

Assessment of low-flow, low-gradient, severe aortic stenosis: an invasive evaluation is required for decision making

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KEYWORDS

- aortic stenosis
- cardiac catheterisation
- echocardiography
- haemodynamic assessment

Abstract

Low-flow, low-gradient severe aortic stenosis (AS) is characterised by a small aortic valve area (AVA) and low mean gradient (MG) secondary to a low cardiac output and may occur in patients with either a preserved or reduced left ventricular ejection fraction (LVEF). Symptomatic patients presenting with low-flow, low-gradient severe AS have a dismal prognosis independent of baseline LVEF if managed conservatively and should therefore undergo aortic valve replacement if feasible. Transthoracic echocardiography (TTE) is the first-line investigation for the assessment of AS haemodynamic severity. However, when confronted with guideline-discordant AVA (small) and MG (low) values, there are several reasons other than severe AS combined with a low cardiac output which may lead to such a situation, including erroneous measurements, small body size, inherent inconsistencies in the guidelines' criteria, prolonged ejection time and aortic pseudostenosis. The distinction between these various entities poses a diagnostic challenge. However, it is important to make a distinction because each has very different implications in terms of risk stratification and therapeutic management. In such instances, cardiac catheterisation forms an integral part of the work-up of these patients in order to confirm or refute the echocardiographic findings to guide management decisions appropriately.

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Introduction

Severe aortic stenosis (AS) is associated with a dismal outcome once symptoms ensue unless the obstruction is mechanically removed^{1,2}. Transvalvular pressure gradient and aortic valve area (AVA) are the most important parameters to determine AS haemodynamic severity, and their accurate measurement is essential to guide patient management^{3,4}. The European Society of Cardiology guidelines define severe AS as an AVA <1.0 cm² and a mean gradient (MG) >40 mmHg in the presence of a normal cardiac output³. Transthoracic echocardiography (TTE) is the first-line investigation for the assessment of AS severity^{3,4}. Invasive evaluation using cardiac catheterisation is recommended by the guidelines when non-invasive data are non-diagnostic or if there is a discrepancy between clinical and echocardiographic evaluation⁴. When MG and AVA are guideline concordant (e.g., AVA <1 cm² and MG >40 mmHg), no further investigations of haemodynamic AS severity are usually required and management decisions are typically straightforward^{3,4}. Diagnostic dilemmas arise when guideline discordant values such as an AVA in the severe range (i.e., AVA <1 cm²) and an MG in the moderate range (i.e., <40 mmHg) are found⁵⁻⁹. In the presence of true severe AS such discordance is related to low transvalvular flow, since the pressure gradient is directly proportional to the squared function of flow such that even a small reduction in flow rate can result in significant reductions in pressure gradient (**Table 1**)¹⁰. While this condition, known as low-flow, low-gradient severe AS, has classically been associated with left ventricular systolic dysfunction (LEF-LG)¹¹, recently it has been shown to occur even among patients with preserved LV systolic function but reduced transvalvular flow, a condition referred to as “paradoxical” low-flow, low-gradient (PLF-LG) severe AS (**Figure 1**)⁹. The prevalence of “classic” LEF-LG severe AS is 5-10%¹², whereas that of PLF-LG is typically higher (5-25%)¹⁰. Patients presenting with symptomatic low-flow, low-gradient severe AS and either reduced or preserved LV systolic function have a poor prognosis if managed conservatively

Table 1. Relation of the stroke volume to the mean gradient.

Stroke volume mL	Mean gradient mmHg
80	83
70	64
60	47
50	32
40	21
30	12
20	5

Data derived by solving the Gorlin equation for mean gradient (MG), i.e., $MG = \left(\frac{\text{Stroke volume}}{44.3 * \text{SEP} * \text{AVA}} \right)^2$ where the aortic valve area (AVA) was assumed to be 0.60 cm² and the systolic ejection period (SEP) was assumed to be 0.33 seconds and the heart rate was assumed to be 80 beats per minute. Stroke volume was calculated as cardiac output/heart rate.

