing the sum of systolic blood pressure and mean transvalvular gradient by the stroke volume index.

C. **Statistical analyses:** Continuous variables were expressed as the means and standard deviations; categorical variables were expressed as proportions. The student t-test was used to test for the differences in normally distributed continuous variables, and the Wilcoxon rank sum test was used for comparisons involving the variables that were not normally distributed. Categorical variables were compared

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with the χ2 test or Fisher exact test as appropriate. A two-sided p- value of less than 0.05 was considered to represent a statistically significant difference.

Results

From the entire cohort study, 60% of 178 patients were women. Age and gender distribution was similar between the two groups. Group I PLFLGAS n=32 (18%) and Group II: HGAS n=146 (82%). Mean age was group I: 82±5.4 yrs and II: 83±5.9 yrs. Euroscore: Group I: 14.49±5.9 and Group II: 17.35±8.7 (P=0.027). Prophetic valves (58 Medtronic Core Valve 32% and 120 Edwards Sapien 68%) had been implanted with no big difference between both groups.

a) **Pre TAVI procedure data:** Baseline characteristics in both groups were similar. Body surface area was similar in both groups (I: 1.64±0.15 kg/m^2 and II: 1.60±0.1 kg/m^2, P=0.18). The values of systolic blood pressure were in the range between 130-160 mmHg (P=0.9) and the heat rate in the range 60-80 bps. The values of LVEF (I: 61±6.8% and II: 64±8.2%) and GLS (I: -15.1±2.5% and II: -16.3±4.1%) were similar in both groups. The stroke volume and flow rate were lower in group I patients than in group II, (SVi: I: 24.01 ml/m^2 and II: 28.16 ml/m^2) (P= 0.09) and patients in group I also had smaller LV end-diastolic volume index (LVEDVi group I: 47.15±13.3 ml/m^2 and II: 50.05±14.5 ml/m^2). Patients in group I had lower gradients despite a similar AVA and indexed AVA compared with patients in the group II (Mean gradient I: 29±5.2mmHg and II: 53±12.8mmHg) (p= <0.001). The valvulo-arterial impedance was higher in group I patients (Zva: 5.7±0.9 mmHg/mL m^2) than in group II (Zva: 5.3±13 mmHg/mL m^2) (p= 0.07). The majority of patients were symptomatic (NYHA class 2 to 4) (CCSA class 1 to 3).

b) **Follow up data:** At one year no statistically significant differences were found between both groups. LVEF (I: 64±8.3% and II: 65±7.9%). Mean gradient (I: 7.2±3.7mmHg and II: 8.3±3.9mmHg). GLS: (I: - 17.85%±3.8% and II: -17.5±5.5%). Indexed Aortic prosthetic valve effective orifice area (EOA) index: (EOA index I: 1.66±0.3 cm2/m2 and II: 1.44±04 cm2/m2). Aortic prosthetic valve regurgitation (AVR I; trivial: 50%, mild: 37%, moderate: 13% and AVR II; trivial: 46%, mild: 45%, moderate: 9%). Regarding prosthesis/patient mismatch (VP-PM); 35% of patients showed mild VP-PM with no big difference between both groups and both types of prosthetic valve. One year global mortality was similar in both groups (group I: 10% and II: 12%, P= 0.9). Both groups showed better CCSA class at follow up. Regarding NYHA class there were no significant differences at follow up; patient's in-group I showed better NYHA class I. The study results are described in (Table 2) and (Figures 1-3).

Table 2: The baseline and one year follow up echocardiography values in both groups.

