

RESEARCH LETTER

Role of exercise echocardiography in paradoxical low gradient severe aortic stenosis



Papel da ecocardiografia de sobrecarga na estenose aórtica grave de gradiente baixo paradoxal

Aortic stenosis (AS) with a valve area (AVA) $<1 \text{ cm}^2$ but mean gradient (MG) $<40 \text{ mmHg}$ in the presence of normal ejection fraction (LVEF ≥ 50) is a matter of concern, when considering the true severity of AS.^{1,2} We hypothesized that exercise echocardiography (ExE) could offer additional information by two pathways: the detection of LV systolic dysfunction and changes in AV hemodynamics.

Consecutive asymptomatic, or low symptomatic/equivocal symptoms patients with paradoxical low gradient (LG) severe AS were studied. We measured AVA, maximum and MG, mitral regurgitation (MR), systolic pulmonary artery pressure (sPAP) and LV early filling/early mitral annulus septal systolic movement (E/e') ratio³ (EPIC 7, Philips). Moderate MR was considered significant.

Patients underwent a treadmill ExE (Bruce protocol 76%).^{4,5} Peak imaging assessed LV systolic function (global, regional) and post-exercise the rest of measurements (MR, E/e' , AVA, gradients, sPAP). The study was approved by our Ethics Committee. End points were all-cause mortality, non-fatal MI, admittance for unstable coronary syndrome or for cardiac failure, or symptomatic progression leading to AV replacement and/or coronary revascularization.

Table 1 shows clinical characteristics and ExE data; low-flow LG-AS was observed in 17 patients (38%), and normal-flow LG ($\geq 35 \text{ ml/m}^2$) in 28 (62%). AVA at exercise was evaluated in 33 subjects, as bad tracing quality/technical reasons prevented assessment in 12. Findings of moderate AS at exercise (AVA $\geq 1 \text{ cm}^2$ plus MG $<40 \text{ mmHg}$) were observed in 10/33 (30%) patients and of definitively severe AS (AVA $<1 \text{ cm}^2$; MG $\geq 40 \text{ mmHg}$) in 7/33 (21%), with no differences in % between low-flow and normal flow. AVA and MG at rest were worse in patients with definitively severe AS in exercise ($p < 0.05$ both) and increase in blood pressure lower ($p = 0.08$). Angiography performed in 32 patients showed coronary artery disease (CAD) in 15 (exercise WMAs

in nine) and was normal in 17 (exercise wall motion abnormalities [WMAs] in three).

During follow-up of 22 ± 18 months, there were 29 events. Resting wall motion score index (WMSI), metabolic equivalents, left ventricular ejection fraction and WMSI at exercise, Δ WMSI, abnormal ExE, significant MR at exercise, and digoxin were associated with events. Independent predictors were digoxin (HR=44.8, $p=0.003$), resting WMSI (HR=87.5, $p=0.001$), Δ in WMSI (HR=11.3, $p=0.002$), and significant exercise MR (HR=6.1, $p=0.006$). Figure 1 shows Kaplan-Meier curves according to ExE results, and an example of moderate AS performance at exercise.

To our knowledge, this is the first study investigating treadmill ExE for defining outcomes in LG-AS. The main findings were that ExE was useful to detect outcome mainly by demonstrating exercise WMAs but failed in exploring the benefit of AV hemodynamics. Our data emphasize that in this scenario, it is not just the AV disease that matters, but that CAD is commonly associated and can affect the outcome.

One study employed dobutamine stress or supine bicycle in paradoxical LG-LF AS,⁶ finding greater severity with stress (smaller AVA, smaller projected AVA, and higher gradients) in patients in whom the anatomical extracted AV during surgery showed greater severity. Also, they observed that projected AVA was an independent predictor of outcome. Hence, exercise could be of interest for assessing outcome, suggesting that lower gradients during exercise, and greater AVA would be data of less severe outcome, therefore, reclassifying these patients.

Some of our patients had findings of non-severe AS such as limited hypertrophy and AV calcification, and moderate AS at exercise. On the other hand, symptom explanations can come from diastolic dysfunction, as well as from the aforementioned associated ischemic CAD. Although our research failed to find any association between exercise hemodynamics and outcome, we would like to encourage others to further look for insights into LG-AS. However, an ExE for assessing ischemia can offer prognostic information on these subjects.

Limitations included the small sample that prevented the study of certain relationships, such as those derived from assessment of AV parameters. AVA at exercise was not assessed in all patients; and ExE results were available to the responsible clinicians.

<https://doi.org/10.1016/j.repc.2023.01.020>

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Table 1 Clinical characteristics in the overall group; and resting and exercise echocardiography data, and changes with exercise in subgroups (low-flow low gradient and normal-flow low-gradient AS).

