

STATE-OF-THE-ART PAPER

Improving Assessment of Aortic Stenosis

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“Degenerative” or calcific aortic stenosis is a complex, multifaceted, systemic disease that is not solely limited to the aortic valve but also includes reduced arterial compliance as well as alterations of left ventricular geometry and function. This particular nature of the disease underscores the need for a more comprehensive evaluation of disease severity going beyond the standard parameters routinely used to assess stenosis severity (i.e., peak jet velocity, pressure gradients, valve effective orifice area) or left ventricle function (i.e., left ventricular ejection fraction). The present paper thus proposes to review newer approaches to improve the quantification of disease severity taking into account the interrelation between the different valvular, arterial, and ventricular variables that may be responsible for the appearance of symptoms and/or poorer prognosis in patients with aortic stenosis. (J Am Coll Cardiol 2012;60:169–80) © 2012 by the American College of Cardiology Foundation

Aortic stenosis (AS) is a complex “systemic” disease. There are compelling epidemiological and histopathological data suggesting that “degenerative” calcific AS is, in fact, an active and multifaceted disease that involves atherosclerotic-like and elastocalcinosis-like processes (1). Hence, it is not surprising that many patients with this disease also have manifestations of these pathologic processes in other target organs. In particular, a large proportion of patients with AS also present with concomitant systolic hypertension, which is related to increased rigidity of the arterial wall (2). Moreover, these patients may have alterations of left ventricular (LV) function that might not only be due to AS but also to concomitant hypertension or coronary artery disease and in varying proportions depending on the severity of each entity (2). In this context, it should be emphasized that the pathophysiology of adverse outcomes in AS is essentially due to an imbalance between the increase in LV hemodynamic load due to the valvular obstruction and/or concomitant arterial hypertension, on the one hand, and the capacity of the left ventricle to overcome this increase in load both at rest and during exercise, on the other hand. The present paper thus proposes to review newer approaches to improve the quantification of disease severity, taking into account the interrelation between the different valvular, arterial, and ventricular variables that may be responsible for the appearance of symptoms or poorer prognosis in patients with AS.

Assessing AS Severity: New Challenges

The American College of Cardiology (ACC)/American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines generally recommend aortic valve replacement (AVR) in patients with severe AS who have symptoms, LV systolic dysfunction, and/or undergo coronary artery bypass graft surgery or other heart surgery (Fig. 1) (3,4). And the criteria proposed in these guidelines to identify severity are a peak aortic jet velocity >4.0 m/s, a mean gradient >40 mm Hg and a valve effective orifice area (EOA) <1.0 cm². These parameters and criteria may, however, have important limitations if used in isolation (Table 1), and it has become evident that the evaluation of AS severity, particularly in patients with the “degenerative” form of the disease, is confronted with specific challenges, as follows.

Accounting for pressure recovery. The current guidelines (3,4) make no distinction between catheterization and Doppler echocardiographic measurements as if values for gradients and EOA measured by either technique were interchangeable (Fig. 1). Yet, Doppler estimates the maximal pressure drop through the valve from the maximal velocity recorded at that level whereas catheterization provides a measure of the net gradient between the left ventricle and the ascending aorta (Fig. 2). However, as blood flow velocity decelerates between the valve and the ascending aorta, part of the kinetic energy is reconverted back to static energy due to a phenomenon called pressure recovery, and hence the net gradient recorded at catheterization is always less than the maximum pressure gradient measured by Doppler (Fig. 2) (2,5–7). Likewise, EOA obtained at catheterization with the use of the Gorlin formula is derived from recovered pressures, such that its value is higher than the Doppler EOA derived by the continuity equation. The

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Abbreviations and Acronyms

ACC	= American College of Cardiology
AHA	= American Heart Association
AS	= aortic stenosis
AVR	= aortic valve replacement
BNP	= brain natriuretic peptide
CMR	= cardiac magnetic resonance
CT	= computed tomography
EOA	= effective orifice area
ESC	= European Society of Cardiology
LV	= left ventricular
LVEF	= left ventricular ejection fraction
Z_{va}	= valvuloarterial impedance

latter measures the actual area occupied by flow at the valvular level whereas the EOA calculated by the Gorlin formula is a coefficient of the energy lost due to the stenosis rather than a true EOA. The extent of pressure recovery is determined by the ratio between the valve EOA and the cross-sectional area of the ascending aorta, a situation that becomes particularly relevant in patients with moderate to severe AS (Doppler EOA between 0.8 cm² and 1.2 cm²) and small aortas (diameter at the sinotubular junction <30 mm) where measurement of EOA by Doppler echocardiography may lead to overestimation of severity (2,5–7). Fortunately, pressure recovery can be accounted for by using the formula proposed by Baumgartner et al. (5) to estimate the net gradient from Doppler measurements, as well as

the formula proposed by Garcia et al. (6) to calculate the energy loss coefficient: $ELCo = (EOA \times A_A / A_A - EOA)$, where A_A is the cross-sectional area of the aorta measured at 1 cm downstream of the sinotubular junction (Table 1) (6). This parameter is more or less equivalent to the EOA obtained by catheterization with the use of the Gorlin formula (6–8), and physiologically, it is more representative than the Doppler EOA of the actual energy loss caused by the stenosis and thus of the increased burden imposed on the ventricle. The stroke work loss, which is the ratio of the mean transvalvular gradient to the estimated LV systolic pressure, is another index that indirectly accounts for the pressure recovery (Table 1). And accordingly, this parameter has also been shown to be superior to the gradient or the EOA for predicting clinical outcomes (9).

Accounting for body size. Valve EOA and energy loss coefficient do not take into account cardiac output requirements in a given patient and, hence, for a similar EOA and cardiac index, gradients and the burden imposed by the stenosis on the ventricle will be higher in patients with a larger body size than in smaller patients. It thus follows that AS severity may be significantly overestimated in smaller patients and underestimated in larger patients when using nonindexed EOA or energy loss coefficient. Conversely, the utilization of parameters indexed for body surface area may overestimate stenosis severity in obese patients.