	PLFLGAS basal	HGAS basal	P value	PLFLGAS FU	HGAS FU	P value
LVEF (%)	61±6.8	64±8.2	0.9	64±8.3	65±7.9	0.7
LV Mass (g)	224±57	245±70	0.9	193±61	209±67	0.8
LV Mass i (g/m2)	131.2±33.9	144.0±41.8	0.7	109.4±30.1	123.3±38.4	0.6
RWT	0.54±0.5	0.51±0.5	0.35	0.49±0.4	0.48±0.4	0.5
LVEDV (ml)	79.7±25	85.6±22	0.49	84.22±22.4	84.17±20.7	0.7
LVEDVi (ml/m^2)	47.15±13.3	50.05±14.5	0.4	48.28±12	49.42±13	0.8
LVSV (ml)	29.84±11.6	30.93±12.9	0.58	29.75±14.5	29.20±10.8	0.29
LVSVi (ml/m^2)	18.59±9.9	18.03±7.6	0.48	16.98±8	17.11±6.7	0.56
SV (ml)	41.03±10	48±11	0.001	42.89±9.4	44.55±10.1	0.6
SVi (ml/m^2)	24.01±6	28.16±7	0.003	25.4±6.1	26.26±6.2	0.06
E/e'	15.05±4.8	14.48±4.3	0.7	15.3±3.4	12.7±4.3	0.18
GLS (%)	-15.1±2.5	-16.3±4.1	0.6	-17.8±3.8	-17.5±5.5	0.7
PSAP (mmHg)	40.7±13	42.3±17	0.2	37.7±11	39.1±12	0.16
Mean G (mmHg)	29±5.2	53±12.8	<0.001	7.2±3.7	8.3±3.9	0.7
Max G (mmHg)	51.4±7.2	87±21	<0.001	17.1±7.8	17.8±8.5	0.4
Vmax (cm/s)	355±30	462±78	<0.001	200.9±41.9	204.3±42.5	0.65
AV VTI (cm)	81.08±14.2	108±22.6	<0.001	38.45±9.9	41.73±21.6	0.5
LVOT VTI (cm)	20.7±6.12	23.5±2.3	0.2	21.24±6.6	23.65±5.8	0.7
LVOT D (mm)	20.8±1.5	19.7±1.9	0.5	19.75±1.1	19.59±1.6	0.4
AVA/EOA (cm2)	0.69±0.11	0.61±0.16	0.02	1.66±0.37	1.49±0.45	0.15
AVAi/EOAi (cm2/m2)	0.4±0.3	0.38±0.4	0.19	0.93±0.21	0.87±0.29	0.14

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FU: Follow Up; I: Index; D: Diameter; G: Gradient; PLFLGAS: Paradoxical Low-Flow Low-Gradient Aortic Stenosis; HGAS: High Gradient Aortic Stenosis; LVEF: Left Ventricle Ejection Fraction; LVEDV: Left Ventricle End Diastolic Volume; LVSV: Left Ventricle Systolic Volume; SV: Stroke Volume; RWT: Relative Wall Thickness; GLS: Global Longitudinal Strain; E/e′ ratio: mitral inflow E- wave divided by annular tissue e′ Wave; SPAP: Systolic Pulmonary Artery Pressure; Vmax : Maximum Velocity; VTI: Velocity Time Integral; LVOT: Left Ventricle Outflow Tract; AVA: Aortic Valve Area; EOA: Effective Orifice Area

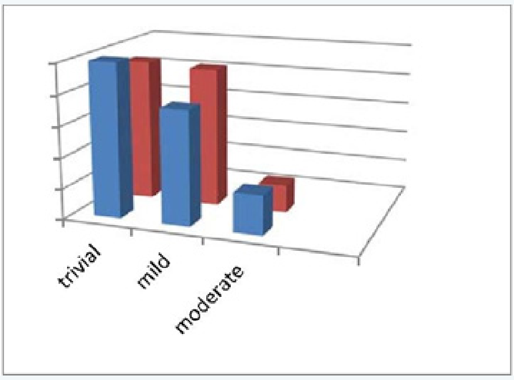

Figure 1: Aortic prosthetic valve regurgitation after one year follow up (percentage of AVR).

PLFLGAS: Paradoxical Low Flow Low Gradient Aortic Stenosis; HGAS: High Gradient Aortic Stenosis; AVR: Aortic Prosthetic Valve Regurgitation.

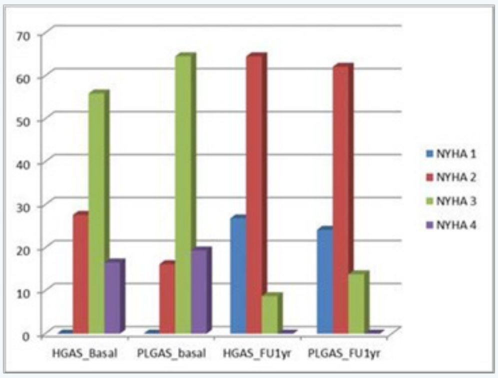

Figure 2: NYHA Functional Classification Baseline and one year of follow up: (percentage of stage NYHA class).