and should undergo aortic valve replacement if feasible^{3,4,9,13-15}. Transcatheter aortic valve implantation (TAVI) is also a feasible therapeutic option for these patients¹⁶⁻¹⁹. However, low-flow, low-gradient severe AS poses a diagnostic challenge as severe AS combined with a low cardiac output is not the only cause of guideline discordant AVA (small) and MG (low) values. Other reasons for this presentation include measurement errors, small body size, inherent discrepancies in the guidelines’ criteria, prolonged left ventricular ejection time and pseudosevere AS^{10,20}. The accurate distinction between these various entities is critical, given that they may have very different implications in terms of risk stratification and therapeutic management. The most reliable and efficient way to do this in a symptomatic patient is to perform an invasive evaluation of AS severity by directly recording the transvalvular pressure gradient and calculating the AVA using the Gorlin equation. Furthermore, a dobutamine stress test assessing the presence of contractile reserve and excluding pseudostenosis can be safely performed in the catheterisation laboratory^{4,21}. These ancillary investigations can be done

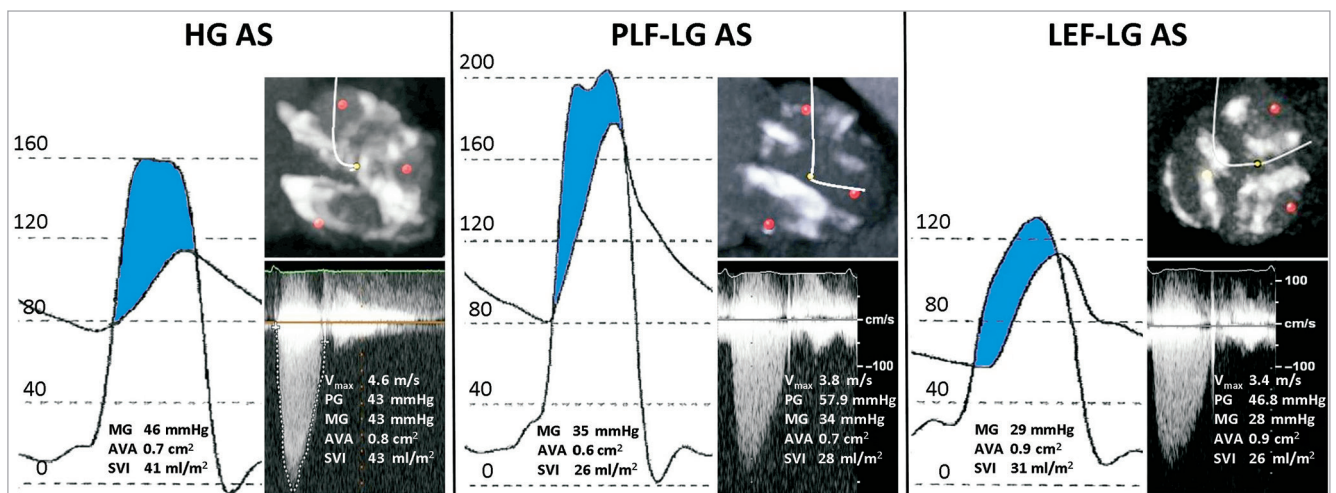


Figure 1. Cardiac catheterisation (simultaneous pressure recording) and echocardiographic findings in patients with high-gradient (HG), paradoxical low-flow, low-gradient (PLF-LG), and low ejection fraction, low-flow, low-gradient (LEF-LG) severe aortic stenosis. Multidetector computed tomography (MDCT) demonstrated comparable levels of aortic valve calcification in all patients.

easily at the time of coronary angiography, which is recommended by the 2014 American Heart Association/American College of Cardiology guidelines before valve intervention in all patients with decreased LV systolic function, history of coronary artery disease, or coronary risk factors (including men aged >40 and post-menopausal women)⁴. This recommendation encompasses all patients with “classic” LEF-LG and most patients with PLF-LG, who typically tend to be older females.

Doppler echocardiography versus cardiac catheterisation

Current guidelines do not distinguish between catheterisation and Doppler measurements, as though values for gradient and AVA derived from either method were synonymous^{3,4}. Furthermore, cut-off values used for defining the haemodynamic severity of AS are based on data derived from catheterisation studies, whereas Doppler measurements are used in routine clinical practice²². The guideline assumptions are problematic for two reasons. First, pressure recovery can cause significant discrepancies between Doppler echo and cardiac catheterisation-derived pressure gradients owing to the fact that kinetic energy of blood is converted back to potential energy downstream in the ascending aorta²³. Therefore, catheterisation-derived gradients are lower than those derived from Doppler echocardiography. This phenomenon is particularly accentuated in patients with small aortic diameters (<30 mm) or aortic valve orifices in the moderate to severe range (AVA 0.8 cm²–1.2 cm²)²². However, it is the net gradient recorded at catheterisation which reflects the true haemodynamic significance of a stenosis²². Second, Doppler echocardiography measures the effective orifice area, whereas cardiac catheterisation attempts to measure the anatomic valve area^{22,24}. Because flow streamlines continue to contract for a variable distance after the anatomical orifice, the echo-derived

effective orifice area is smaller than the anatomic AVA²⁴. The net effect is that echo tends to yield larger pressure gradients and smaller valve areas as compared with catheterisation measurements (assuming no measurement errors), and therefore systematically overestimates AS severity.

