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Discordance between aortic valve gradient and area: do I trust the significant gradient?

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Aortic stenosis is an increasingly relevant pathology not only for its high prevalence in the population (especially elderly), but also because in recent decades traditional surgery has been accompanied by transcatheter aortic valve implantation, a technique that has allowed a significant increase in effective therapeutic procedures, even in patients previously considered at high surgical risk. It has become essential to make precise diagnoses, based mainly on echo-Doppler that allows to identify the aetiology and severity of the valvular disease. A stenosis is considered severe when the area is <1 cm^2, the mean gradient exceeds 40 mmHg and the peak velocity is >4 m/s. Although in many cases these cut-offs are decisive, in others a discrepancy between area (<1 cm^2) and gradient (<40 mmHg) is observed, requiring the inclusion of other variables such as ejection fraction (EF > or <50%) and the systolic volume index (normal SVi >35 mL/m^2 or reduced <35 mL/m^2) to define the severity of the stenosis. This article describes the reasons for this discrepancy, identifies echo-Doppler parameters that further improve the classification of stenosis severity, and defines the indications for second-level examinations such as computed tomography and transoesophageal echocardiography.

Introduction

Aortic stenosis is a fairly common condition, with a prevalence of 12.4% among people over 75 years of age, of which ∼3% have a severe form.[1] It can also occur at a younger age, particularly in subjects with bicuspid aortic valve or, more rarely, due to rheumatic diseases. The diagnosis is clinical and non-invasive, and transthoracic echocardiography is essential to assess the severity of the stenosis, establish the prognosis, and define therapeutic indications. In recent decades, the introduction of TAVI (transcatheter aortic valve implantation) which has been added to traditional surgical techniques, has led to increasing attention in defining the indications for therapeutic procedures based on very specific echocardiographic criteria.

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Echocardiographic criteria of severity and treatment guidelines

Doppler echocardiographic diagnosis of aortic stenosis is based on parameters such as mean aortic gradient, peak gradient, peak Doppler velocity, and valve area. In particular, a stenosis is considered severe when the area is <1 cm^2, the mean gradient exceeds 40 mmHg and the peak velocity is >4 m/s.[2] Echocardiography also provides a detailed assessment of valvular anatomy, the function of both ventricles, the thickness and mass of the left ventricle (LV), as well as identifying any concomitant valvular pathologies, dilation of the aortic bulb and ascending aorta, and pulmonary systolic pressure.

Is the aortic gradient sufficient to define the degree of severity of the stenosis?

The functional haemodynamic classification of aortic stenosis is based on the aortic gradient and the valve

Table 1 Severity of aortic stenosis defined by four functional conditions

Definition	Criteria	Observations
High gradient aortic stenosis	Mean gradient >40 mmHg, peak velocity >4.0 m/s, area <1 cmq (or <0.6 cmq/mq)	Stenosis is severe regardless of LV systolic function.
Low flow, low gradient aortic stenosis	Mean gradient <40 mmHg, area <1 cm^2 (or <0.6 cm^2/m^2), LV EF <50%, SVi <35 mL/m^2	The Dobutamine test is indicated to verify the increase in the gradient based on the increase in flow.
Low flow, low gradient aortic stenosis with preserved EF	Mean gradient <40 mmHg, area <1 cm^2 (or <0.6 cm^2/m^2), LV EF >50%, SVi <35 mL/m^2	Elderly, hypertensive patients, small LV, coexisting mitral regurgitation. Difficult diagnosis, cardiac CT useful (calcium score).
Normal flow aortic stenosis, normal EF	Mean gradient <40 mmHg, area <1 cm^2 (or <0.6 cm^2/m^2), LV EF >50%, SVi >35 mL/m^2	Error in assessment? Moderate stenosis?

