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Letter to the Editor

Severe aortic valve stenosis with normal left ventricular function and low vs. high pressure gradient: Different hemodynamic profiles but similar clinical presentation, comorbidity and outcome

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The paradoxical condition characterized by severely reduced aortic valve area (AVA) and low mean gradient (low-MG) has been described both in patients with reduced and preserved left ventricular (LV) ejection fraction (EF) [1,2]. Retrospective studies on unselected patients showed that the survival rate of low-MG was detrimental and equal to or worse than that of patients with high-MG [2–4]. On the contrary, the SEAS study, enrolling AS asymptomatic patients without major comorbidities, showed that the outcome of low-MG patients was better than that of high-MG patients and comparable to that of patients with moderate AS [5]. So, it could be speculated that not only the variable mortality rates of low-MG patients but also the different survival rates between low-MG and high-MG might be at least partially determined by the different burdens of comorbidities in such populations. Thus, we hypothesized that the high mortality rate observed in retrospective studies in low-MG compared to high-MG patients [2–4] might be due to a higher prevalence of systemic and or cardiac co-morbidities and/or a worse clinical presentation, rather than to the severity of aortic valve disease per se.

Our study population consisted of consecutive symptomatic patients with severe AS (defined as AVA$<$0.6 cm^2/m^2) with preserved EF ($>$50%). At admission patients underwent a detailed clinical history, physical examination, blood tests, electrocardiogram, and chest radiogram. Accurate assessment of major cardiac and non cardiac comorbidities was performed. A comprehensive echocardiographic analysis was obtained according to the recommendations of the American Society of Echocardiography [6]. Patients were then divided according to MG higher or lower than 40 mm Hg.

The baseline glomerular filtration rate (eGFR) was estimated using the abbreviated Modification of Diet in Renal Disease Study equation. Patients with eGFR$<$60 ml/m^2/1.73 m^2 were considered as having at least moderate chronic kidney disease (stage 3 nephropathy). Diabetes mellitus was defined as overnight fasting serum glucose$>$7 mmol/l (126 mg/dl) or drug therapy. Chronic obstructive pulmonary disease (COPD): long term use of bronchodilators or steroids for lung disease or spirometry diagnosis of pulmonary disease. Cerebrovascular disease: history of previous stroke or transient ischemic attack (TIA) and carotid artery occlusion or $>$50% stenosis on Doppler or previous percutaneous/surgical angioplasty. Peripheral artery disease: any or more of the following: claudication, limb artery occlusion or $>$50% stenosis, and previous or planned intervention on the abdominal aorta or limb arteries. Cancer: previous or current neoplastic disease. Hemoglobin value was reported, and severe anemia was considered when HB$<$8 g/dl.

Continuous data are presented as mean$\pm$1 standard deviation. Comparisons of all measurements were made using the unpaired *t* test, chi square test or ANOVA, as appropriate.

The primary end-point was all-cause mortality. Survival rate was assessed by means of the Kaplan–Meier method. A p value$<$0.05 was considered statistically significant. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [7].

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A total of 330 consecutive patients with AVA<0.6 cm^2/m^2 and preserved EF formed the study population. Mean age was 79±9 (73% >75) years, 68% were female, AVA was 0.39±0.11 cm^2/m^2, MG was 54±16 mm Hg, and EF was 57±5%. Table 1 shows the demographic and clinical characteristics of the patient population divided according to MG > or <40 mm Hg (high-MG vs. low-MG). There were no differences in terms of age, gender and symptoms at presentation between the two groups. Both raw and indexed AVAs were larger in low-MG patients. LV stroke volume index (SVi) was significantly lower in low MG patients; in particular, 29% of low-MG patients but only 6% of high-MG patients were characterized by SVi<35 ml/m^2 (p=0.003).

Neither associated cardiac abnormalities nor non-cardiac comorbidities differed between low-MG and high-MG patients (Table 2). At 24-month follow-up, all-cause mortality was similar in low-MG and high-MG patients (25% vs. 15% respectively; p=0.3). Results did not change when the analysis was limited to the group of patients undergoing surgical or percutaneous valve replacement, or to the group of patients treated medically or with balloon valvuloplasty (see Fig. 1).

The main findings of this study are that severe AS patients and low-MG compared with high-MG patients: a) are comparable in terms of demographics, clinical presentation, and cardiac and systemic comorbidities; b) have a similar all-cause mortality rate independent of the therapeutic strategy applied. Thus, in our study cohort, the adverse outcome of patients with low-MG was mainly determined by the severity of the aortic valve disease per se.

Previous studies describing the high mortality rate for patients with low-MG did not provide sufficient detail regarding clinical presentation, and cardiac and non cardiac co-morbidities; consequently they could not rule out that the poor prognosis was related to reasons other than the severity of valve disease. It is noteworthy that in a systematic diagnostic work-up of a large group of patients with severe AS, a high prevalence of significant comorbidities was identified [8]. Of interest, our results contrast those reported in a recent study which showed that low-MG had a better outcome compared with high-MG [5]. We acknowledge that there are important differences in the patient populations enrolled in the two studies. While we included symptomatic patients with severe AS irrespective of clinical condition or associated comorbidities, the SEAS population was characterized by asymptomatic patients with AS of variable severity, in whom the presence of a comorbid condition, such as coronary artery disease, diabetes, renal insufficiency, history of stroke and peripheral vascular disease, was an exclusion criterion. However the clear difference in outcome seen in that study between groups regarded the need for valve replacement. Since the use of valve replacement as a clinical end-point is strongly related to the perception of disease

Table 1
Demographic, clinical presentation and echocardiographic severity of aortic stenosis.