Limitations with echocardiographic MG and AVA calculation

All TTE measurements are operator-dependent and require sufficient image quality to obtain accurate recordings. For example, a non-parallel intercept angle between the ultrasound beam and the left ventricular outflow tract (LVOT) and aortic Doppler signals may lead to underestimation of the transvalvular aortic gradient (Figure 2). Measurements of the LVOT diameter are particularly prone to error due to considerable inter- and intra-observer variability. For example, in patients presenting with a densely calcified aortic valve or irregular calcium mass at the level of the aortic annulus, accurate assessment of the LVOT dimensions may be particularly challenging. This can potentially result in overestimation or underestimation of the AVA as the LVOT diameter is squared in the continuity equation. Furthermore, the continuity equation assumes a circular LVOT cross-section, whereas anatomic studies and three-dimensional imaging observed an elliptical shape in most patients²⁵. As a consequence, LVOT area and EOA are systematically underestimated using two-dimensional imaging. Another potential source of error is the exclusion of the subvalvular velocity from the calculation of the transvalvular gradient, which is always considered negligible (<1 m/s) using the simplified Bernoulli equation. However, this assumption is not applicable in the presence of significant subvalvular stenosis. As a consequence, Doppler echocardiography may overestimate the transvalvular gradient when serial stenoses are present²⁶.

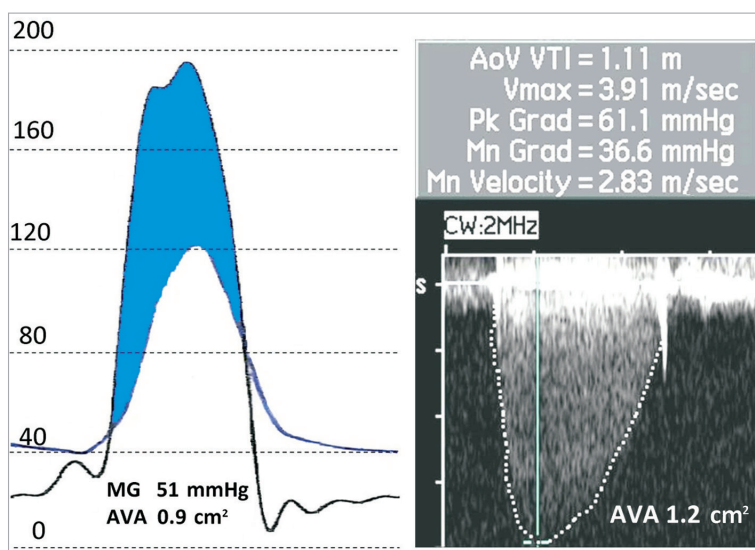


Figure 2. Underestimation of the mean gradient with the use of echocardiography due to measurement error. This patient was confirmed as having high-gradient severe aortic stenosis during cardiac catheterisation and subsequently underwent transcatheter aortic valve implantation with marked symptomatic improvement.

Limitations with invasive AVA calculation

AVA is calculated in both the non-invasive and invasive laboratories using the same basic hydraulic formula, i.e., flow=area*velocity,

$$\text{therefore area} = \frac{\text{flow}}{\text{velocity}}.$$

During cardiac catheterisation the denominator in the equation (i.e., velocity) is not directly measured but can be imputed with the Torricelli law from the catheter-derived pressure gradient using the following formula: velocity= $\sqrt{2g\Delta P}$, where g is the velocity of acceleration resulting from gravity (i.e., 980.67 cm.s⁻²) and ΔP is the pressure gradient²⁴. The numerator, cardiac output, can be determined using either the Fick method (i.e., $\frac{\text{oxygen consumption}}{\text{oxygen content}}$)

