Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 62, No. 24, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.08.1621

The Complex Nature of Discordant Severe Calcified Aortic Valve Disease Grading

New Insights From Combined Doppler Echocardiographic and Computed Tomographic Study

Marie-Annick Clavel, DVM, PhD,* David Messika-Zeitoun, MD, PhD,†‡
Philippe Pibarot, DVM, PhD,§ Shivani R. Aggarwal, MBBS,* Joseph Malouf, MD,*
Phillip A. Araoz, MD,* Hector I. Michelena, MD,* Caroline Cueff, MD,† Eric Larose, MD, MSc,§
Romain Capoulade, MSc,§ Alec Vahanian, MD,†‡ Maurice Enriquez-Sarano, MD*

Rochester, Minnesota; Paris, France; and Quebec City, Québec, Canada

Objectives With concomitant Doppler echocardiography and multidetector computed tomography (MDCT) measuring aortic valve calcification (AVC) load, this study aimed at defining: 1) independent physiologic/structural determinants of aortic valve area (AVA)/mean gradient (MG) relationship; 2) AVC thresholds best associated with severe aortic stenosis (AS); and 3) whether, in AS with discordant MG, severe calcified aortic valve disease is generally detected.

Background Aortic stenosis with discordant markers of severity, AVA in severe range but low MG, is a conundrum, unresolved by outcome studies.

Methods Patients ($n = 646$) with normal left ventricular ejection fraction AS underwent Doppler echocardiography and AVC measurement by MDCT. On the basis of AVA-indexed-to-body surface area (AVAi) and MG, patients were categorized as concordant severity grading (CG) with moderate AS (AVAi >0.6 cm^2/m^2, MG <40 mm Hg), severe AS (AVAi ≤0.6 cm^2/m^2, MG ≥ 40 mm Hg), discordant-severity-grading (DG) with low-MG (AVAi ≤0.6 cm^2/m^2, MG <40 mm Hg), or high-MG (AVAi >0.6 cm^2/m^2, MG ≥40 mm Hg).

Results The MG (discordant in 29%) was strongly determined by AVA and flow but also independently and strongly influenced by AVC-load ($p < 0.0001$) and systemic arterial compliance ($p < 0.0001$). The AVC-load (median [interquartile range]) was similar within patients with DG (low-MG: 1,619 [965 to 2,528] arbitrary units [AU]; high-MG: 1,736 [1,209 to 2,894] AU; $p = 0.49$), higher than CG-moderate-AS (861 [427 to 1,519] AU; $p < 0.0001$) but lower than CG-severe-AS (2,931 [1,924 to 4,292] AU; $p < 0.0001$). The AVC-load thresholds separating severe/moderate AS were defined in CG-AS with normal flow (stroke-volume-index >35 ml/m^2). The AVC-load, absolute or indexed, identified severe AS accurately (area under the curve ≥0.89, sensitivity ≥86%, specificity ≥79%) in men and women. Upon application of these criteria to DG-low MG, at least one-half of the patients were identified as severe calcified aortic valve disease, irrespective of flow.

Conclusions Among patients with AS, MG is often discordant from AVA and is determined by multiple factors, valvular (AVC) and non-valvular (arterial compliance) independently of flow. The AVC-load by MDCT, strongly associated with AS severity, allows diagnosis of severe calcified aortic valve disease. At least one-half of the patients with discordant low gradient present with heavy AVC-load reflective of severe calcified aortic valve disease, emphasizing the clinical yield of AVC quantification by MDCT to diagnose and manage these complex patients. (J Am Coll Cardiol 2013;62:2329–38) © 2013 by the American College of Cardiology Foundation