Accounting for inconsistencies in the guidelines criteria. The guidelines (3,4) are inconsistent from 2 standpoints. First, the criteria used to define severe AS are derived

from outcome studies based on catheterization data, yet the guidelines make no distinction between echo and catheterization data although, due to pressure recovery (as discussed earlier), gradients will always tend to be higher and EOA lower by echocardiography than by catheterization. Second, the severity criteria are also inherently inconsistent with each other (10,11). Indeed, in a patient with normal transvalvular flow rate, the mean gradient that theoretically corresponds to an EOA value of 1.0 cm² is closer to 30 to 35 mm Hg rather than to the 40 mm Hg cutoff value as proposed in the guidelines (3,4). In light of these findings, some investigators have suggested to lower the cutoff value of EOA for severe AS from 1.0 cm² to 0.8 cm² (11). However, several studies report that a valve EOA <1.0 cm² does indeed predict excess mortality and morbidity irrespective of the level of gradient and the presence of symptoms (12,13). Hence, further studies are needed to determine the outcome of the particular subset of patients with an EOA between 0.8 cm² and 1.0 cm², especially when treated conservatively.

Accounting for vascular load. Elderly patients with calcific AS may also have arterial atherosclerosis as well as medial elastocalcinosis. Young subjects with a bicuspid aortic valve also commonly have reduced aortic elasticity as a result of structural abnormalities of the aortic wall and/or aortic dilation (14). Hence, it is not surprising that patients with calcific AS often have reduced compliance in the large arterial circulation and thereby ensuing systolic hypertension (2,14). Briand et al. (2) reported that total systemic arterial compliance estimated by dividing the stroke volume index as measured by echocardiography by pulse pressure (systolic minus diastolic blood pressures) is severely reduced (<0.6 ml·m⁻²·mm Hg⁻¹) in approximately 40% of patients with AS (Table 1). Furthermore, reduced arterial compliance contributes to increase the LV afterload and thus the occurrence of myocardial dysfunction and adverse events. Besides the pulsatile component of the arterial load reflected by the systemic arterial compliance, there is also the steady component that is estimated by calculating the systemic vascular resistance (SVR) as follows: $SVR = (80 \times \text{mean arterial pressure}) / \text{cardiac output}$, where cardiac output is measured in the LV outflow tract by Doppler echocardiography and mean arterial pressure is defined as diastolic pressure plus one-third of pulse pressure (Table 1). Finally, it should be emphasized that a normal blood pressure does not exclude an increase in vascular load since these pressures may be pseudo-normalized in up to 30% of patients with decreased systemic arterial compliance due to LV dysfunction and a concomitant decrease in cardiac output (2,12).

Interaction between hypertension and aortic stenosis severity criteria. In light of the above, concomitant arterial hypertension is found to be present in a large proportion (35% to 51%) of patients with AS (2,12,15–17). Hence, there should be awareness that the parameters of AS severity may be noticeably altered by the presence of hypertension, and that

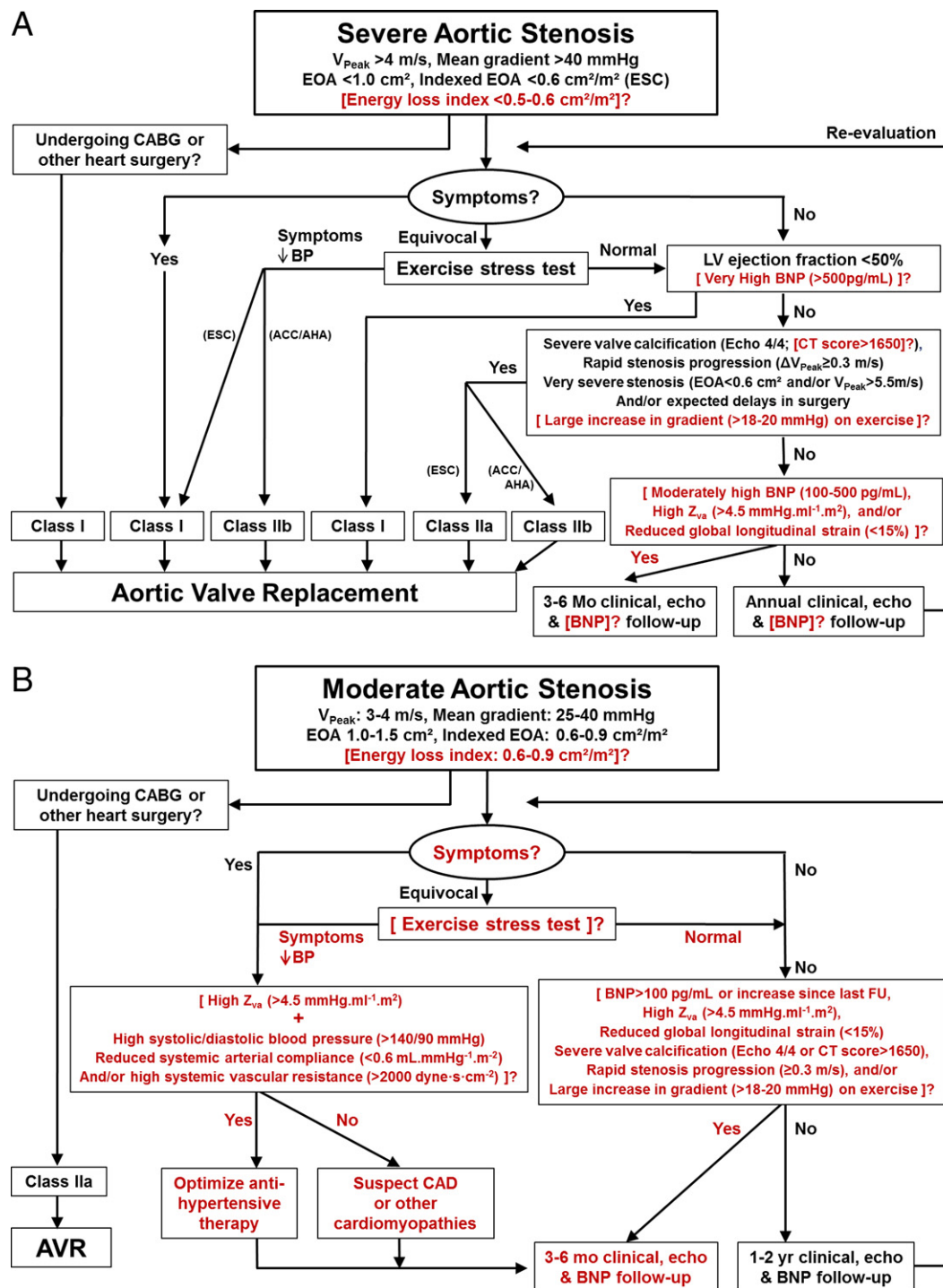


Figure 1 Algorithm for Management of Patients With AS

Algorithms for the management of (A) severe aortic stenosis (AS) and (B) moderate AS. The text in **black** refers to the recommendations proposed in the American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines whereas the text in **red** and between []? represents the new emerging parameters that may eventually contribute to improving the assessment and management of AS. However, these new parameters will need to be further validated in future studies. AVR = aortic valve replacement; BNP = brain natriuretic peptide; BP = blood pressure; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CT = computed tomography; echo = echocardiography; EOA = effective valve orifice area; FU = follow-up; LV = left ventricular; V_{Peak} = peak aortic jet velocity.

