Two main causes of aortic stenosis are rheumatic involvement of the valve, observed primarily in developing countries, and calcification of the valve (calcific aortic stenosis, CAS) without the apparent involvement of an infective process. The latter is thought of as a chronically progressive “degenerative” disease of calcium deposition and subclinical inflammation akin in nature to atherosclerosis.

CAS in particular is the third most common heart disease in the western world, following coronary heart disease and hypertension. Its prevalence in the elderly (age 65 and older) ranges from 2-4%, when only severe aortic stenosis is considered, to 25% when aortic sclerosis is included. Furthermore, CAS represents the second most prevalent cause for heart surgery and is responsible for approximately 15,000 deaths annually in North America. Even though CAS is a well-known disease entity and we are able to assess numerous hemodynamic parameters using cardiac catheterization or ultrasonography (as well as cardiac computed tomography and cardiac magnetic resonance imaging in the near future), several aspects remain only partially resolved. This article will focus on novel indices, viewing the study of CAS from a clinical aspect. First, newer proposed indices of disease severity will be presented, namely energy loss index (ELI) and valvulo-arterial impedance (Zva), that promote an understanding of CAS beyond the simple calculation of valve area; second, the use of brain natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) as a guide to treatment choice will be introduced; and finally low-flow–low-gradient aortic stenosis with preserved ejection fraction will be described.

New indices of CAS severity

Hemodynamic approach to aortic valve stenosis

A basic understanding of the events that follow the flow of blood as it passes through the stenotic orifice of the valve is essential, in view of the newly proposed changes in the guidelines and new indices of CAS severity. When blood encounters a stenotic valve, it accelerates, gaining kinetic energy, while the static pressure it exerts on the wall diminishes (according to the principles of mass and energy preservation). After crossing the anatomic orifice of the valve, flow streamlines will continue to converge due to their inertia. As a result, the blood reaches a maximum velocity, a minimum static pressure and a minimum cross-sectional area, termed the effective orifice area (EOA). Then, as streamlines begin to diverge, two phenomena occur. First, their kinetic energy is partly converted to static pressure, dilating the aortic root and ascending aorta; then, the velocity reached due to the preceding stenosis causes the formation of
vortices and friction at the boundary layer between the newly ejected and the relatively stationary blood, resulting in energy dissipation as heat. In diastole, the aortic root and ascending aorta, by virtue of their elastic properties, contract, increasing regional static pressure (“pressure recovery phenomenon”) and assisting in forward blood flow. In this way static pressure is finally reconverted to kinetic energy.

During Doppler interrogation of the aortic valve, peak and mean pressure gradients are determined. This is ideally done by acquiring a continuous wave Doppler reading at the point and time of maximal flow conversion, which is located at the EOA during systole.7,8 However, this measurement does not take into account the abovementioned pressure recovery phenomenon occurring in diastole, and as a result there is an overestimation of peak and mean gradient. The term “overestimation” does not imply that gradients calculated during systole are false: numerically they are accurate. What this term does imply is that, had pressure absorption in systole and pressure recovery in diastole not occurred, the pressure in the aortic root would have risen more in systole and reduced calculated gradients. Consequently, physiologically it might be more relevant to use energy as a whole (kinetic and potential) rather than one of its constituents (kinetic through Doppler mode) to study aortic stenosis.

The orifice of the valve is calculated by means of the continuity equation:

\[ EOA = \frac{\pi}{4} \times LVOT^2 \times \frac{VTI_{LVOT}}{VTI_{AV}} \]

(LVOT – left ventricular outflow tract; VTI_{LVOT} – velocity-time integral at LVOT; VTI_{AV} – velocity-time integral at the point of maximal flow convergence, i.e. the EOA). The resulting surface yields the EOA (point of maximal flow convergence), which is smaller than the anatomic orifice. During cardiac catheterization, the peak gradient is acquired by subtracting the peak pressure measured in the ascending aorta (that is in diastole, after pressure recovery has occurred) from the peak pressure measured in the left ventricle, thus yielding a smaller peak gradient. Aortic valve area (AVA) is calculated by means of the Gorlin formula:9

\[ AVA = \frac{CO}{44.3 \times HR \times SEP \times \sqrt{MG}} \]

(CO – cardiac output in ml/min; HR – heart rate in beats per minute; SEP – systolic ejection period in s; MG – mean gradient in mmHg; and 44.3 is an empirical constant).

