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How to Diagnose Low-Gradient Critical Aortic Stenosis

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KEY WORDS: *aoetic stenosis; low gradient low EF; paradoxical low flow low gradient*

ABBREVIATIONS
AS = aortic stenosis
AVA = aortic valve area
AVAi = aortic valve area index
EAE = European Association of Echocardiography
EF = ejection fraction
ASE = American Society of Echocardiography
LGSAS = low gradient severe aortic stenosis
MPG = mean pressure gradient
SV = stroke volume
SVi = stroke volume index

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Aortic stenosis (AS) has become the most frequent type of valvular heart disease in Europe and North America, accounting for 34% of all native valve disease and 43% of all single valve disease.[1,2] Echocardiography remains the diagnostic method of choice in the evaluation and management of patients with AS. Current American and European guidelines[3] both recommend an aortic valve area (AVA) cut-off value of <1 cm^2, or indexed by body surface area (AVAi) <0.6 cm^2/m^2, mean pressure gradient (MPG) >40 mmHg and peak velocity >4 m/sec for severe aortic stenosis, in patients with normal left ventricular ejection fraction (EF). Jander et al[4] report the influence of AVAi on the prevalence of severe stenosis. Inconsistent grading related to discrepancy in guidelines criteria has now been studied and one out of three patients exhibits inconsistent severe AS grading.[5]

LOW GRADIENT SEVERE AORTIC STENOSIS (LGSAS)

Under the term LGSAS we refer to two separate entities,[6] low gradient/low EF AS (described first by Carabello et al in 1980) and paradoxical low-flow/low-gradient severe AS despite preserved EF.

The term " low gradient/low EF AS" represents about 5-10% of all cases of severe AS and is usually applied to patients with a mean gradient <30 mmHg (or <40 mmHg), an AVA<1 cm^2 and an EF<35% (or <40%). The main difficulty for clinicians is to distinguish true severe low-flow AS, responsible for low EF, from pseudo-severe AS comprising mild to moderate AS associated with another cause of left ventricular dysfunction. [4-8] A very low gradient may be seen in true severe low- flow AS, while the decreased AVA seen in pseudo-severe AS reflects poor opening of the aortic valve directly related to low transvalvular flow. Dobutamine echocardiography is very helpful to potentially distinguish severe from non severe AS. [7,8] Dobutamine may increase the stroke volume (SV) and consequently the aortic transvalvular flow. In pseudo-severe AS, an increase in SV results in an increase of AVA to reach a non-severe range (>1.2 cm^2), whereas the gradient (<30 mmHg) is not significantly altered owing to the larger AVA. True severe AS is characterized by <0.2 cm^2 increase in AVA, while still <1.0 cm^2 with an increase in MPG to >40 mmHg. Absence of contractile reserve does not help differentiate between true AS or pseudo-AS because there is no change in forward stroke volume.

The new entity of "paradoxical low-flow/low-gradient severe AS despite preserved EF" refers to patients with severe AS on the basis of AVA (<1 cm^2), indexed AVA (<0.6 cm^2/m^2) who paradoxically have a low transvalvular flow rate (SVi<35 ml/m^2) despite the presence of a preserved left ventricular EF >50%. It represents 25% of

the total AS population (30% of all patients who undergo echocardiographic assessment of AS severity).[9] This is a highly challenging subset of patients in terms of diagnosis and clinical decision making, especially if they are symptomatic. In fact these patients often have a higher global hemodynamic load and a more pronounced impairment of intrinsic myocardial function, consistent with a more advanced stage of the disease. They carry a poorer prognosis.

The chronic exposure to a high level of afterload (due to the combination of severe AS and reduced arterial compliance) eventually exceeds the limit of left ventricular compensatory mechanisms and leads to an intrinsic impairment of myocardial function and a decrease in cardiac output. This results in pseudo-normalization of transvalvular gradients and peripheral blood pressure. This situation is highly insidious because AS and hypertension may appear less severe on the basis of gradient and blood pressure, whereas these patients are at a more advanced stage of their disease.[10] They need a more comprehensive evaluation of AS severity going beyond the classical measurements to include indices that are less flow-dependent.