Table 1 Parameters for the Assessment of Aortic Stenosis

Parameter	Criteria for Severe	Utility and Advantages	Limitations
Quantification of valvular obstruction			
Peak aortic jet velocity (V_{Peak})*†	>4 m/s	Easy to measure Low interobserver/intraobserver variability High specificity	Highly flow dependent Over-estimates LV energy loss in patients with small aortas May under- or over-estimate stenosis severity in presence of hypertension Under-estimates stenosis severity in low flow states
Mean gradient*†	>40 mm Hg	Same as peak aortic jet velocity	Same as peak aortic jet velocity
Valve effective orifice area*†	$\leq 1.0 \text{ cm}^2$	Less flow dependent than gradient or peak velocity	Susceptible to measurements errors
$\text{EOA} = \text{SV}_{\text{LVOT}}/\text{VTI}_{\text{Ao}}$	$\leq 0.6 \text{ cm}^2/\text{m}^2$	Reflects intrinsic severity of valvular obstruction	Over-estimates LV energy loss in patients with small aortas May under- or over-estimate stenosis severity in presence of hypertension May over-estimate stenosis severity in low flow states EOA may over-estimate severity in patients with small body size. Indexed EOA may over-estimate severity in obese patients
Indexed EOA*			
$\text{EOAI} = \text{EOA}/\text{BSA}$			
Energy loss index	$\leq 0.5\text{--}0.6 \text{ cm}^2/\text{m}^2$	Less flow dependent than gradient or peak velocity Takes into account pressure recovery and is $\pm$ equivalent to EOA measured by catheter Reflects true LV energy loss caused by stenosis Should be measured in patients with small aortas	Susceptible to measurements errors May under- or over-estimate stenosis severity in presence of hypertension May over-estimate stenosis severity in low flow states
$\text{ELI} = [\text{EOA} \times A_A/A_A - \text{EOA}]/\text{BSA}$			
Stroke work loss	>25%	Less flow dependent than gradient or peak velocity Takes into account pressure recovery	May under-estimate stenosis severity and LV energy loss in presence of hypertension
$\text{SWL} = 100 \times (\Delta P_{\text{Mean}}/\text{SBP} + \Delta P_{\text{Mean}})$			
Aortic valve calcification score†	Echo 4/4† CT >1,650 AU	Can be estimated by echo and quantitatively measured by multislice CT Correlates well with stenosis severity and predicts rapid stenosis progression Independent of hemodynamic conditions Useful in low flow states when echo assessment of stenosis hemodynamic severity is inconclusive	Echo, semiquantitative assessment CT, exposure to radiation
Quantification of vascular load			
Systemic BP*	>140/90 mm Hg	Easy to measure	Highly flow dependent Often pseudonormalized in AS patients Underestimates severity of hypertension in low flow states
SBP/DBP			
Systemic arterial compliance*	$\leq 0.6 \text{ ml}\cdot\text{mm Hg}^{-1}\cdot\text{m}^{-2}$	Can be measured by Doppler echocardiography Most frequent cause of increased arterial load in AS patients Can unmask hypertension in patients with pseudonormalized blood pressure	Susceptible to measurements errors
$\text{SAC} = \text{SVI}/\text{SBP} - \text{DBP}^*$			
Systemic vascular resistance*	>2,000 dyne·s·cm ^{−5}	Can be measured by Doppler echocardiography Can unmask hypertension in patients with pseudonormalized blood pressure	Susceptible to measurements errors
$\text{SVR} = 80 \times \text{MBP}/\text{CO}$			

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there is no readily available mean of accounting for this phenomenon. Indeed, reduced arterial compliance tends to abolish the peak-to-peak gradient as recorded during catheterization (18) as well as modify the other parameters of AS severity (2,18,19). These latter modifications occurring with changes in blood pressure are essentially related to the con-

comitant changes in mean transvalvular flow rate, and stenosis severity may be over- or under-estimated depending on the direction of these flow changes (18,19).

Accounting for low flow states. The chronic exposure to a high level of afterload may eventually exceed the limit of LV compensatory mechanisms, and lead to an intrinsic impair-

Table 1 Continued

Parameter	Criteria for Severe	Utility and Advantages	Limitations
Quantification of global LV hemodynamic load			
Valvuloarterial impedance (Z_{va})* $Z_{va} = SBP + \Delta P_{Mean}/SVI$	$>4.5 \text{ mm Hg} \cdot \text{ml}^{-1} \cdot \text{m}^2$	Can be measured by Doppler echocardiography Reflects global (valvular+arterial) load imposed on LV Potentially superior to predict occurrence of symptoms and events	Susceptible to measurements errors Does not permit to discriminate the valvular versus the arterial contribution to the global LV load
Quantification of LV systolic dysfunction			
LVEF*†	$<50\%$	Widely used and validated with regard to outcome data	Susceptible to measurements errors Also influenced by LV geometry Under-estimates the degree of myocardial systolic dysfunction in presence of LV concentric remodeling
Global longitudinal strain*	$<15\%$	Less influenced by LV geometry Superior to LVEF to assess intrinsic myocardial function	Cutoff values need to be further validated
Myocardial fibrosis		Can be measured by CMR Predicts poor outcomes after AVR	High cost and low availability of CMR
Plasma natriuretic peptides* BNP or NT-ProBNP		Easy and inexpensive to measure Reflects total burden of disease on myocardium Correlates well with myocardial systolic dysfunction and symptoms Predicts poor outcomes before and after AVR	High variability in the threshold values reported in the literature to predict poor outcomes Increase in BNP during serial follow-up may be superior to isolated measure Does not permit discriminating impact of valvular stenosis versus hypertension versus other cardiovascular disease NT-ProBNP may be more sensitive to detect early LV systolic dysfunction but more age dependent

*Indicates the parameters we think should be part of the routine assessment of patients with aortic stenosis (AS). †Indicates the parameters that are included in the algorithms presented in the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines for the management of AS.