	Low-MG 61 patients	High-MG 269 patients	p-Value
Age (years)	80±9	79±9	0.5
Gender (% female)	69	68	0.7
Body surface area (m^2)	1.8±0.2	1.8±0.2	0.6
NYHA class	2.5±0.8	2.5±0.7	0.9
BMI (kg/m^2)	26±4	26±4	0.8
Angina (%)	23	25	0.9
Syncope (%)	11	18	0.4
Statin (%)	50	50	0.8
ACE inhibitor (%)	50	57	0.4
Beta blockers (%)	26	33	0.1
Diuretic (%)	74	65	0.5
SVi (ml/m^2)	38±15	56±16	<0.0001
AVA (cm^2)	0.85±0.3	0.66±0.2	<0.0001
Indexed AVA (cm^2/m^2)	0.47±0.2	0.37±0.1	<0.0001
Peak gradient (mm Hg)	47±10	89±20	<0.0001
Mean gradient (mm Hg)	30±6	59±14	<0.0001
Septum thickness (mm)	13.7±2.1	14.7±2.2	0.003
Relative wall thickness	0.53±0.13	0.56±0.11	0.3
LV mass (g/m^2)	178±32	204±57	0.01
Ejection fraction	58±5	58±5	0.7
LV diastolic volume (ml/m^2)	75±31	68±26	0.1
LV diastolic diameter (cm/m^2)	2.9±0.5	2.8±0.4	0.2
PAP (mm Hg)	39±14	40±13	0.7
Atrial fibrillation (%)	29	30	0.9
Left bundle branch block (%)	13	10	0.8
Pacemaker (%)	25	13	0.09
AR>2/4° (%)	29	23	0.6
MR>2/4° (%)	63	45	0.4
Mitral stenosis (%)	6	4	0.6
Bicuspid aortic valve (%)	6	4	0.9
Coronary artery disease (%)	35	32	0.6

Abbreviations: NYHA: New York Heart Association; BMI: body mass index; ACE: angiotensin converting enzyme; SVi: indexed stroke volume; AVA: aortic valve area; LV: left ventricular; PAP: systolic pulmonary artery pressure; AR: aortic regurgitation; MR: mitral regurgitation.

Table 2
Non cardiac comorbidities.

	Low-MG 61 patients	High-MG 269 patients	p-Value
Hypertension (%)	77	67	0.3
Diabetes (%)	37	22	0.08
Dyslipidemia (%)	64	58	0.7
Total cholesterolemia (mg/dl)	188±69	170±47	0.02
Creatinine (mg/dl)	1.27±0.7	1.3±1.0	0.8
Mean eGFR ($ml/min/1.73\ m^2$)	54±29	53±28	0.8
Moderate/severe chronic kidney disease (%)	50	51	0.8
Hemoglobin (g/dl)	11.6±1.4	11.6±1.6	0.8
Severe anemia (hemoglobin<8 g/dl) (%)	13%	10%	0.5
Chronic obstructive pulmonary disease (%)	20	23	0.8
Previous ictus cerebri (%)	3	8	0.3
Stent carotidei	11	11	0.9
Peripheral vascular disease (%)	11	10	0.9
Aortic aneurism (%)	3	4	0.7
Previous cancer (%)	15	11	0.6
Current cancer (%)	5	4	0.9
Logistic Euroscore	18±14	19±16	0.8
Logistic Euroscore>20	26	35	0.4

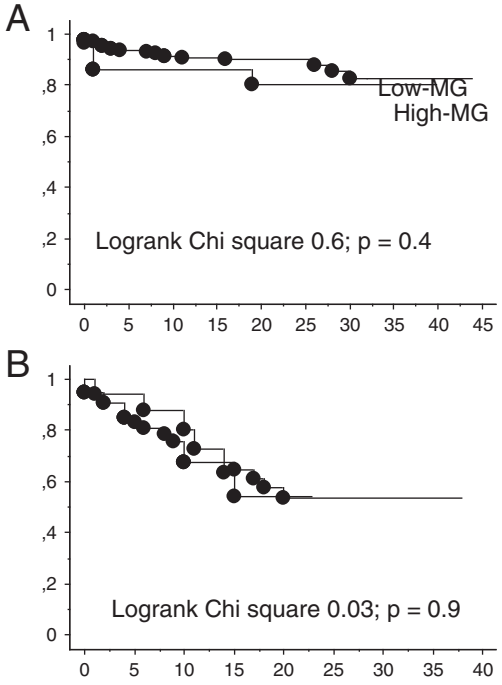

Fig. 1. Panel A: survival rate of low and high MG patients undergoing surgical or percutaneous aortic valve replacement. Panel B: survival rate in patients treated medically or with balloon valvuloplasty.

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severity on the part of the referral physician and the increased gradient is a much clearer expression of valve obstruction, it is not surprising that high-MG determines more frequent clinical evaluations, a higher surgical referral and, consequently, a higher event rate.

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