Potentially other diagnostic tests (exercise stress echocardiography, computed tomography, magnetic resonance imaging, plasma natriuretic peptides, and invasive studies) may be required to confirm disease severity and guide therapeutic management. There is a list of various parameters suggested by EAE/ASE guidelines for the diagnosis of LGSAS.[11] In particular, blood pressure should be recorded in every patient,

TABLE 2. Comprehensive Doppler Echocardiographic Examination of Low Gradient Severe Aortic Stenosis (LGSAS)

Quantification of valvular obstruction
Maximal velocity
Mean gradient
Aortic valve area
Indexed aortic valve area
Energy loss index
Quantification of vascular load
Peripheral blood pressure
Systemic arterial compliance
Systemic vascular resistance
Quantification of global LV haemodynamic load
Valvulo-arterial impedance
Quantification of LV geometry
LV end-diastolic internal diameter
LV end-diastolic volume index
Relative wall thickness
Quantification of LV systolic function
LVOT stroke volume index
Cardiac index
Ejection fraction by Simpson method
Ejection fraction by Dumesnil method
Mid-wall fractional shortening

LV = left ventric-le(-ular); LVOT = left ventricular outflow tract

TABLE 1. EAE/ASE Guidelines for the diagnosis of Low Gradient Severe Aortic Stenosis (LGSAS)

	Units	Formula / Method	Cutoff for Severe	Concept	Advantages	Limitations
LV % Stroke Work Loss [27]	%	$\%SWL = \frac{\overline{\Delta P}}{\Delta P + SBP} \cdot 100$	25	Work of the LV wasted each systole for flow to cross the aortic valve, expressed as a % of total systolic work	Very easy to measure. Related to outcome in one longitudinal study.	Flow-dependent. Limited longitudinal data
Recovered Pressure Gradient [13, 32]	mm Hg	$P_{distal} - P_{vc} = 4 \cdot v^2 \cdot 2 \cdot \frac{AVA}{AA}\left(1 - \frac{AVA}{AA}\right)$	-	Pressure difference between the LV and the aorta, slightly distal to the *vena contracta*, where distal pressure has increased.	Closer to the global hemodynamic burden caused by AS in terms of adaptation of the cardiovascular system. Relevant at high flow states and in patients with small ascending aorta.	Introduces complexity and variability related to the measurement of the ascending aorta. No prospective studies showing real advantages over established methods.
Energy Loss Index [35]	cm^2/m^2	$ELI = \frac{AVA \cdot AA}{AA - AVA} \Big/ BSA$	0.5	Equivalent to the concept of AVA, but correcting for distal recovered pressure in the ascending aorta	(As above) Most exact measurement of AS in terms of flow-dynamics. Increased prognostic value in one longitudinal study.	Introduces complexity and variability related to the measurement of the ascending aorta.
Valvulo-Arterial Impedance [31]	mm Hg/ml/m^2	$Z_{VA} = \frac{\overline{\Delta P_{net}} + SBP}{SVI}$	5	Global systolic load imposed to the LV, where the numerator represents an accurate estimation of total LV pressure	Integrates information on arterial bead to the hemodynamic burden of AS, and systemic hypertension is a frequent finding in calcific-degenerative disease.	Although named "impedance", only the steady-flow component (i.e. mean resistance) is considered. No longitudinal prospective study available.
Aortic Valve Resistance [28, 29]	dynes/s/cm [5]	$AVR = \frac{\overline{\Delta P}}{Q} = \frac{\overline{4 \cdot v^2}}{\cdot r_{LVOT}^2 \cdot v_{LVOT}} \cdot 1333$	280	Resistance to flow caused by AS, assuming the hydrodynamics of a tubular (non flat) stenosis.	Initially suggested to be less flow-dependent in low-flow AS, but subsequently shown to not be true.	Flow dependence. Limited prognostic value. Unrealistic mathematic modelling of flow-dynamics of AS.
Projected Valve Area at Normal Flow Rate [30]	cm^2	$AVA_{proj} = AVA_{rest} + VC \cdot (250 - Q_{rest})$	1.0	Estimation of AVA at normal flow rate by plotting AVA vs. flow and calculating the slope of regression (DSE)	Accounts for the variable changes in flow during DSE in low flow low gradient AS, provides improved interpretation of AVA changes	Clinical impact still to be shown. Outcome of low-flow AS appears closer related to the presence / absence of LV contractility reserve.

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and systemic arterial compliance and valvulo-arterial impendence routinely calculated. It also should be mentioned that energy loss index (ELI) is a parameter taking into account pressure recovery, from a practical standpoint, it is most useful in patients with a small aortic diameter (<30 mm) where the recorded gradients and AVA may significantly overestimate AS severity.[12]

In conclusion, the most important message is that the presence of a moderately increased transvalvular gradient (<40 mmHg) or velocity (<4 m/sec) does not necessarily exclude the presence of a severe aortic stenosis, and that particular attention should be paid to patients with discordant AVA-gradient findings, especially if they are symptomatic. Complex measures that integrate the ventricular, valvular and vascular components of the disease may allow optimal timing of intervention. The clearest indication for valve replacement is symptoms due to outflow obstruction.[13] In patients with low-flow/low-gradient AS and left ventricular systolic dysfunction (EF <50%), it may be useful to re-measure aortic velocity (or mean pressure gradient) and valve area during low-dose dobutamine infusion stress testing to determine whether AS is severe or only moderate and to evaluate for contractile or flow reserve.[14]

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