A_a = cross-sectional area of the ascending aorta measured just downstream of the sinotubular junction; AVR = aortic valve replacement; BNP = brain natriuretic peptide; BSA = body surface area; CMR = cardiac magnetic resonance; CO = cardiac output; DBP = diastolic blood pressure; Echo = echocardiography; LV = left ventricular; LVEF = left ventricular ejection fraction; MBP = mean blood pressure; NT-ProBNP = N-terminal pro-B-type natriuretic peptide; SBP = systolic blood pressure; SVI = stroke volume index.

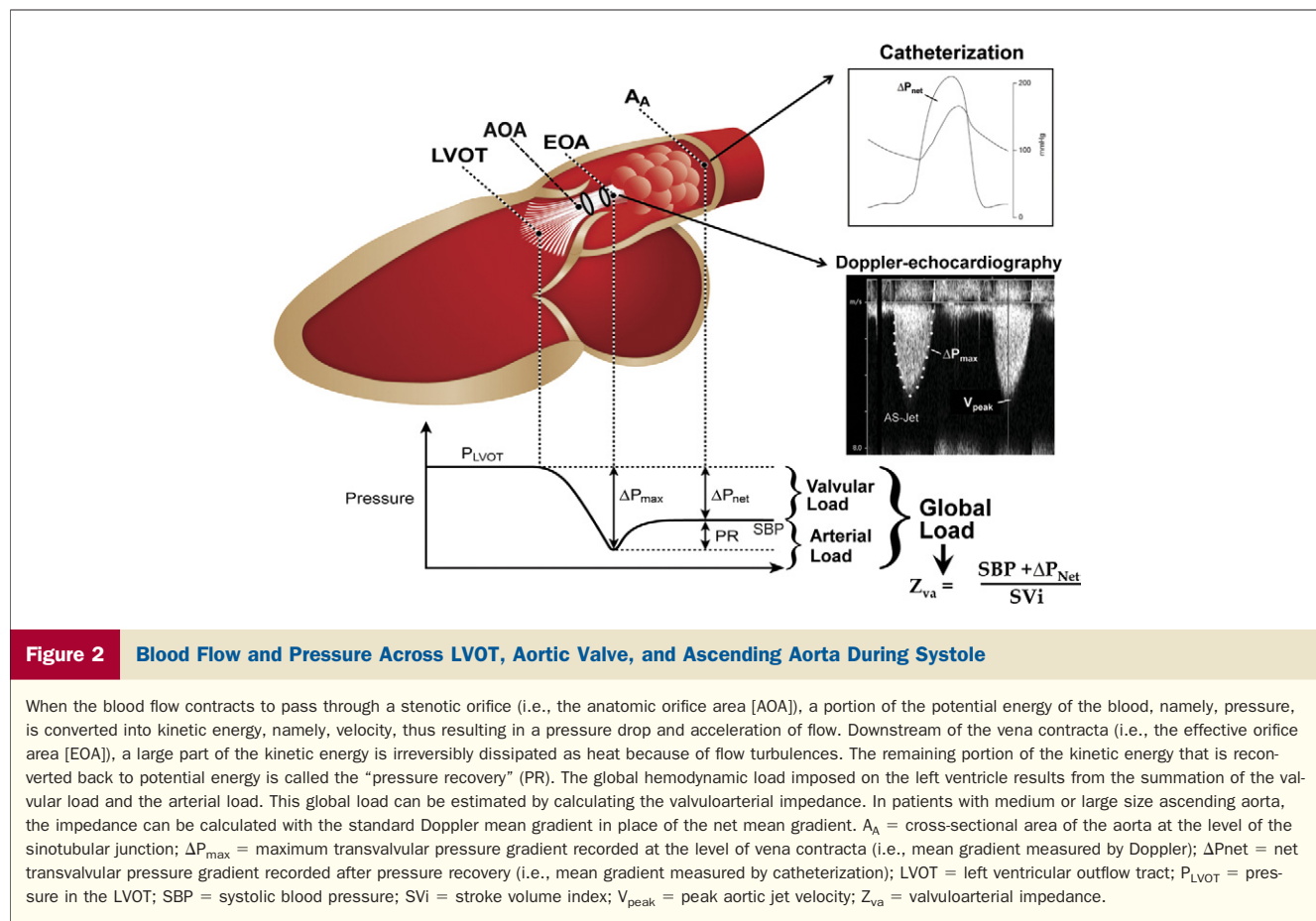
ment of myocardial function and a decrease in cardiac output resulting in a decrease in transvalvular gradients and a pseudonormalization of peripheral blood pressure. This situation is highly insidious because both AS and hypertension may appear less severe on the basis of the gradient and blood pressure, whereas, in fact, these patients are at a more advanced stage of their disease. Low-flow, low-gradient AS may occur with reduced or preserved LV ejection fraction, and both situations are among the most challenging encountered in patients with AS. (This topic will be addressed in detail in a forthcoming state-of-the-art paper in the *Journal*.)

Assessment of AS Severity: New Solutions

Many patients with AS can still be managed adequately with the use of simple parameters of disease severity such as peak jet velocity, mean gradient, EOA, valve morphology, and LV ejection fraction (LVEF) (Figs. 1 and 2, Table 1). However, in light of the earlier noted considerations, it becomes evident that the mode of presentation of many patients with calcific AS is more complex than previously believed and thus warrants more comprehensive evaluations, which can include the following:

Assessment of valvular load. The energy loss index is the energy loss coefficient divided by body surface area; it takes into account the effects of both pressure recovery and body size. In a substudy of the SEAS (Simvastatin Ezetimibe in Aortic Stenosis) trial (20), 47.5% of patients classified as having severe AS by indexed EOA were reclassified to nonsevere AS when using energy loss index. Moreover, this parameter allows easier comparison between echocardiographic and catheterization data (21). The threshold value for severe stenosis is ≤ 0.5 to $0.6 \text{ cm}^2/\text{m}^2$ (Table 1) (6,7,20).