The use of AVA in the equation, as opposed to EOA, denotes the distinction between the anatomic and functional orifice of the valve. Theoretically, AVA should coincide with EOA. However, it is extremely rare and rather coincidental to have the catheter in the ascending aorta perfectly aligned with the jet coming through the stenotic orifice in order to record the “maximal” mean gradient, in a way similar to that achieved with ultrasonography. Therefore, in patients with normal cardiac output the invasive method would yield a lower peak gradient and larger orifice area, which is, however, thought to better reflect the anatomical area.6,10

Clinical implications of aortic valve stenosis severity calculations

The implications of these aortic valve stenosis severity calculations for the clinician are obvious. Guidelines regarding the choice of therapeutic approach for patients are based on gradients and orifices obtained during invasive studies and autopsy examinations. Consequently, since the echocardiographic method overestimates the stenosis, it is possible that certain patients will be misclassified. Even worse, the guidelines for diagnosing severe aortic stenosis are found to be inherently inconsistent, even in patients with normal ejection function. For example, in a study conducted by Minners et al,11 which included a population of 3400 patients, 69% would be diagnosed with severe aortic stenosis based on EOA, whereas the percentage when using other guidelines-endorsed parameters (EOA index, maximum velocity and mean gradient) would be 76%, 45% and 40% respectively. Minners et al11 suggested that this inconsistency can be attributed to the discrepancy between maximum velocity and mean gradient on one hand and EOA on the other, since an EOA of 1 cm² corresponds to a mean gradient of 26 mmHg and a maximum velocity of 3.1 m/s, whereas a maximum velocity and mean gradient of 4 m/s and 40 mmHg, respectively, correspond to an EOA of 0.81 cm². Therefore, they propose resetting the AVA criterion to 0.8 cm² when calculated by ultrasonography, that is, when EOA is calculated.

An interesting approach that attempted to compensate for the pressure recovery phenomenon was made by Garcia et al,5 who introduced the concept of energy loss index. In applying this index they do not calculate pressure gradients or valve area but rather the energy lost, more accurately dissipated as heat, after all inter-conversions have ceased. Based on the princi-
The following expression for energy loss (EL):

\[ EL = 4V_C^2 \left(1 - \frac{EOA}{A_A}\right)^2 \]

\[ EL = 4\left(V_C^2 \cdot \frac{EOA}{A_A}\right) - \left(\frac{1}{EOA} - \frac{1}{A_A}\right)^2 = 4Q^2\left(\frac{1}{EOA} - \frac{1}{A_A}\right)^2 \]

\( V_C \) – velocity of vena contracta; measured at EOA point; \( Q \) – cardiac output; and \( A_A \) – cross-sectional area of the ascending aorta.

It follows that energy loss is dependent, not only on purely valvular features, but also on \( A_A \), in fact increasing as the latter increases. It is interesting to note that when \( \frac{EOA}{A_A} \to 0 \), that is when EOA is minimal compared to \( A_A \), the equation reduces to \( EL = 4V_C^2 \Delta P_{max} \). This can be conceptually derived from the fact that the greater the \( A_A \), the less compliant the vessel wall is, being unable to store any energy so as to release it afterwards; this effectively nullifies the pressure recovery phenomenon and makes the energy loss equal to the maximal pressure gradient on either side of the valve. Also, regardless of the \( A_A \), a minimal EOA also qualifies for no significant pressure (energy) recovery since, due to the highly turbulent flow at the EOA, excess kinetic energy is dissipated as heat. Finally, energy loss is highly dependent on cardiac output (\( EL \propto Q^3 \)), implying that when cardiac output is increased, such as in the case of tachycardia, energy loss is greatly amplified. By rearranging the above equation and taking into account unit conversion, Garcia et al reach the following expression for energy loss:

\[ \frac{EOA \times A_A}{EOA - A_A} = \frac{Q}{SO \sqrt{EL}} \]

By assuming that cardiac output at rest is mainly dependent on body surface area, they define \( \frac{EOA \times A_A}{BSA} \) as the “energy loss index” (ELI), allowing for comparisons among patients with different resting cardiac outputs—provided that heart contractility is normal, so that cardiac output at rest depends only on body surface area (BSA).