Clinical characteristics			
Age, y			74±12
Female gender, n (%)			32 (71)
Diabetes, n (%)			13 (29)
Hypertension, n (%)			33 (73)
Hypercholesterolemia (51%)			23 (51)
Atrial fibrillation, n (%)			9 (20)
History of CAD, n (%)			13 (29)
Calcium channel blockers, n (%)			10 (22)
Nitrates, n (%)			6 (13)
AECI/ARAs, n (%)			20 (44)
Digoxin, n (%)			1 (2)
Diuretics, n (%)			7 (16)
Betablockers, at the time of the ExE, n (%)			7 (16)
Symptoms, n (%)			
Asymptomatic			16 (36)
Chest pain			10 (22)
Equivocal/low grade dyspnea			12 (27)
Any chest pain plus equivocal dyspnea			7 (15)
Resting echocardiography			
Myocardial thickness, mm			12.3±2.4
Global LV longitudinal strain			-19.3±4.0
Calcium score ≥2*			15 (34)
Resting WMAs			3 (7)
Exercise echo data			p values intergroup (rest, exercise)
>85% of the age-predicted maximum heart rate, n (%)	37 (82)		
LFLG	16 (94)	NS	
NFLG	21 (75)		
Achieved METs	6.6±2.2		
LFLG	6.2±2.2	NS	
NFLG	6.7±2.1		
Symptoms with exercise, n (%)	14 (31)		
LFLG	4 (24)	NS	
NFLG	10 (36)		
Blunted blood pressure response, n (%)	17 (38)		
LFLG	4 (24)	NS	
NFLG	13 (46)		
Ischemia, n (%)	15 (33)		
LFLG	4 (24)	NS	
NFLG	11 (39)		
Changes from rest to exercise		Rest	Exercise
Heart rate (bpm)	79±18	139±20	
LFLG	89±19	145±24	Rest NS
NFLG	73±14	135±16	Ex. NS
Blood pressure (mmHg)	136±28	164±31	
LFLG	135±31	170±28	Rest NS
NFLG	137±26	160±32	Ex. NS
LV ejection fraction (%)	61±7	64±8	
LFLG	57±5	64±10	Rest 0.001
NFLG	63±6	64±8	Ex. NS

Table 1 (Continued)

Changes from rest to exercise	Rest	Exercise	
<i>Wall motion score index</i>	1.03±0.15	1.13±0.24	
LFLG	1.06±0.24	1.17±0.33	Rest NS
NFLG	1.00±0.03	1.10±0.16	Ex. NS
<i>Aortic valve area, cm²</i>	0.84±0.16	0.95±0.25	
LFLG	0.81±0.19	0.86±0.14	Rest NS
NFLG	0.85±0.23	1.00±0.25	Ex. 0.06
<i>Mean aortic gradient (mmHg)</i>	27±7	35±9	
LFLG	25±8	34±11	Rest 0.08
NFLG	28±6	35±7	Ex. NS
<i>Maximal aortic gradient (mmHg)</i>	51±12	68±19	
LFLG	48±15	63±23	Rest NS
NFLG	52±10	71±15	Ex. NS
<i>Systolic pulmonary artery pressure, mmHg (n)</i>	42±13 (23)	56±18 (21)	
LFLG	42±13	54±17	Rest NS
NFLG	42±14	58±13	Ex. NS
<i>E/e' >15 and/or restrictive pattern</i>	17 (38)	18 (40)	
LFLG	8 (47)	7 (41)	Rest NS
NFLG	9 (32)	11 (39)	Ex. NS
<i>Moderate or severe MR, n (%)</i>	4 (9)	3 (7)	
LFLG	1 (6)	1 (6)	Rest NS
NFLG	3 (11)	2 (8)	Ex. NS

METs depicts metabolic equivalents; ACEI: angiotensin converting enzyme inhibitors; ARAs: angiotensin receptor antagonists; LFLG: low-flow low-gradient aortic stenosis; NF: normal flow; Ex.: exercise.

* The aortic valve calcium score was semi-quantitatively measured by echocardiography, scoring small area of calcification as 1, moderate extension affecting 1–2 valves as 2, and extensive calcification affecting 2–3 valves as 3; ExE: exercise echocardiography; MR: mitral regurgitation; WMAs: wall motion abnormalities.

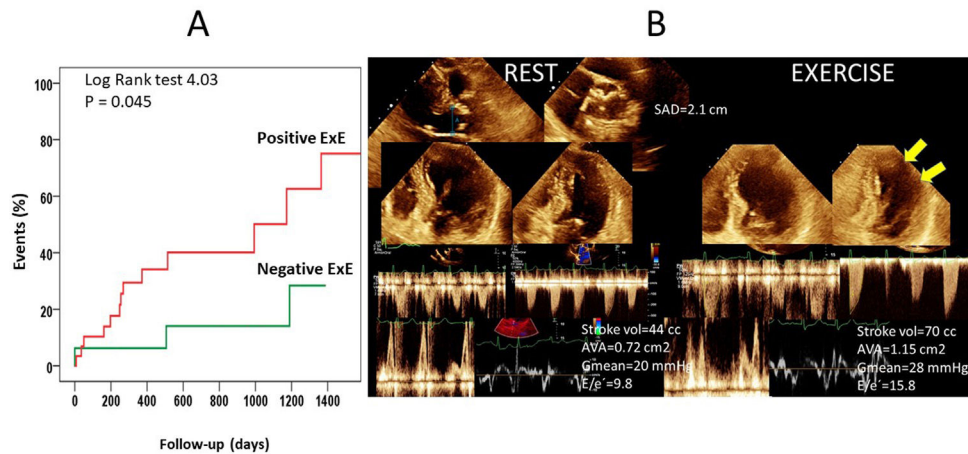


Figure 1 (A) Event-free survival Kaplan-Meier curves for patients with normal and abnormal exercise echocardiography findings. (B) Example of a patient with low-gradient severe AS, that developed hemodynamic data of moderate AS with exercise. Arrows: lateral ischemia. Post-test angiography demonstrated CAD.

Authors' contributions

All authors have read and approved the manuscript. It has not been published and is not being considered for

publication elsewhere. Jesús Peteiro and Alberto Bouzas-Mosquera participated in the design, data acquisition, and data analysis, whereas Lucia Valmisa revised it critically and gave final approval.

Funding

This work was supported by the Spanish Society of Cardiology (Project of Clinical Research in Cardiology Dr. Pedro Zarco 2017).

Conflict of interest

There is no conflict of interest to disclose.

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