Assessment of vascular load. The increase in global LV hemodynamic load due to decreased systemic arterial compliance and/or increased vascular resistance can be important in many patients. Accordingly, Antonini-Canterin et al. (15) have observed that symptoms of AS develop at a lower degree of stenosis severity in hypertensive patients, most likely because of the additional hemodynamic load due to hypertension. Hence, blood pressure should be routinely recorded in patients evaluated for AS, and systemic arterial compliance and vascular resistance should also be calculated as blood pressure can be pseudonormalized in as many as 30% of patients (Table 1). Given that hypertension may interfere with the assessment of AS severity and that



there is no easy means of correcting for this distortion, the following should also be considered: 1) evaluation of AS severity by echocardiogram or catheterization should ideally be performed when blood pressure control is optimal; 2) serial evaluations should take into account if the patient's blood pressure and flow levels are within the same range as the previous evaluation; and 3) in case of discrepancies between Doppler echocardiographic and catheterization data, potential differences in blood pressure and transvalvular flow rates during each examination should be considered.

Assessment of global LV hemodynamic load. To assess the global (valvular plus arterial) LV hemodynamic load in AS patients, one can calculate the valvuloarterial impedance (Z_{va}) (Fig. 2) by dividing the estimated LV systolic pressure (systolic blood pressure plus mean transvalvular gradient) by the stroke volume indexed for body surface area (Table 1) (2). This parameter provides an estimate of the cost in mm Hg for each systemic milliliter of blood indexed for body size pumped by the left ventricle. Values of $Z_{va} > 3.5$ and $4.5 \text{ mm Hg} \cdot \text{ml}^{-1} \cdot \text{m}^{-2}$ indicate moderately and severely increased global LV hemodynamic load respectively (17). The Z_{va} has been shown to be superior to the standard parameters of AS severity (i.e., gradients and EOA) in predicting LV dysfunction and patient clinical outcomes (2,16,17,22,23). This parameter is useful with regard to prog-

nosis but it remains important, from the standpoint of treatment, to delineate the relative contributions of the valvular and vascular components to the increased load.

Assessment of LV geometry. The pattern of the LV response to pressure overload in AS is highly heterogeneous and includes concentric remodeling, concentric hypertrophy, and eccentric hypertrophy (24–26). Hence, relative wall thickness should be systematically measured in addition to LV mass because a large proportion of patients with AS have abnormal LV geometry (relative wall thickness > 0.42 ; i.e., concentric remodeling) despite absence of LV hypertrophy defined as indexed LV mass $> 95 \text{ g/m}^2$ in women and $> 115 \text{ g/m}^2$ in men (16,25,26). More severe LV concentric remodeling or hypertrophy has been linked to worse myocardial function (16), increased risk of cardiovascular events (27), and increased operative and late mortality after aortic valve replacement (28). The pattern and magnitude of the LV adaptive response to AS is influenced by several factors including stenosis severity, age, sex, obesity, metabolic syndrome, and diabetes mellitus (24–26).

Assessment of intrinsic LV function, going beyond LVEF. Left ventricular systolic dysfunction on the basis of LVEF is a class I indication for AVR in patients with severe AS irrespective of symptoms, and LVEF is the only parameter of LV function included in the guidelines (3,4). Yet, several

studies report that as many as one-third of asymptomatic patients with preserved LVEF have a significant impairment of intrinsic myocardial systolic function (16,22,29,30) and that the parameters of LV longitudinal kinetics are superior to other indices of LV systolic function to detect

myocardial dysfunction and damage (Fig. 3) (23,29–33) as well as to predict symptoms, exercise tolerance, and outcomes (22,31,34–36). From a pathophysiological standpoint, these data are consistent with the concept that: 1) the increase in wall stress and intramyocardial pressure as well as

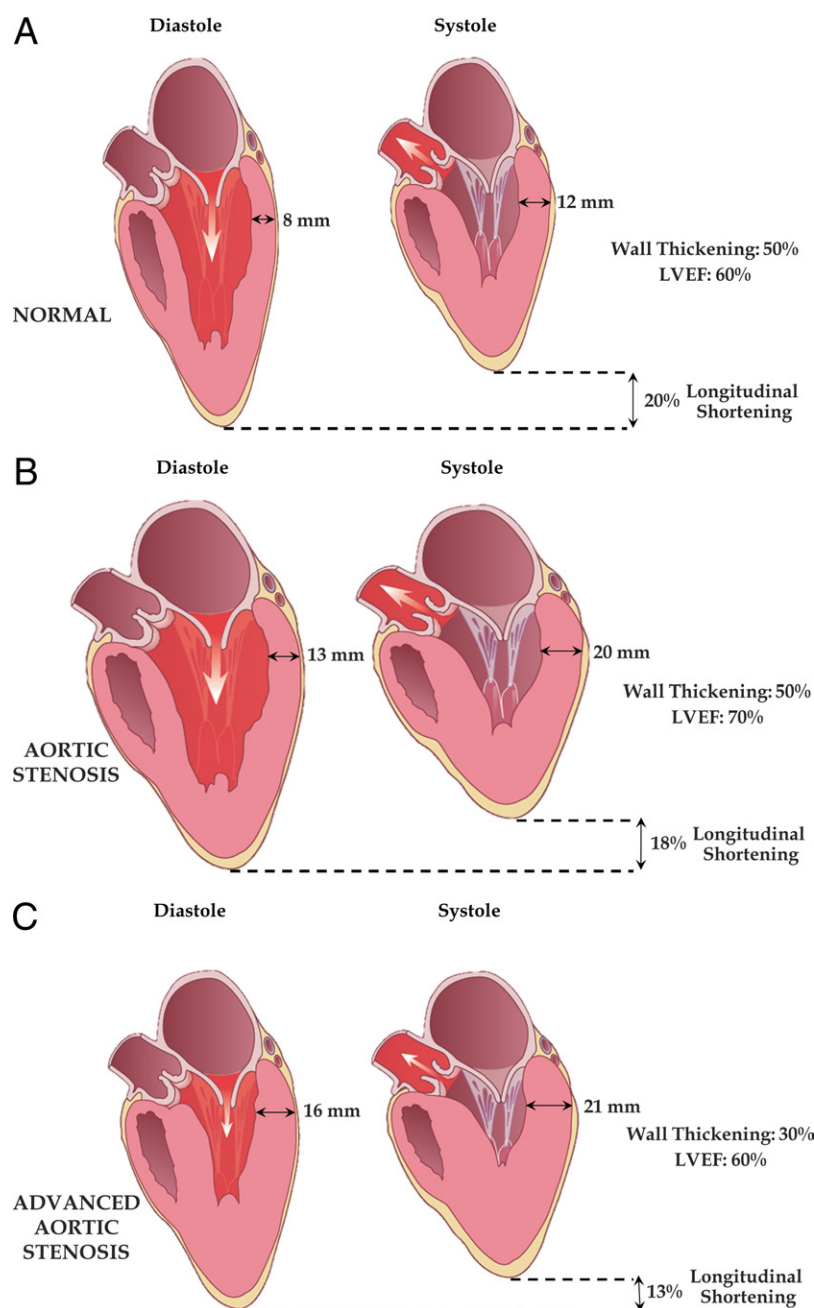


Figure 3 Superiority of LV Longitudinal Shortening Over LVEF to Identify Myocardial Systolic Dysfunction in AS