Garcia et al also performed a retrospective in vivo study of 138 patients in order to test the validity of the newly proposed index, as well as to establish a possible threshold value with predictive significance. Using a clinical endpoint—in this case death or aortic valve replacement—in the univariate analysis, age, peak gradient, mean gradient, EOA, EOA indexed for body surface, and ELI were found to be strongly associated with the outcome (\( p < 0.01 \) for all). However, in the multivariate analysis only ELI and patient age remained significant predictors of the outcome, with \( p \)-values <0.0001 and =0.014 respectively. The threshold value that yielded the best results in terms of prediction was ELI ≤0.52 cm²/m² (sensitivity 68%, specificity 67% and positive predictive value 67%). Notably, 65% of patients with an ELI in the defined range died or underwent aortic valve replacement within 8 months of the evaluation, compared to 31% in the group with an ELI >0.52 cm²/m².

To summarize, ELI offers significant aid in correctly assessing the severity of CAS, incorporating not only the area of the valve but also the aortic cross-sectional area, which can affect the energy lost due to the valve. Its significance increases in cases with smaller aortas and marginally moderate to severe CAS, where it can prevent an overestimation of stenosis by calculating EOA, since in these cases energy loss is significantly reduced due to the pressure recovery phenomenon, as demonstrated above. A theoretical threshold value of 0.50 cm²/m² is proposed, below which patients should be closely monitored for the appearance of symptoms.

Role of left ventricular function in aortic stenosis severity

CAS is thought to be related to atherosclerosis in terms of pathogenesis. It is well known that atherosclerosis is one of the primary causes of arterial stiffening, which may or may not be clinically apparent as elevated blood pressure. Arterial stiffening imposes an increased load on left ventricular function through multiple mechanisms. First, it elevates the force of contraction required to achieve expansion of the stiffened arteries and accommodation of the ejected blood. Second, it reduces blood flow in the coronary circulation through induced concentric hypertrophy and elevated diastolic pressure. Third, because of the increased pulse wave velocity, reflected waves reach the ascending aorta not during diastole, but while systole is still occurring, thus imposing a greater load on the left ventricle. It is therefore conceivable that, inasmuch as the detrimental effects of CAS are due to deteriorating left ventricular function, an index incorporating both sources of left ventricular afterload, valvular and arterial, might be more clinically relevant than indices limited to the valve or the ascending aorta. Finally, several studies have demonstrated that hypertension can mask aortic stenosis when assessed with pressure gradients; yet aortic stenosis can also conceal hypertension due to decreased stroke volume, leading to the erroneous conclusion that vessel
function is normal when in fact it is profoundly altered and affecting the left ventricle, as assessed by means of systemic arterial compliance (SAC).\textsuperscript{3,12}

A study by Briand et al\textsuperscript{12} attempted to investigate the occurrence of reduced arterial stiffness in a population with CAS and to introduce a potential parameter for assessing global left ventricular afterload. They retrospectively studied a population of 208 individuals with at least moderate aortic stenosis based on American Heart Association criteria. Valvular and arterial load were calculated using the ELI equation and by implementing the equation:

$$SAC = \frac{SVI}{PP}$$

(SVI= stroke volume index = SV/BSA; PP = pulse pressure). They also introduced the concept of valvulo-arterial impedance ($Z_{va}$) defined as:

$$Z_{va} = \frac{LVSP}{SVI} = \frac{SAP + MG_{net}}{SVI}$$

(LVSP = left ventricular systolic pressure; $MG_{net}$ = mean transvalvular gradient after taking into account pressure recovery phenomenon, i.e. net mean gradient; SAP = systolic arterial pressure) in order to assess global LV afterload. Net mean gradient calculation entails using the equation proposed by Baumgartner et al:\textsuperscript{10}

$$PR = 8V_{vc}^2 \times \frac{EOA}{A_A} \times (1 - \frac{EOA}{A_A})$$

(PR = pressure recovery; EOA, $V_{vc}$, $A_A$ – as above) and subtracting the result from the Doppler-derived mean gradient. $Z_{va}$ may be thought of as the energy (in mmHg) required in order to pump a milliliter of blood against the load imposed by both valve and vessels. In multivariate analysis, no other hemodynamic parameter was found to be a significant predictor of either left ventricular systolic (cutoff point of $Z_{va}$ ≥ 5 mmHg/ml/m$^2$) or left ventricular diastolic (cutoff point of $Z_{va}$ ≥ 4.5 mmHg/ml/m$^2$) dysfunction. According to the authors, the fact that both ELI and SAC lost their prognostic value implies that $Z_{va}$ indeed represents the combined contribution of these variables to left ventricular dysfunction.