From the *Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota; †Cardiology Department, AP-HP, Bichat Hospital, Paris, France; ‡INSERM U698 and University Paris 7–Diderot, Paris, France; and the §Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Quebec City, Québec, Canada. The study was funded in part by grants from the Assistance Publique–Hopitaux de Paris (PHRC national 2005 and PHRC regional 2007) and a grant (MOP# 114997) from the Canadian Institutes of Health Research, Ottawa, Ontario, Canada. Dr. Clavel holds a Vanier Canada Graduate Scholarship and a Michael Smith Foreign Study Supplements Scholarship, Canadian Institutes of Health Research, Ottawa, Ontario, Canada. Dr. Messika-Zeitoun has served as consultant to and received lecture fees from Edwards, Valtech, and Abbott. Dr. Pibarot holds the Canada Research Chair in Valvular Heart Diseases, Canadian Institutes of Health Research. R. Capoulade was supported by a studentship grant of International Chair of Cardiometabolic Risk, Quebec, Quebec, Canada. Dr. Vahanian has received honoraria and/or Speakers fees from Edwards Lifesciences, Abbot, Medtronc, and Valtech. Dr. Enriquez-Sarano has received research support from Abbott Vascular; and has served on the board of Valtech. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received May 2, 2013; revised manuscript received July 17, 2013, accepted August 17, 2013.

Abbreviations and Acronyms

AU = arbitrary units

AVAi = aortic valve area indexed to body surface area

AVC = aortic valve calcification

AVCd = aortic valve calcification indexed to the cross-sectional area of the aortic annulus

AVCi = aortic valve calcification indexed to body surface area

CG = concordant grading

DG = discordant grading

LV = left ventricular

LVEF = left ventricular ejection fraction

LVOT = left ventricular outflow tract

MDCT = multidetector computed tomography

MG = mean gradient

ROC = receiver-operating characteristic

SV = stroke volume

SVi = stroke volume indexed to body surface area

Vmax = peak aortic jet velocity

According to American and European clinical guidelines for the management of patients with valvular heart disease, severe aortic stenosis (AS) is defined by several criteria, including aortic valve area (AVA) $\leq$1.0 cm^2 or AVA indexed to body surface area (AVAi) $\leq$0.6 cm^2/m^2 and transvalvular mean gradient (MG) $\geq$40 mm Hg or peak aortic jet velocity (Vmax) $\geq$4 m/s (1,2).

See page 2339

This combination of criteria is simple to apply in clinical practice when concordant, but recent studies emphasized the frequency of discordant severity grading (DG), most often the coexistence of AVA $\leq$1 cm^2 or AVAi $\leq$0.6 cm^2/m^2 consistent with severe AS, with MG <40 mm Hg or Vmax <4 m/s that conversely indicates moderate AS (3–5). This situation raises uncertainty with regard to actual severity of AS and the potential indication of aortic valve replacement. Such decisions are crucial in mostly elderly patients, who incur high natural risks of AS if they are not referred to surgery (6) but also notable risks of cardiac surgery when referred to aortic valve replacement (7). These hesitations and risks are potential reasons for under-treatment of AS emphasized in publications from multiple sources, European and U.S., in academic centers or in the community (5,6,8,9).

A discordance in the AVA-gradient findings (i.e., tight AVA but low MG) is best known with depressed left ventricular ejection fraction (LVEF), understood as a low flow state (10) and widely considered logical. Patients with preserved LVEF and tight AVA might also present with low-gradient, and AS severity in such cases is controversial. This entity is described with variable prevalence and labeled "paradoxical low-gradient AS" (4,11) and is controversial in that it is considered alternatively severe (4,5) or moderate (12). Thus, it is currently unclear whether patients who present with AS and DG carry or do not carry a severe valve lesion and, clinically, which criteria to use in defining those severe valve lesions, warranting the use of an independent method to assess severity of the calcified aortic valve disease. Aortic valve calcification (AVC) load can be accurately quantified by multidetector computed tomography (MDCT) and is a fundamental marker of the aortic valve lesion of "degenerative" AS (13,14). This method provided important insight into sex differences with regard to pathophysiology of calcified aortic valve disease (15).

The objectives of our multi-imaging study of AS were to: 1) identify independent variables affecting the AVA-MG relationship and yielding low gradient; 2) define AVC load thresholds best segregating moderate and severe AS in the unadulterated AS form with normal LVEF, normal flow, and concordant grading (CG); and 3) assess, with these thresholds, the severity of calcified aortic valve disease in AS with discordant grading.

Methods

We prospectively recruited 646 adult AS patients with normal LVEF and at least moderate AS (MG $\geq$25 mm Hg, Vmax $\geq$2.5 m/s or AVA $\leq$1.5 cm^2) who underwent comprehensive Doppler echocardiography and MDCT within the same episode of care (<3 months between evaluations) in 3 centers: Mayo Clinic (Rochester, Minnesota), Hôpital Bichat (Paris, France), and Institut Universitaire de Cardiologie et de Pneumologie (Québec City, Québec, Canada). We excluded children <18 years of age, patients with identified sequels of rheumatic disease or endocarditis, those with moderate or severe mitral valve disease, and those with previous valve repair or replacement.