The panels show the left ventricles (LV) of (A) a normal healthy subject, (B) a patient with aortic stenosis (AS) and normal myocardial function, and (C) a patient with advanced AS and myocardial dysfunction. The LV ejection fraction (LVEF) markedly underestimates the extent of myocardial systolic impairment in presence of LV concentric hypertrophy such as is often the case in AS patients (C). The increase in wall thickness associated with LV concentric hypertrophy results in a greater contribution of wall thickening to endocardial inward displacement (B and C). As a consequence, LVEF as well as any parameter based on endocardial displacement remains normal in presence of concentric hypertrophy, despite a significant impairment of intrinsic myocardial shortening and function (C). The longitudinal strain (LS) is thus more sensitive than LVEF to identify intrinsic myocardial dysfunction.

the reduction in myocardial blood flow in AS occur mainly in the subendocardium; and 2) the subendocardial myocardial fibers are oriented longitudinally. Hence, as hypothesized by Dumesnil et al. (29) 30 years ago, the selective impairment in longitudinal LV shortening is likely the consequence of increased subendocardial wall stress and resulting subendocardial ischemia and/or fibrosis. Global longitudinal myocardial strain measured by speckle tracking can now be measured routinely and reproducibly and has emerged as the most promising alternative to detect and quantify intrinsic myocardial systolic dysfunction (30–32); pend-

ing further validation, a threshold value of <15% has been proposed for this purpose (22,30).

Identifying myocardial damage by measuring fibrosis and BNP levels. Recent studies (33,37) have reported that about one-third of patients undergoing AVR for severe AS have severe myocardial fibrosis documented by cardiac magnetic resonance (CMR) and intraoperative myocardial biopsies (Fig. 4). Moreover, myocardial fibrosis is often not, or only partially, reversible and is associated with increased risk of cardiovascular events and mortality during follow-up as well as persistence of LV dysfunction and symptoms