Notably, in a recent study by Rosenhek et al\textsuperscript{15} of asymptomatic patients with very severe aortic stenosis (defined as peak velocity >5 m/s), event-free survival was found to correlate with peak velocity (76% at one year and 17% at four years for patients with $V_{max}$ <5.5 m/s, compared to 44% and 4% respectively for patients with $V_{max}$ ≥5.5 m/s, p<0.0001), but not with valve area as calculated by ultrasonography. One possible explanation might be that, given patients with similar valve areas, LVOTs and contractility (and consequently similar VTI_{LVOT}) based on the EOA equation, the one with a greater $V_{max}$ would necessarily have a shorter ejection time (so that VTI_{LVOT} is the same), implying a greater ventricular afterload (even though the orifice size is the same), consistent with the concept of $Z_{va}$.

These new indices may lead to a different conceptual approach to aortic stenosis, accepting that the stenotic valve represents part of the underlying disease process that encompasses the circulatory system as a whole. This system may impose an increased afterload on the left ventricle through any of its constituents, valve and/or vessels.\textsuperscript{3} This is vividly seen in hypertensive patients with concomitant aortic stenosis, who begin experiencing symptoms earlier than their normotensive counterparts despite having EOAs that may not even be classified in the severe stenosis range according to current criteria. Therapeutic strategies may also need to be reconsidered, since the primary target will be to reduce the aforementioned global afterload, a feat that is achievable through reduction of either one of its components. More explicitly, should an abnormal value of $Z_{va}$ be calculated (≥5 mmHg/ml/m$^2$), the relative contributions of valvular and arterial load may be estimated using the equations for ELI and SAC, respectively. Consequently, the culprit could be targeted and treated accordingly, in order to alleviate the major source of left ventricular strain. This strategy may advocate in favor of a more aggressive, albeit more carefully initiated and titrated, control of blood pressure (arterial load) in patients with moderate or severe aortic stenosis who cannot undergo surgery. It could also lead, in cases of uncontrolled hypertension—which occur more often in patients with aortic stenosis due to the high prevalence of reduced SAC\textsuperscript{12}—to operating on patients and performing aortic valve replacement to reduce the valvular component, even when their stenosis is not severe. Purportedly, this would lead to reduced global afterload and impede progression of left ventricular dysfunction.

Clearly, given the operational risk of aortic valve replacement surgery,\textsuperscript{16} more studies, prospective-ly designed, will be needed to advocate in favor of a change in the timing of surgery in aortic stenosis, which currently applies only to symptomatic patients with severe aortic stenosis, either on echocardiographic or catheter evaluation, whose average survival when treated medically is 2 to 3 years.\textsuperscript{17} It has been anecdotally stated that the optimum timing for
surgery would be “the exact day before symptom onset”, emphasizing the need to compromise between preserving as much of left ventricular function as possible and justifying an operation with a mortality rate rising up to 33% in cases of severe stenosis with a reduced ejection fraction (<35% – something that may occur while waiting for symptoms to appear). Consequently, a biomarker that would accurately predict the appearance of symptoms in the near future would be most valuable for timing the surgery at the exact point when the left ventricle is on the verge of being overcome by the imposed afterload, but can still recover should the burden be alleviated.