LV, left ventricle; EF, ejection fraction; CT, computed tomography; SVi, stroke volume index.

area derived from the continuity equation, distinguishing four categories (*Table 1*). This classification is useful because it allows to identify different haemodynamic conditions based on objective criteria and precise threshold values. However, the main limitation is the possibility of errors in the calculation of both the aortic gradient and the valve area through the continuity equation. In fact, a correct Doppler alignment is essential; in cases where the septum-aortic angle is pronounced, it is important to measure the gradient not only from the apical window (which tends to underestimate the values), but also from the right parasternal view.[3] *Figure 1* summarizes the main parameters offered by Doppler echocardiography.[4]

Stroke volume is calculated using Doppler, through the integral of the outflow tract velocity and the dimensions of the outflow tract. However, these dimensions are often underestimated in the parasternal long-axis echocardiographic view, because the outflow tract has an ovoid shape and the measured diameter does not represent the true maximum dimension. Consequently, the calculation of the area derived from the diameter leads to an underestimation, reducing the calculated stroke volume and overestimating the severity of the stenosis. Recent studies have shown that only three-dimensional (3D) echocardiographic measurements (transthoracic or transoesophageal), computed tomography (CT), or magnetic resonance imaging (MRI) techniques, are able to accurately estimate the outflow tract area.[5,6]

Furthermore, the measurement of the flow integral in the subvalvular outflow tract can also be complicated, not so much for the alignment, but for the sampling position. As the valve plane approaches, the velocity increases, and the gradient must be measured when the flow is still laminar. The situation becomes even more complicated in patients with an acceleration of the subvalvular flow, due to the presence of gradients caused by obstructions such as septo-basal hypertrophy.

The main problem with the guidelines is not technical, but conceptual. In fact, in the latest editions of the guidelines, the area threshold for the definition of severe valve stenosis has been raised to 1 cm^2. Originally, an area <0.7 cm^2 was considered to be an expression of severe stenosis, since at this level the gradient was always significant, almost independently of the flow. The increase in the threshold from 0.7 to 1 cm^2 was justified for prognostic reasons, but led to a discrepancy between area (<1 cm^2) and gradient (<40 mmHg), requiring the inclusion of other variables such as ejection fraction (EF > or <50%) and stroke volume index (normal SVi >35 mL/m^2 or reduced <35 mL/m^2) to define the severity of the stenosis. These new definitions have inevitably introduced confounding aspects and greater complexity in the calculations.[7,8]

How to overcome the limitations of these calculations in the presence of discordance between valve area and gradients?

Before considering parameters obtainable with other methods, such as cardiac CT, it is essential to review any technical errors and use simple parameters that are independent of flow.

Technical errors

As already mentioned, it is essential to always measure the maximum Doppler velocity and the integral of the aortic flow from multiple echocardiographic windows (*Figure 1*). In the right parasternal window, the use of a ‘pencil’ Doppler probe may be useful, which allows to orient precisely the aortic flow towards the optimal right intercostal space.[3]

With regard to the outflow tract, it is important to measure the diameter near the valve annulus, since in many cases (especially in the elderly) the outflow tract can assume an hourglass shape. If the measurement is taken 5–10 mm from the valve plane, as previously suggested, there is a risk of significantly underestimating the diameter and, consequently, overestimating the severity of the stenosis.

When difficulties are encountered in accurately calculating the outflow tract velocity-time integral (with pulsed Doppler), it may be useful to perform an internal validation during the echocardiographic examination, comparing the stroke volume calculated from the LV volumes with that obtained with Doppler, to identify any relevant discrepancies. It is important to remember that there is no direct relationship between the EF and the stroke volume of the LV. For example, patients with a dilated LV and a reduced EF may have a significantly higher stroke volume than patients with a normal or even high EF, but a small and hypertrophic LV.