or thermodilution method²⁴. Oxygen content is directly assessed in catheterisation laboratories employing the Fick method by calculating the arteriovenous oxygen difference. Conversely, oxygen consumption (VO₂) is frequently estimated using various normograms and formulas usually based on age, weight, body surface area (BSA) or a combination thereof (e.g., LaFarge formula), because direct measurement of VO₂ is time-consuming, cumbersome and uncomfortable for the patient²⁴. However, Gertz et al showed that, as compared with direct VO₂, estimates of VO₂ based on body size significantly overestimate the cardiac output, while use of the LaFarge formula significantly underestimated it and *ipso facto* resulted in misclassification of AS severity²⁷. In fact, the same investigators found that the best equations for estimating VO₂ in both an elderly population and patients with low cardiac output and severe AS were 2.5*weight (kg) and 100**BSA²⁸. Many laboratories now use thermodilution based on an indicator dilution methodology to measure cardiac output. This method is usually accurate in patients with a normal or high output who are in normal sinus rhythm. However, it becomes inaccurate in patients with low-cardiac-output states, significant tricuspid regurgitation, irregular rhythms and intracardiac shunts²⁴. The original Gorlin formula for calculating AVA stated that $A_{\text{anat}} = F / (C_c * C_v * \sqrt{2g\Delta P})$, where A_{anat} is anatomical AVA, F is flow or stroke volume, C_c and C_v are the coefficients of contraction and velocity loss, respectively²⁹. C_c attempts to correct the flow area to the anatomic area, whereas C_v allows for the fact that not all of the pressure gradient is converted to flow because some of the velocity is lost to friction within the valve. Because blood viscosity, turbulence, pulsatile flow, and the inconstant shape of deformed valves made it almost impossible to predict the discharge coefficient analytically, the Gorlins used an empirical constant to make their calculated mitral valve areas align better with actual valve areas obtained at autopsy or surgery²⁹. However, an empirical constant was not developed for the aortic valve and is in fact assumed to be 1, which is theoretically impossible. Therefore,

$$\text{the final Gorlin formula is } A_{\text{anat}} = \frac{F}{44.3\sqrt{\Delta P}} \text{ where } 44.3 = \sqrt{2 * 980.67},$$

although the equation ignores the conversion of cmH₂O to mmHg and the mass density of blood²². These factors are important in understanding that invasively calculated valve areas also have limitations in the assessment of AS haemodynamic severity.

Invasive work-up of “classic” low-flow, low-gradient severe AS: differentiating “true-severe” from “pseudo-severe” aortic stenosis

True severe AS is considered present when the MG increases to greater than 30-40 mmHg but the AVA remains fixed at <1.0-1.2 cm² at peak dobutamine infusion¹². Conversely, pseudosevere AS is present when the MG remains unchanged but the AVA increases in size with increasing dobutamine doses¹². Nishimura et al previously demonstrated the safety and diagnostic efficacy of performing a dobutamine challenge in the catheterisation laboratory²¹. This can easily be performed at the time of coronary angiography and is arguably safer than in the echocardiography laboratory since the patient can be intensely monitored and promptly treated for any occurrences of dobutamine-induced arrhythmias. This is reflected in the 2014 AHA/ACC guidelines which state that low-dose dobutamine stress testing can be performed using either echocardiographic or invasive haemodynamic measurements⁴. The MG threshold at which a low-dose dobutamine challenge should be performed has been debated. The AHA/ACC guidelines recommend stress testing among LEF-LG patients with an MG <40 mmHg⁴. However, a previous study argued that only patients with an MG ≤30 mmHg require stress testing since all LEF-LG patients with an MG >30 mmHg in conjunction with a small AVA were observed to have severe AS at the time of operation in this particular study²¹.

Contractile reserve is absent in about one third of patients with classic LEF-LG severe AS. This poses a diagnostic challenge because the degree of stenosis severity often remains indeterminate after DSE¹⁰. In such situations the mean transvalvular flow rate (Q) can be derived by dividing stroke volume by LV ejection time (echo) or systolic ejection period (catheterisation) to derive the simplified projected AVA to determine the projected valve area at normal flow rate:

$$AVA_{\text{proj}} = \frac{AVA_{\text{peak}} - AVA_{\text{rest}}}{Q_{\text{peak}} - Q_{\text{rest}}} \times (250 - Q_{\text{rest}}) + AVA_{\text{rest}}$$

where AVA_{rest} and Q_{rest} are AVA and Q at rest, and AVA_{peak} and Q_{peak} are AVA and Q measured at peak dobutamine infusion³⁰. However, in ≈10-20% of cases the increase in Q is insufficient to determine the AVA_{proj} , and in such cases multidetector computed tomography (MDCT) may be useful for determination of the aortic valve calcium load and density, with patients having higher values being more likely to have severe AS¹⁰.