**Natriuretic peptides as a guide to treatment choice**

Natriuretic peptides, particularly brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP), are hormones secreted from cardiac chambers whenever an increased strain is imposed on them.\(^\text{18}\) Their main function is to promote natriuresis in the kidneys through direct inhibition of Na\(^+\) transport, stimulation of their guanylyl cyclase receptor, and inhibition of the renin–angiotensin–aldosterone axis, vasodilation being induced via the latter mechanism. They have been used by clinicians in order to differentiate between dyspnea of cardiac and non-cardiac origin, and may potentially assist in prognosis in the setting of heart failure, myocardial infarction and pulmonary embolism.\(^\text{19}\) Since in aortic stenosis an increased strain is imposed on the left ventricle, and these peptides have been shown to correlate with transvalvular gradients and left ventricular hypertrophy, it would be reasonable to examine the possible use of natriuretic peptides for improving prognosis of the time of symptom onset.

Bergler-Klein et al\(^\text{19}\) undertook such a study, enrolling 130 consecutive patients with severe aortic stenosis and following them for 377 ± 150 days. Not only did natriuretic peptides predict symptom-free survival, they also predicted operative survival, postoperative symptomatic status and postoperative ejection fraction. More specifically, in patients with NT-proBNP <80 pmol/L the percentage lacking symptoms at 6 and 9 months was 88 ± 7% and 88 ± 7%, as opposed to 58 ± 14% and 35 ± 15% for those with NT-proBNP ≥80 pmol/L. Overall, in the multivariate analysis only NT-proBNP and ejection fraction remained independent predictors of symptom onset. Concerning operational mortality, postoperative symptomatic status and left ventricular function, in the multivariate analysis, only NT-proBNP was an independent predictor (along with preoperative ejection fraction in the case of postoperative ejection fraction). Clearly, it can be deduced from this study that should an asymptomatic patient with severe aortic stenosis appear with an NT-proBNP value <80 pmol/L, one may consider the onset of symptoms within the next 6 to 9 months to be highly unlikely (12%). However, in the case of an NT-proBNP value exceeding 80 pmol/L, symptoms are likely to occur in 35% of patients during the next 6 to 9 months, thus prompting the clinician to either monitor the patient more closely for milder unreported symptoms or refer them for early elective surgery. The same authors advanced this concept further by implementing it in the case of low-flow–low-gradient aortic stenosis. They showed that, in terms of 1-year survival postoperatively, patients with BNP <550 pg/ml had excellent results (survival 92 ± 7%) compared to those with BNP ≥550 pg/ml (survival 53 ± 13%), implying that in the latter case heart transplantation might be a more appropriate approach.

During assessment of aortic stenosis in patients exhibiting low-flow–low-gradient stenosis, and in order to exclude pseudo-stenosis, a stress study is performed, aiming to assess the contractile reserve of the myocardium — a parameter associated with survival following aortic valve replacement.\(^\text{20}\) Monin et al,\(^\text{16}\) following a series of studies, reached the conclusion that individuals lacking contractile reserve following stress test evaluation (ejection fraction increase <20%) should be referred for surgery, even though their perioperative mortality is high. The reason is that, should they survive, their benefits in terms of symptoms and left ventricular ejection fraction are comparable to those of patients demonstrating an adequate contractile reserve. Obviously, it is crucial to distinguish between these two groups of patients lacking contractile reserve and BNP values seem to accomplish that, since 1-year postoperative survival was 50 ± 14% in those with BNP ≥550 pg/ml versus 100% in those with BNP <550 pg/ml.\(^\text{21}\)

**Low-flow–low-gradient aortic stenosis with preserved ejection fraction**

Following the development of aortic stenosis, the left ventricle is extensively remodeled in order to compensate for the increased afterload. The molecular sensors of pressure overload triggering the cascade of events culminating in concentric hypertrophy are thought to be the proteins of the Z-disks of cardio-
myocytes. Concentric hypertrophy has profound effects on ejection fraction calculation. Dumesnil et al have shown that the ratio R/h (R – midwall radius; h – wall thickness) may lead, for the same ∆R/R and ∆L/L, i.e. for the same fractional shortening, to variations in ejection fraction reaching 20%. More specifically, in cases of aortic stenosis with consequent concentric hypertrophy, the left ventricle may demonstrate a higher ejection fraction (>65%) than its non-hypertrophied counterpart (typical ejection fraction values around 60%), while no difference in contractile function exists. Furthermore, the ejection fraction of such a ventricle may appear normal, or at the lower threshold of normal, when in fact its contractile reserve has diminished (yet the calculated ejection fraction remains normal due to the effects of a high R/h ratio). Intuitively, it is conceivable that a small, thick-walled ventricle, with concomitant impaired diastolic filling, only needs to contract slightly in order to eject a small amount of blood, which nevertheless constitutes 50% or 60% of its end-diastolic volume.