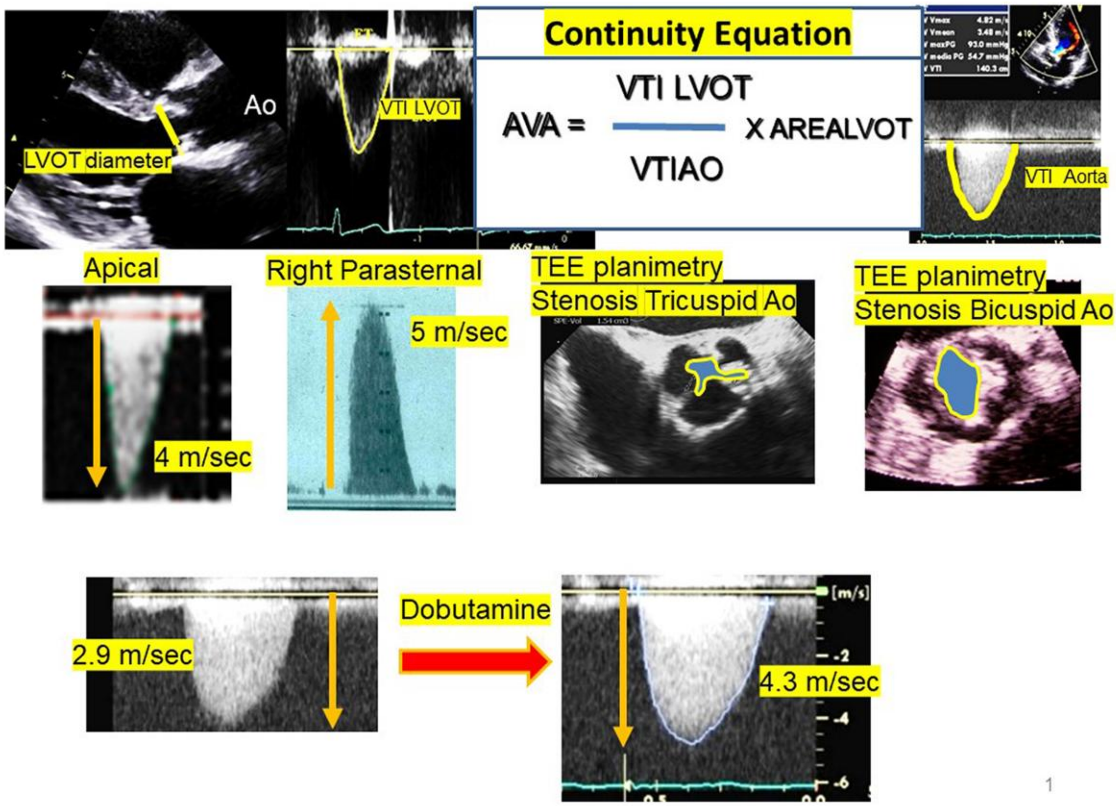

Figure 1 Main measurements, calculations, and formulas for estimating the severity of aortic stenosis. Top: Formula of the continuity equation. Centre: Doppler calculations of the valve gradient and echocardiographic planimetries. Bottom: Example of the aortic gradient at baseline and after the Dobutamine test. LVOT, left ventricular outflow tract; AVA, aortic valve area; VTI, velocity-time integral; TEE, transoesophageal echocardiography; Ao, aortic valve.

Practical examples:

End-diastolic volume: 300 mL and end-systolic volume: 200 mL → EF: 33%, stroke volume: 100 mL.

End-diastolic volume: 80 mL and end-systolic volume: 30 mL → EF: 62%, stroke volume: 50 mL.

These examples highlight how it is possible to obtain very different stroke volumes with the same EF, underlining the importance of in-depth analysis and measurement validation.

Flow-independent parameters

One of the most relevant flow-independent parameters is the Doppler velocity index (DVI), a dimensionless index calculated as the ratio of the outflow tract integral to the aortic integral. This index is useful because it does not require calculation of the outflow tract dimensions and, when other parameters are ambiguous or discordant, a value <0.25 indicates severe stenosis.

It is also advisable to perform the planimetry of the aortic valve area by transthoracic or transoesophageal echocardiography (TEE) (*Figure 1*). Although there are technical limitations due to the difficulty of defining the internal edges of the residual systolic area, especially in the presence of marked calcifications, 3D probes allow obtaining a correct short-axis cutting plane to measure the optimal area (the minimum systolic area at maximum cuspid opening). These data can help estimate the severity of the stenosis and direct the operator to further investigations if the results are discordant with the calculation of the continuity equation.

In cases of asymptomatic patients with borderline gradients or symptoms associated with non-elevated gradients, the guidelines recommend stress echocardiography to highlight any symptoms, verify abnormal increases in blood pressure, and evaluate changes in gradients during peak exercise. However, this test must be recommended with caution, based on the clinical condition of the patient, and is not very popular.