It is important to note that retrograde catheterisation of the aortic valve in valvular stenosis is associated with an increased risk of cerebral embolism³¹.

Invasive work-up of “paradoxical” low-flow, low-gradient severe AS

Guideline discordant AVA (small) and MG (low) values are present in up to a third of patients with aortic stenosis and preserved LV systolic function (LVEF ≥50%) and may be due to measurement errors, small body size, inherent inconsistencies in the guidelines' criteria, a prolonged ejection time or PLF-LG severe AS^{5,6,10}.

Because symptomatic patients with the latter condition have a dismal outcome if managed conservatively^{9,15}, it is important to exclude other causes of guideline discordant presentations which do not require aortic valve replacement. An invasive evaluation can play a critical role in helping to accomplish this, as demonstrated in **Figure 3**.

Measurement errors

Measurement errors can occur with the use of TTE for the various reasons discussed above. However, several methods may be used to corroborate AVA and stroke volume measurements non-invasively. For example, in the absence of significant mitral regurgitation, measurement errors in stroke volume calculation occurring with the use of TTE can be reduced by corroborating Doppler stroke volumes with volumetric stroke volume obtained by multiplying the LVEF by the LV end-diastolic volume derived by the Teichholz formula and by measuring the peak aortic jet velocity in all available transducer windows using a non-imaging continuous wave Doppler transducer⁷. Nevertheless, measurement error may persist despite these methods, particularly in patients with poor acoustic windows, and in such cases an invasive evaluation is essential to determine the invasive MG and AVA calculated using the Gorlin equation.

Small body size

Patients with small body size tend to have smaller LV cavities and therefore produce lower stroke volumes and ultimately have lower mean gradients. Therefore, small body size may result in discordant AVA and MG values. However, this situation can easily be resolved

by indexing the AVA to body surface area with patients having an indexed AVA $\leq 0.6 \text{ cm}^2 \cdot \text{m}^{-2}$ having severe AS¹².

Inherent inconsistencies in the guidelines' criteria

Carabello previously demonstrated that an AVA of 0.9 cm^2 in fact corresponds to a mean gradient of 32 mmHg in the presence of a normal cardiac output (six litres per minute) meaning that the guidelines themselves are inherently inconsistent¹. Therefore, patients with discordant AVA (small) and MG (low) values with normal flow (SVI $>35 \text{ mL} \cdot \text{m}^{-2}$) are most likely to have severe AS secondary to the inherent inconsistencies in the guidelines' criteria.

Prolonged LV ejection time

Because LV ejection time is in the denominator of the equation for calculating the transvalvular flow rate (i.e., $\text{transvalvular flow rate} = \frac{\text{stroke volume}}{\text{LV ejection time}}$), a prolonged ejection period results in a lower gradient for a given AVA and stroke volume¹⁰.

Paradoxical low-flow, low-gradient severe AS

Once the reasons above have been ruled out, patients presenting with a low-gradient, small AVA and preserved LV systolic function probably have PLF-LG severe AS if the stroke volume index is reduced ($\leq 35 \text{ mL} \cdot \text{m}^{-2}$)^{9,15}. However, pseudostenosis may also occur in this patient population, and dobutamine stress echocardiography may be required to diagnose true severe AS as proposed by Cavel et al³². No studies to date have validated the use of invasive