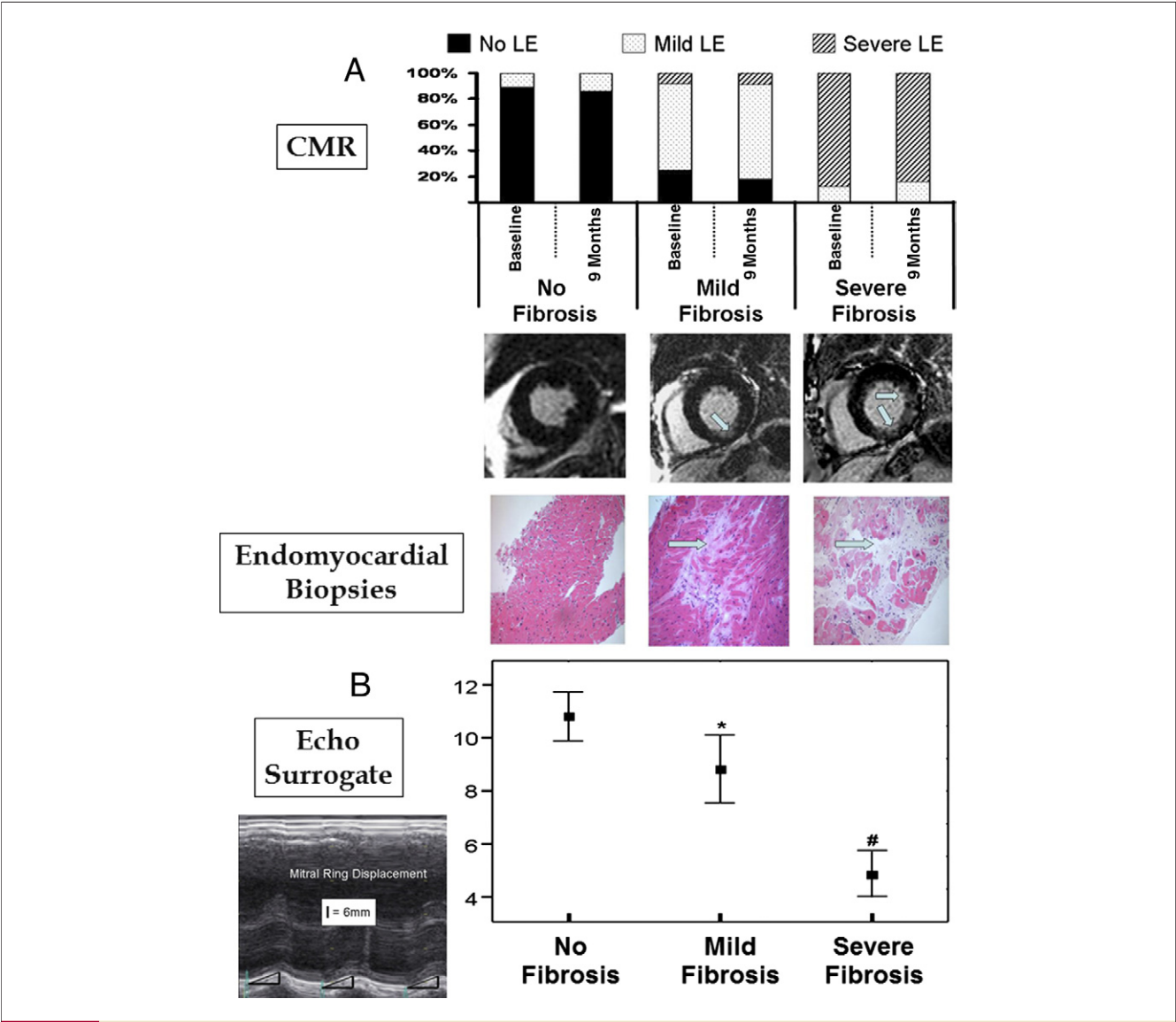


Figure 4 **Assessment of Myocardial Fibrosis by CMR and Echocardiography in AS**

(A) The distribution of late gadolinium enhancement (LE) (**top**), expressed as percentage (range 0% to 100%) at baseline and 9 months post-AVR within the 3 groups, is defined according to the severity of fibrosis in endomyocardial biopsies. The concordance between (**middle**) cardiac magnetic resonance (CMR) and (**bottom**) endomyocardial biopsy for the quantification of myocardial fibrosis in patients with severe aortic stenosis (AS) undergoing aortic valve replacement (AVR). **(B)** The left ventricular longitudinal shortening assessed with the use of the mitral ring displacement provides a good surrogate marker of the extent of myocardial fibrosis. Adapted with permission of the American College of Cardiology (23).

(23,33,37,38). The nonreversibility of myocardial fibrosis and associated dysfunction after AVR most likely depends on the type (replacement vs. interstitial) and extent (severe vs. mild) of fibrosis. Hence, the quantification of myocardial fibrosis by CMR could potentially be useful to improve risk stratification and follow-up as well as to recommend AVR before extensive fibrosis and ensuing irreversible myocardial dysfunction have developed. The implementation of such a measure is, however, unrealistic due to high cost and low availability. Conversely, it has been shown that the parameters of LV longitudinal function correlate well with the degree of myocardial fibrosis (Fig. 4) (23,29,33). Hence, an alternate approach could be to routinely measure global LV longitudinal strain during follow-up and to perform CMR in selected cases.

Recent studies also show that brain natriuretic peptide (BNP) levels correlate better with myocardial abnormalities (i.e., LVEF, LV longitudinal shortening, degree of myocardial fibrosis) and clinical outcomes than the usual parameters of AS severity (23,31,33,36,39–42). These findings further corroborate the concept that myocardial damage and clinical outcomes are primarily determined by the total burden of disease on the ventricle rather than by AS severity alone (Table 1). First, levels of BNP may also have an added advantage over the indices of global load such as Z_{va} in that they also likely reflect the impact of other associated conditions (e.g., coronary artery disease, cardiomyopathy, and so forth) on the myocardium. However, BNP levels are not specific to AS severity alone but rather reflect the total burden of disease on the left ventricle. They should thus be interpreted in light of the parameters more specifically reflecting AS severity as well as arterial and global loads (Table 1). Second, the threshold values for adverse events appear to vary considerably from one study to the other. Third, BNP response is also influenced by age and sex. Hence, unless the value are unequivocally elevated (e.g., BNP >500 pg/ml) (40,41), an individual result should not be interpreted in isolation but rather in light of other clinical variables as well as variations with time, which may be superior to an individual measurement to predict development of symptoms (43). For NT-proBNP, which is influenced by age, reference values in relation to the different age strata also need to be established. Nonetheless, BNP remains a robust predictor of outcomes in AS, and we believe it should be routinely measured and become an integral part of the clinical decision making process. Moreover, it may have added value from the standpoint of cost-benefit since the continued observation of low and stable levels in an asymptomatic patient might preclude the unnecessary use of more expensive investigations.

Exercise testing to unmask symptoms. The onset of symptoms is one of the cornerstones in the decision-making algorithm presented in the ACC/AHA and ESC guidelines for the indications of AVR (Fig. 1) (3,4). However, the concept proposed 40 years ago, of patients with AS remaining asymptomatic for a long time and then developing

explicit symptoms portending poor outcomes (44), is no longer congruent with the new face of the disease that we encounter nowadays. Indeed, elderly patients have more comorbidities and are less physically active, which renders the assessment of symptoms much more complex and unreliable. Patients may also reduce their level of physical activity to avoid or minimize symptoms, and the overall presentation often predisposes to under-reporting and/or under-estimation of symptoms. Conversely, because of associated comorbidities, it may be difficult to determine if the symptoms are really due to the valvular stenosis per se. Women are referred to AVR at a more advanced stage of the disease compared to men, which may, at least in part, contribute to the increased operative risk frequently associated with female sex (45).

Several studies have now demonstrated that exercise testing can be done safely in patients without apparent symptoms (46) and that the results can be used to identify patients at high risk of adverse events over the next 1 to 2 years (47–50). Both the ACC/AHA and ESC guidelines (3,4) now support the role of exercise testing in asymptomatic AS patients, with recommendations that AVR be considered in those with exercise-induced symptoms or abnormal blood pressure responses (Fig. 1). The strength of this recommendation, however, differs between the 2 guidelines, with a Class IIb recommendation from the ACC/AHA compared to Class I (symptoms) and Class IIa (abnormal blood pressure) recommendations from the ESC. For older or less active patients, the negative predictive value of exercise testing remains high so that the absence of exercise-limiting symptoms or fall in blood pressure is reassuring; however, the positive predictive value is lower in these patients (49) so that the results of exercise testing should be interpreted in light of other risk markers (i.e., Z_{va} , BNP, and so forth) and comorbidities (Fig. 1). Finally, 2 studies have shown that among patients with moderate or severe AS, those who display an increase in mean gradient of ≥ 18 to 20 mm Hg during exercise testing have a higher risk of progression to symptoms and adverse events (50,51). These observations might become an argument for combining exercise testing with stress echocardiography when evaluating these patients.

Other factors related to more rapid disease progression.

Several other factors have been identified as predisposing to more rapid disease progression (Fig. 1). 1) Patients with a more severe stenosis defined as a valve EOA <0.6 cm² or peak aortic jet velocity >5.5 m/s have a more rapid progression to symptoms and LV systolic dysfunction (52–54). 2) The degree of aortic valve calcification is also a powerful predictor of more rapid stenosis progression (53). Semi-quantitative scoring of valve calcification can be done by echocardiography but multislice computed tomography (CT) allows more accurate and quantitative assessments (55). The concern of radiation exposure, however, limits the use of this procedure for routine follow-up. 3) Previous studies report an association between several traditional

cardiovascular risk factors (i.e., hypercholesterolemia, hypertension, obesity, smoking) and faster stenosis progression but there is until now no evidence that this situation can be altered by medications targeting these risk factors (e.g., statins, inhibitors of the renin-angiotensin system) (1). Moreover, there is mounting evidence that the metabolic syndrome and type 2 diabetes are also associated with faster stenosis progression and faster deterioration of LV function (25,56), but it remains to be determined if the course of the disease can be altered by changes in lifestyle and/or therapies targeting the associated metabolic abnormalities.