Finally, the aortic acceleration time (AT), which represents the time interval from the beginning of continuous Doppler flow to its peak, has been validated to evaluate obstruction in aortic valve prostheses. Studies have shown that, if the AT is prolonged (over 100 ms), the gradient is not functional due to obstruction of the prosthesis. This concept can also be applied to native aortic stenosis, and a ratio of AT to ejection time (ET) >35 indicates a high risk of adverse events. In such cases, it is advisable to consider intervention before the onset of symptoms in patients with severe stenosis (*Table 2*).[9,10]

Other methods (multimodality)

In situations of discordance between the area and the aortic gradient, the use of cardiac CT can provide a significant diagnostic contribution. Quantification of

Table 2 Main echo-Doppler parameters for the evaluation of the severity of aortic stenosis

Valve area: continuity equation	$AVA = \frac{VTI\ LVOT}{VTIAO} \times AREALVOT$ (cmq)
DVI (Doppler velocity index)	DVI (LVOT)/DVI aorta (Ratio)
AT (acceleration time)	Time from start of continuous Doppler flow to peak flow (ms)
AT/ET	Acceleration time/ejection time (Ratio)
TTE or TEE valve planimetry	Ao area (possibly 3D guided); minimum systolic area planimetrically plotted at maximum cusp opening (cmq)
Stroke volume	$LVOT_{area} \times$ LVOT flow (mL)
Stroke volume ECHO	LV end-diastolic volume – LV end-systolic volume (mL)

LVOT, left ventricular outflow tract; TTE, transthoracic echo; TEE, transoesophageal echocardiography; LV, left ventricle.

valvular calcium through Agatston units allows to establish the probability that the stenosis is severe, intermediate, or unlikely. Calcium score values differ between men and women and the most recent studies indicate the following ranges to define the severity:

Very likely severe stenosis: men >3000, women >1600.
Possible severe stenosis: men >2000, women >1200.
Unlikely stenosis: men <1600, women <800.

Computed tomography is widely used because it is essential in planning TAVI or surgery, allowing to evaluate the dimensions of the thoracic aorta, coronary arteries, and vascular accesses. Furthermore, it is crucial in choosing the most suitable device, considering the dimensions of the aortic annulus, the aortic bulb, the coronary ostia, and other anatomical features.[11,12]

Importance of correct definition of severity of aortic stenosis

Figure 2 illustrates an integrated stepwise approach to address cases of gradient-area discordance in the evaluation of aortic stenosis. As mentioned, a correct definition of the severity of stenosis has significant clinical implications. The guidelines, with some differences between the European and American ones, offer increasingly precise and complex indications not only on the indication for intervention, but also on the choice of procedure. The starting point of the evaluation is always clinical: the presence of symptoms requires intervention in case of severe stenosis. However, for asymptomatic patients, different scenarios open up and a trend towards ‘early’ intervention is emerging also thanks to the reduced risk associated with TAVI. This change in approach has fuelled discussions and controversies.

For years, the standard approach has been to wait for the onset of symptoms to proceed with the intervention, but many studies indicate that this strategy requires frequent monitoring and accurate echocardiographic assessments of systolic function (e.g. strain) and haemodynamic load of the stenosis. The goal is to avoid unexpected events or to arrive at the surgical or percutaneous procedure with fewer benefits and greater risks. Consequently, much importance is given to predictors of adverse events or rapid onset of symptoms. These include clinical factors (age, atherosclerotic risk factors), echocardiographic factors (marked valvular calcification, peak velocity >5 m/s, EF <50%, gradient progression over time, severe left ventricular hypertrophy, reduced global longitudinal strain), and biomarkers such as natriuretic peptides.

Criteria for early intervention

In the presence of these factors, early intervention can be considered only if the surgical or TAVI risk is low. A multidisciplinary Heart Team is essential to evaluate the indication, and the discussion should take place in centres with a high volume of aortic surgery and TAVI. The presence of coronary or aortic pathologies can influence the decision: for example, aortic dilatation (bulb or ascending aorta), both in cases of bicuspid and degenerated tricuspid valve, or the presence of coronary artery disease (need for bypass), may make valve replacement necessary even in cases of moderate stenosis.[13,14]

Importance of echocardiography and follow-up

Transthoracic echocardiography plays a central role, evaluating not only the aetiology and severity of the stenosis and the haemodynamic parameters, but also the dimensions of the thoracic aorta. Recent recommendations indicate that transthoracic echocardiography can be accurate and comparable to CT in measuring the aortic bulb and ascending aorta, making it ideal for patient follow-up.