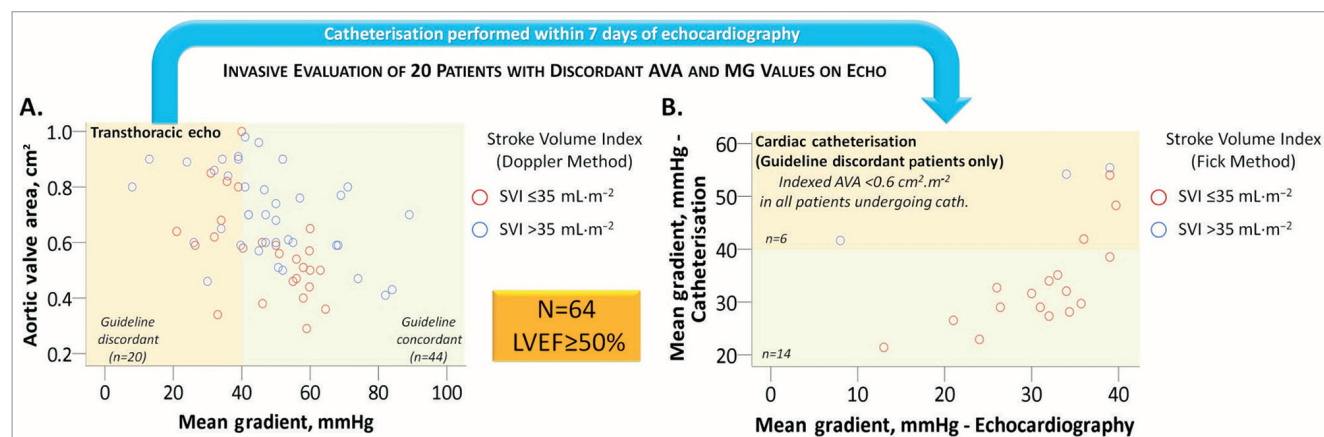


Figure 3. Invasive evaluation of symptomatic patients with guideline discordant aortic valve area (AVA) and mean gradient (MG) values on transthoracic echocardiography (TTE). A) Scatter plot of 64 patients with preserved left ventricular ejection fraction ($\geq 50\%$) undergoing TTE prior to transcatheter aortic valve implantation (TAVI) at our institution*. 44/64 (69%) patients had guideline concordant MG and AVA values, whereas 20/64 (31%) had guideline discordant values. B) Scatter plot of the 20 patients with guideline discordant AVA and MG values on TTE who subsequently underwent cardiac catheterisation within seven days of TTE. Six patients were found to have a high gradient on catheterisation, whereas 14 patients were confirmed to have a low gradient. All 14 patients with a low MG on catheterisation had a low stroke volume index ($\leq 35 \text{ mL} \cdot \text{m}^{-2}$) calculated using the Fick method, thereby confirming the diagnosis of “paradoxical” low-flow, low-gradient severe aortic stenosis. All 20 patients were therefore subsequently referred for TAVI. Had the invasive evaluation not been performed, the TTE-diagnosed normal-flow, low-gradient patients (blue circles) in panel A might have been deemed to have guideline discordant values secondary to the inherent discrepancies in the guidelines' criteria and might have been inappropriately treated medically. *Bern University Hospital, Switzerland.

dobutamine stress testing among patients with PLF-LG severe AS, and therefore further studies are required in this area. Previous studies have shown that patients with PLF-LG have clinical outcomes similar to patients with high-gradient severe AS; yet, symptomatic patients are less likely to be referred for aortic valve replacement because treating physicians often misinterpret the low gradient to imply only moderate AS^{9,12,15}. It is also important to note that systemic hypertension can influence the assessment of AS severity (generally causing overestimation of severity)³³. Eleid et al demonstrated in an invasive haemodynamic study that the administration of a vasodilator reduced the arterial afterload in patients with PLF-LG severe AS, which resulted in an increased stroke volume and higher gradients³³. This elegant study demonstrated that the left ventricles of patients with PLF-LG severe AS in fact face a double load, i.e., a valvular load from the severe AS and an arterial load from the systemic hypertension. Therefore, patients with PLF-LG severe AS and co-existent hypertension should first have their blood pressure controlled prior to reassessing AS severity and symptomatic status. This has been recommended by the recent AHA/ACC valvular heart disease guidelines⁴.

Parameters to assess aortic stenosis haemodynamic severity other than mean gradient and AVA

In addition to AVA and MG, there are in fact several other parameters which may be considered in the global evaluation of AS

haemodynamic severity (**Table 2**)³⁴. The valvuloarterial impedance (Zva) is a haemodynamic measure of the global load (i.e., valvular+arterial load) faced by the left ventricle³⁵. The Zva can be assessed indirectly using echocardiography or directly using catheterisation (**Table 2**)²⁰. Whether invasively derived Zva is associated with worse outcomes after TAVI has yet to be determined.

Conclusion

Patients presenting with symptomatic low-flow, low-gradient severe aortic stenosis and either reduced or preserved LV systolic function have a dismal prognosis if managed conservatively and should therefore undergo aortic valve replacement if feasible. However, other causes for small AVA and low MG measurements must first be excluded. Because erroneous measurements are not infrequent with echocardiography and non-invasive corroborative methods may remain inconclusive, an invasive evaluation should be considered a sine qua non in the evaluation of low-flow, low-gradient AS haemodynamic severity.