Dumesnil et al elaborated on this concept by attempting to define a group of patients featuring “low-flow–low-gradient aortic stenosis with preserved ejection fraction.” They defined this group by means of flow (SVi<35 ml/m²), mean gradient (<40 mmHg, even <30 mmHg in 55% of individuals of the group), ejection fraction (EF>50%) and stenosis severity (indexed EOA<0.6 cm²/m²). They reported that it may represent up to 35% of patients with aortic stenosis and normal ejection fraction, although Pai et al found a prevalence of 7% in the total severe aortic stenosis population. Furthermore, patients falling into this category tend to be elderly, female, with thicker and smaller ventricles, and ejection fractions that place them in the lower range of normal (±50%). Dumesnil et al suggested that this cluster of features indicates that this group represents individuals at a more advanced stage of the disease. Through chronic pressure overload, the left ventricle experiences concentric hypertrophy, thus becoming smaller and less compliant, unable to dilate properly. This diastolic impairment accounts for “low flow”. Low flow leads to low gradient, since a smaller volume of blood has to be propelled through the orifice in a given time, hence its velocity can be smaller and ∆P = 4V². The term “paradoxically low flow” was introduced to denote the apparent inconsistency of low flow despite a preserved ejection fraction. As the disease progresses, the left ventricular intrinsic contractile function is impaired (∆L/L decreases) yet, as discussed above, ejection fraction is only marginally affected, accounting for “preserved ejection fraction”. However, the calculation of Zva is revealing, as all these patients are found to have a higher global left ventricular afterload (Zva≈5.2 mmHg/ml/m²) compared to patients with normal ejection fraction, normal flow and high gradients (Zva≈4.2 mmHg/ml/m²).

Clearly, identifying these patients is not an issue, inasmuch as EOA calculation reveals the severity of the disease. However, the clinically relevant issue is the fact that, contrary to what might intuitively be perceived by calculating ejection fraction, these patients have impaired contractile function of the ventricle and additionally an increased afterload, despite what the low pressure gradients may suggest. Furthermore, their referral rate for surgery is much lower (36%) than that of patients with a normal ejection fraction and high gradients (80%), which raises concerns for their outcome. Indeed, as two recent studies suggest, when medical therapy is chosen, the results range from inferior to devastating. More specifically, in the study by Hachicha et al, where 50% of patients had mean gradients ranging from 30 mmHg to 40 mmHg, that is lower than in the study by Hachicha et al, where 50% of patients had mean gradients ranging from 30 mmHg to 40 mmHg. This probably indicates a group with even more advanced intrinsic contractile dysfunction and consequently worse prognosis if treated medically. Finally, if these patients are referred for surgery, every effort should be made to avoid a patient-prosthesis mismatch, since otherwise Zva would only be partially reduced; the smaller prosthesis would add afterload to the left ventricle, and the dysfunctional ventricle would continue to face a taxing burden.

The estimation of aortic valve resistance can also
be helpful in the evaluation of the resistance to forward flow caused by the aortic stenosis. Although the estimation can be obtained easily by the use of the equation \( AVR = \frac{mean \, \Delta P}{Q} \) (where \( \Delta P \) is the mean gradient and \( Q \) the flow in the LVOT, \( m^2 \) VTI, with values above 280 meaning high resistance), the method is highly flow-dependent, with limited prognostic value and unrealistic mathematical modeling of the aortic valve’s dynamics.\(^{27,28}\) Additionally, another index that has been introduced is the projected valve area at normal flow rate. Although this proposed index, by using dobutamine stress echocardiography, can provide information about aortic valve area changes, its clinical impact remains unknown.\(^{29}\)

Nowadays, as new intervention techniques have been developed for the treatment of symptomatic severe aortic stenosis, even in patients with a high perioperative risk,\(^{30}\) we are seeing the implementation of comprehensive evaluation of the global aspects is promising, yet even more inspiring is the perspective of combining their implications in order to promote the understanding and treatment of this disease for the benefit of our patients.

**References**