Methodological aspects

It is crucial to perform a comprehensive echocardiographic assessment, maintaining consistency between serial controls, preferably in the same laboratory or with access to previous examinations. Standardizing the measurement of the outflow tract is important, since even a small change in size can significantly influence the calculation of the valve area, even if the gradient remains stable. During the examination, it is useful to measure blood pressure, since hypertension can affect both the gradient and the valve area, increasing systemic vascular resistance and reducing the aortic gradient.

Measurement of global afterload (Zva)

A proposed formula to measure the global afterload of the LV is

$$Zva = sBP + \Delta Pnet/SV$$

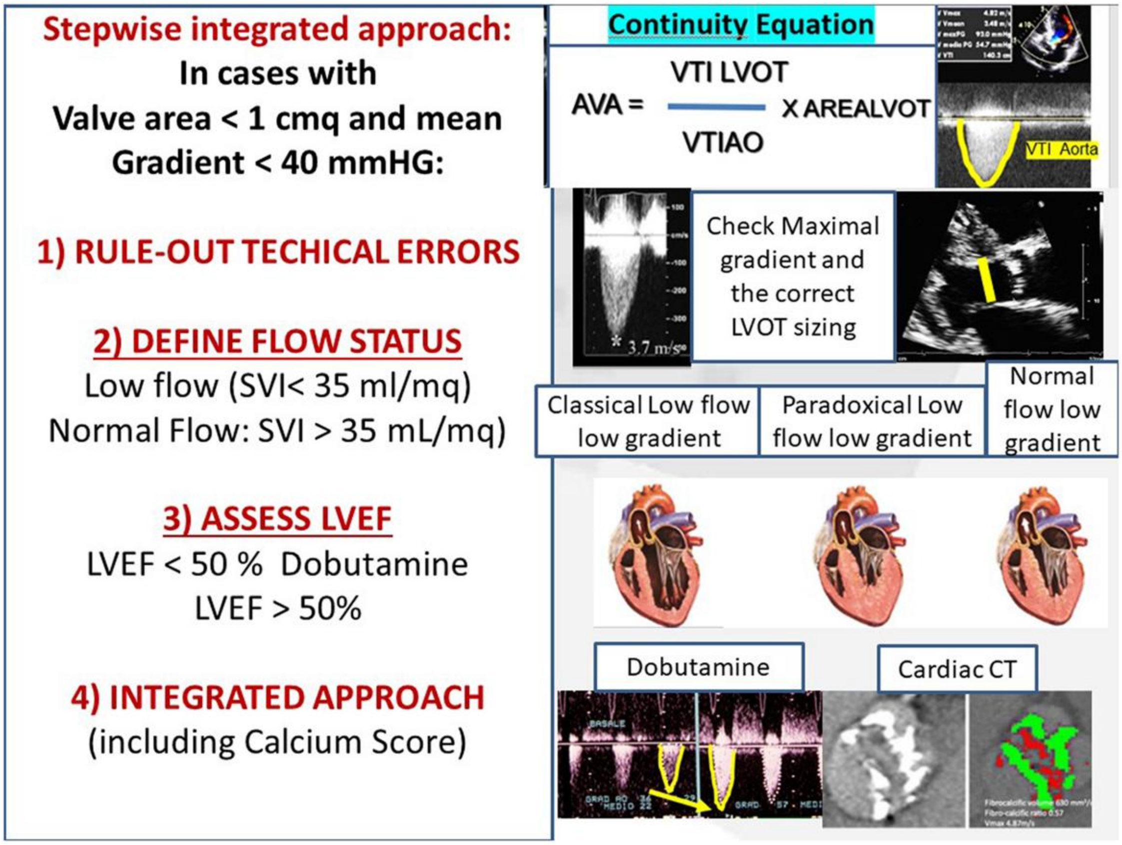

Figure 2 Stepwise integrated approach in cases of discordance between mean gradient and Doppler area. Evaluation of the main parameters according to four main steps is useful for evaluating the severity of aortic stenosis. LVOT, left ventricular outflow tract; AVA, aortic valve area; VTI, velocity-time integral; SVI, stroke volume index; Ao, aortic valve; EF, ejection fraction.

where, Zva represents the global afterload of the LV, sBP is the systolic blood pressure, ΔPnet is the mean gradient, and SV is the stroke volume.