Funding

This study was supported in part by an unrestricted research grant from Medtronic to the University of Bern, Switzerland.

Conflict of interest statement

S. Windecker has received research contracts to the institution from Biotronic and St. Jude. P. Wenaweser has received proctoring and

Table 2. Comparison of non-invasive and invasive parameters for the assessment of aortic stenosis.

Parameter	Modality	Echocardiography	Catheterisation	Values meeting severe criteria
Aortic jet velocity	Echo	Measured directly	$\sqrt{2g\Delta P}$	$>4 \text{ m} \cdot \text{s}^{-1}$
Transvalvular gradient	Echo/Invasive	$4V^2$	Measured directly	$>40 \text{ mmHg}$
Aortic valve area	Echo/Invasive	$\frac{SV_{LVOT}}{VTI_{aortic\ valve}}$	$\frac{SV_{Fick}}{44.3 * SEP * \sqrt{\Delta P}}$	$\leq 1.0 \text{ cm}^2$ *
Energy loss index	Echo	$EOA * A_A / A_A - EOA / BSA$	n/a	$\leq 0.5 - 0.6 \text{ cm}^2 \cdot \text{m}^{-2}$
Stroke work loss	Echo/Invasive	$100 * (\Delta P_{mean} / (SBP + \Delta P_{mean}))$	$100 * (\Delta P_{mean} / (SAP_{invas} + \Delta P_{mean}))$	$>25\%$
Valvular resistance	Echo/Invasive	$(1333 * \Delta P_{mean}) / Q_{mean}^\ddagger$	$(\Delta P_{mean} * HR * SEP / CO) * 1.33$	$>250 \text{ dyne} \cdot \text{s} \cdot \text{cm}^{-5}$
Arterial load				
Systemic blood pressure	Non-invasive/Invasive	Measured non-invasively	Measured directly	$>140/90 \text{ mmHg}$
Systemic arterial compliance	Echo/Invasive	$SVI / SBP - DBP$	$SVI / SAP_{invas} - DAP$	$\leq 0.6 \text{ ml} \cdot \text{mmHg}^{-1} \cdot \text{m}^{-2}$
Systemic vascular resistance	Echo/Invasive	$80 * MAP / CO$	$80 * MAP / CO$	$>2,000 \text{ dyne} \cdot \text{s} \cdot \text{cm}^{-5}$
Valvular+Arterial load				
Valvuloarterial impedance	Echo/Invasive	$SBP + \Delta P_{mean} / SVI$	$\frac{LV \text{ systolic pressure}}{SVI}$	$>4.5 \text{ mmHg} \cdot \text{ml}^{-1} \cdot \text{m}^2$
Ventricular parameters				
LVEF	Echo/Invasive	Various methods	$\frac{LVEDV - LVESV}{LVEDV} * 100$	$<50\%$
LV stroke work	Echo/Invasive	$(MAP + \Delta P_{mean}) * SV_{Doppler} * 0.0136$	$(MAP + \Delta P_{mean}) * SV_{Fic} * 0.0136$	g.m.

*Hakki formula can also be used to calculate aortic valve area: $\frac{\text{Cardiac output}}{\sqrt{\Delta P_{mean}}}$; Q_{mean} = mean transvalvular flow rate $\frac{\text{stroke volume}}{\text{systolic ejection time}}$; A_A : cross-sectional area of the ascending aorta measured at 1 cm downstream of the sinotubular junction; BSA: body surface area; CMRI: cardiac MRI; CO: cardiac output; DAP: diastolic arterial pressure; EOA: effective orifice area; g: velocity of acceleration resulting from gravity (i.e., $980.67 \text{ cm} \cdot \text{s}^{-2}$); HR: heart rate; LV: left ventricular; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; n/a: non-applicable; MAP: mean arterial pressure (diastolic arterial pressure + 1/3 pulse pressure); ΔP_{mean} : mean aortic pressure gradient; SAP_{invas} : systolic arterial pressure measured invasively; SBP: systolic blood pressure; SEP: systolic ejection period; SV: stroke volume; SVI: stroke volume index; V: velocity; VTI: velocity time integral

lecture fees from Medtronic and Edwards Lifesciences. The other authors have no conflicts of interest to declare.

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