NYHA: New York Heart Association, Basal: Baseline, 1yr: One Year Follow Up.

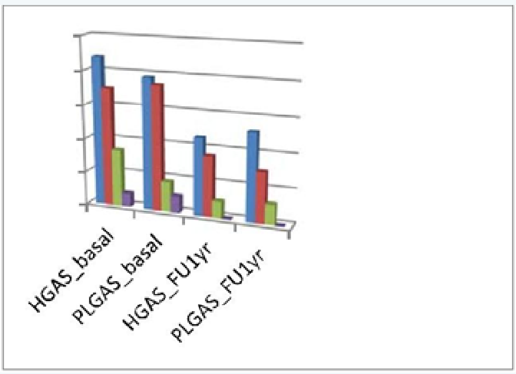

Figure 3: CCSA grading baseline and one year of follow up: percentage of grading.

CCSA: Canadian Cardiovascular Society Grading of Angina Pectoris; Basal: Baseline; 1yr: One Year Follow Up.

Discussion

In this work, we showed that PLFLGAS presented the typical Doppler echocardiographic features reported in previous published studies [1-3] including small LV cavity size and increased LV global hemodynamic load as reflected by high valvulo-arterial impedance [4]. But in contrast to studies [5,6] revealed those patients with PLFLGAS had more myocardial fibrosis and a markedly reduced LV longitudinal systolic function which contribute to the reduced LV outflow and transvalvular gradient and to the worse outcomes in these patients, our study showed the reduced baselines values of GLS in both groups were detected with no significant difference and the patients with PLFLGAS showed improvement in values of global longitudinal strain similar to patients with HGAS after one year follow up.

Although several studies reported patients with PLFLGAS, compared to patients with HGAS, had worse symptomatic status and prognosis after aortic valve replacement [7-9], we found after one year follow up, compared to the basal evaluation, all echocardiography parameters showed improvement in values of LV structure and the functional capacity of the patients and ultimately clinical outcome similar to HGAS patients. Furthermore, with regard to one paper [9] that have pointed to the influence of body mass index on the gradient across the valve and may lead to underestimation of stroke volume index, the majority of PLFLGAS patients had the body mass index in the normal range. Based on these results and in respect of studies which had shown the patients with PLFLGAS have worse symptomatic status, our prospective study, however, showed these patients have feature similar to that of patients with HGAS after one year follow up, compared to the basal evaluation, like previous published studies [4,10] and a new published study [11] which had reported the mid-term prognosis after TAVI procedure in PLFLGAS patients is similar to HGAS patients despite higher preoperative mortality.

In addition to the above, respecting to recent data [12-14] that confirmed lower values of indexed LV stroke volume are independently associated with increased mortality following TAVI, our study showed approximately 60% of patients in group II had low SVI (<35 ml/ m²) with high mean gradient (≥40 mm Hg), that makes regarding not only myocardial contractile reserve in TAVI risk algorithms, but also LV stroke volume reserve in HGAS with low SVI as well as in PLFLGAS would probably be more appropriate and more clinical useful [15]. Although Dobutamine stress echocardiography should not be used in these groups of patients, estimation of LV stroke volume reserve, beyond the gradient across the aortic valve, should be considered in therapeutic decision-making of this challenging subset of patients. Finally, we emphasize paradoxical low flow low gradients aortic stenosis is still a challenging clinical entity that requires special attention and careful approach including

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assessment of hypertension and stenosis severity and raised many questions if this aortic-incompetence population would be a good target for TAVI in this time when the new generation valves become available.

Study Limitation

i. It is a small cohort of patients referred for TAVI in a single center.

ii. The relation between myocardial contractile, stroke volume and gradient across aortic valve is not fully understood and studying their impact on TAVI outcomes require further research about their mismatch in big group of AS disease.

iii. It is a mid-term single center study, long-term multi-center studies are needed to evaluate TAVI effectiveness and outcome in patients with PLFLGAS.

Conclusion

In this real world sample, the clinical and echocardiographic outcome of patients with PLFLGAS is similar to that of patients with HGAS. There is lack of information regarding the specific cause of low flow-low gradient in these patients, but apparently and at least in this series has no impact on the outcome.

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