Although this formula is not widely used, it is useful for evaluating the diagnostic and prognostic impact in patients with arterial hypertension. A Zva value >3.5 mmHg/mL m^2 is considered a predictor of poor prognosis in asymptomatic patients.

Special clinical and diagnostic conditions

Amyloidosis

Approximately 15% of patients undergoing TAVI for severe aortic stenosis have inappropriate left ventricular hypertrophy associated with amyloidosis, identifiable by advanced imaging techniques such as bone scan and cardiac magnetic resonance, or by biopsy.[15] These patients, who have a restrictive disease, show specific haemodynamic characteristics: a low-flow, low-gradient profile, reduced ventricular volumes, and variable systolic function (from normal to reduced) based on the clinical history and duration of the disease. This picture is often associated with significant diastolic dysfunction.

In case of suspected amyloidosis associated with aortic stenosis, it is essential to pay attention to the possibility of low gradients despite a small valve area (<1 cm^2). In these cases, it is crucial to use all the echocardiographic parameters described above, carefully evaluate the patient's clinical history (such as the presence of carpal tunnel, or renal or neurological problems), and resort to second-level methods. Bone scintigraphy is considered the reference test for the diagnosis of cardiac amyloidosis, with the alternative of MRI, while the biopsy is reserved for selected cases where other methods are not conclusive.

Artificial intelligence: new perspectives for the diagnosis of aortic valve stenosis and indication for procedures

Recently, several studies have explored the possibility of using convolutional neural networks to automatically define the severity of aortic stenosis from standard echocardiographic images. In a study conducted by Wessler *et al.*,[16] the use of neural networks for the analysis of transthoracic echocardiographic images acquired from the parasternal long-axis and short-axis showed a remarkable diagnostic accuracy. The validation, performed on over 8000 patients, achieved an area under the receiver operating characteristic curve of 0.91, highlighting the high ability to distinguish the severity of stenosis.

In the context of interventional procedures, artificial intelligence has also found an increasing role in the evaluation of cardiac CT images. In particular, the use of deep learning algorithms based on CT images of the aortic annulus is proposed for several purposes:

(1) Automatic estimation of the aortic annulus: to calculate with high precision the dimensions of the aortic annulus, facilitating the choice of the optimal device for the TAVI procedure, both in terms of type and size.
(2) Identification of anatomical interferences: to identify possible interferences with the structures surrounding the valve plane during implantation, such as the outflow tract, the mitral valve plane, and potential obstacles to the transit towards the coronary ostia. This is essential to plan the procedure and avoid complications, especially in the case of future coronary interventions such as angioplasty.
(3) Management of complex TAVI reimplantation cases: to address complex situations, such as the insertion of a second TAVI in patients who have already undergone a first implant (procedure known as 'TAVI-in-TAVI'). Artificial intelligence can provide precise and personalized measures to better plan the intervention. The algorithms can in fact perform an automatic and accurate assessment of the dimensions of the residual annulus, the position, and characteristics of the first implanted valve, identifying any risks of overlap or interference with nearby anatomical structures. This 'tailored approach' allows to optimize the choice of the new device, reducing risks and improving the effectiveness of the procedure.

Conclusions

The topic discussed, as suggested by the title 'I trust the gradient', correctly emphasizes the need for an accurate assessment of the aortic gradient, since this parameter guides most clinical and therapeutic decisions. However, it is possible to 'trust' the gradient only if it is measured accurately and contextualized in a well-defined haemodynamic condition, which can vary depending on ventricular systolic function, transaortic flow, systolic blood pressure, and other factors described above.

For these reasons, in addition to using the aortic gradient as a basis for classifying the severity of stenosis, it is often necessary to resort to more complex echo-Doppler parameters or complementary methods such as TEE or CT. This multimodal approach allows for a more complete and accurate assessment of the patient's haemodynamic condition, improving clinical management and the definition of therapeutic strategies.

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