Important caveats. The utility, advantages, and limitations of the various parameters used to evaluate stenosis severity are summarized in Table 1 and have been extensively discussed in the American Society of Echocardiography/European Association of Echocardiography guidelines (21). Given that all parameters of stenosis severity have limitations and may be subject to measurement errors, a comprehensive, multiparametric approach is thus recommended. Hence, AS severity is best characterized by flow-independent parameters such as EOA, indexed EOA, and energy loss index, but their estimation, however, requires the inclusion of several parameters and they are therefore more prone to measurement errors.

The degree of valve calcification measured by multislice CT can also be used to corroborate stenosis severity, a calcium score $>1,650$ AU being indicative of severe AS with a sensitivity and specificity $\geq 80\%$ (55). The main advantage of this parameter is that it is not influenced by hemodynamic conditions, and it may thus be particularly useful in the presence of low LV outflow states. The disadvantage of CT calcium scoring is exposure to ionizing radiation (1 to 3 mSv per examination), which limits serial short-time interval follow-up. This radiation risk is, however, a less important issue in the elderly patients who represent an important proportion of the AS population. Future studies are needed to further validate and standardize the utilization of such multiparametric/multimodality approach as well as to determine the potential clinical benefits and cost effectiveness of multidisciplinary specialized heart valve clinics.

Resolving Difficult Clinical Situations in AS

Management of patients with asymptomatic severe AS. The management of patients with asymptomatic severe AS remains a source of debate (3,4), and recent studies have suggested that those treated surgically may have better survival than those treated medically (57). This difference may be related to under-estimation of symptoms and/or stenosis severity, especially in the elderly sedentary patients (12). Moreover, a “wait for symptoms” strategy may result in some patients being operated too late, namely, at a stage of the disease when myocardial impairment has become, at least in part, irreversible (Fig. 4).

As emphasized in the guidelines (3,4), an important objective in asymptomatic patients with severe AS and normal LVEF is to ensure that the patient is truly asymptomatic to the extent of performing an exercise test if the symptomatic status is equivocal. Otherwise, earlier referral for AVR despite the absence of symptoms can also be considered (Class IIa or IIb indication in the guidelines) when the following markers of rapid disease progression are present (Fig. 1A): 1) severe aortic valve calcification (53,55); 2) rapid hemodynamic progression of the stenosis at serial echocardiographic examinations (52,53); and/or 3) very severe AS (54).

In addition to the standard parameters (i.e., peak jet velocity, gradient, EOA, valve calcification, and LVEF) proposed in the guidelines to assess disease severity, several other emerging parameters may also be used to further enhance risk stratification and clinical decision making in these patients: 1) energy loss index to more precisely assess stenosis severity in patients with EOA between 0.8 and 1.0 cm^2 and small aorta diameter (<30 mm); 2) Z_{va} to determine the global (valvular plus arterial) LV hemodynamic load; 3) plasma BNP to assess the global impact of the diseases on the myocardium; and 4) global longitudinal strain to confirm that myocardial systolic function is intrinsically normal. If 1 or more of these parameters is clearly abnormal (Table 1), it would appear preferable to follow the patients more closely with a clinical, BNP level and/or echocardiographic evaluation every 3 to 6 months. If, however, those parameters are only mildly or moderately abnormal, the same follow-up could be extended to 6 to 12 months. These emerging parameters as well as proposed composite risk scores incorporating several parameters (42) will have to be further validated in large prospective studies before being implemented in routine practice.

Management of patients with symptomatic moderate AS. In patients with moderate AS who nonetheless have symptoms, the objectives are first to confirm that the stenosis is really moderate rather than severe, and then to determine the probable etiology of the symptoms (Fig. 1B). In this context, it is important to reiterate that adverse outcomes in AS are in fine determined by the imbalance between global LV load and LV myocardial reserve. Hence, a patient with moderate AS and concomitant arterial hypertension may have a global hemodynamic load that is equivalent or superior to that of a patient with severe AS and no hypertension, and thus be symptomatic on that basis (15). The calculation of Z_{va} may thus be useful in these cases to reconcile the apparent discrepancy between the moderate stenosis and the severity of the symptoms (17). If Z_{va} is high, an optimal and prudent treatment of hypertension would appear reasonable. Future studies are necessary to determine if AVR should nonetheless be contemplated in patients with optimal treatment of hypertension and persistence of symptoms. If Z_{va} is low, associated conditions such as coronary artery disease, cardiomyopathy, pulmonary disease, and so forth, should be considered (Fig. 1B).

Finally, AS severity may progress rapidly in a substantial proportion of patients with moderate AS even if asymptomatic. Hence, closer follow-up (6 to 12 months) would appear judicious with such patients if there is presence of severe valve calcification at echocardiography or CT, large increase in gradient on exercise stress echocardiogram, or progressive increase in BNP from one examination to the other (Fig. 1B).

Conclusions

“Degenerative” or calcific AS is a complex, multifaceted, and systemic disease that is not solely limited to the aortic valve but also includes reduced arterial compliance as well as alteration of LV geometry and function. This changing face of the disease underlines the need for a more comprehensive assessment of AS severity going beyond the simple measurement of the standard parameters of stenosis severity (i.e., peak jet velocity, pressure gradients, EOA) or LV function (i.e., LVEF) to include the following parameters: 1) the energy loss index for the assessment of valvular load; 2) the systemic arterial compliance and valvular resistance for the assessment of arterial load; and 3) the valvuloarterial impedance and BNP to quantify the global LV hemodynamic load and its repercussion on the myocardium, and 4) the global longitudinal strain to assess the presence and severity of intrinsic myocardial dysfunction. Moreover, exercise stress testing and exercise stress echocardiography provide important tools to unmask symptoms, lack of valve opening reserve, and/or latent myocardial systolic dysfunction unrevealed by assessment in the resting state. Hence, a comprehensive approach integrating these novel parameters is often essential to appropriately assess the type of patient presenting nowadays with this type of pathology. Moreover, other imaging modalities such as CT and CMR may also be helpful to complement or confirm the information obtained by clinical evaluation, Doppler echocardiography, or blood biomarker measurements.

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