Patients from Hôpital Bichat and IUCPQ were enrolled in 3 ongoing prospective studies on AVC/stenosis (COFRASA [Aortic Stenosis in Elderly: Determinant of Progression (French Cohort)]; GENERAC [Genetic of Aortic Valve Stenosis–Clinical and Therapeutic Implications], and PROGRESSA [Metabolic Determinants of the Progression of Aortic Stenosis]). Mayo patients were enrolled in a prospective clinical research study initiated in the Valvular Heart Disease Clinic. An informed consent was obtained according to approval by each institutional review board.

Doppler echocardiography measurements. The left ventricular (LV) dimensions and LVEF were measured according to recommendations of the American Society of Echocardiography. Doppler echocardiographic left ventricular outflow tract (LVOT), Vmax, and time velocity integral allowed calculation of mean transvalvular pressure gradient (MG) by modified Bernoulli formula, dimension less velocity index, stroke volume (SV), and AVA by continuity equation. The AVA was also indexed to body surface area (AVAi). Peak aortic flow was obtained as the product of LVOT area and maximal flow velocity.

On the basis of AVAi and MG, patients were categorized in 4 groups:

2 CG groups:

- with moderate AS (AVAi >0.6 cm^2/m^2, MG <40 mm Hg) (CG-ModerateAS)
- with severe AS (AVA $\leq$0.6 cm^2/m^2, MG $\geq$40 mm Hg) (CG-SevereAS)

2DG groups:

- with low-MG (AVAi $\leq$0.6 cm^2/m^2, MG <40 mm Hg) (DG-LowMG)
- with high-MG (AVAi >0.6 cm^2/m^2, MG $\geq$40 mm Hg) (DG-HighMG)

Systemic arterial pressure was measured by arm-cuff sphygmomanometer simultaneous to Doppler SV measurement. The ratio of SV indexed to body surface area (SVi) to systemic pulse pressure was used as an indirect measure of systemic arterial compliance:

$$\textit{Systemic Arterial Compliance} = \frac{\textit{Stroke Volume Index}}{\textit{Systolic Blood Pressure} - \textit{Diastolic Blood Pressure}}$$

Multidetector computed tomography measurements. The non-contrast computed tomography was performed with multidetector scanners (SENSATION or SOMATOM, Siemens Medical Systems, Fordheim, Germany; MX 8000 IDT 16, Phillips Medical Systems, Andover, Massachusetts). The same methodology of image acquisition and interpretation was used in the 3 centers and was previously described (14,15).

Briefly, a scan run consisted of contiguous transverse slices triggered at 75% to 80% of the electrocardiographic R-to-R-wave interval. These were performed with a tube current of 42 to 1,312 A and a voltage of 120 to 130 kV. No contrast enhancement was needed, nor was beta-blocker administered for the purpose of the examination. Measurements of AVC were performed offline on dedicated workstations with validated software (heartbeat calcium scoring; Philips Medical Systems or Aquarius iNtuition, TeraRecon, Foster City, California) with the use of the Agatston method (16) and expressed in arbitrary units (AU). The aortic valve was visualized in multiple planes, and careful measurement section by section aimed to accurately exclude contiguous calcium in coronary arteries, mitral valve annulus, or aortic wall. Radiation exposure was typically 2 to 3 mSV. To account for inter-individual variability in body size, we calculated, besides the total AVC load, the following indexes: 1) AVC index (AVCi), where AVC was indexed to body surface area; and 2) AVC density (AVCd), where AVC was indexed to the cross-sectional area of the aortic annulus calculated from LVOT diameter measured by echocardiography at insertion of aortic valve cusps:

$$AVCd = \frac{AVC}{\pi \times \left(\frac{\textit{LV Outflow Tract Diameter}}{2}\right)^2}$$

The technologists and cardiologists performing the CT acquisitions and measurements were kept blinded to the clinical and Doppler echocardiographic data.

Statistical analysis. Results are expressed as mean $\pm$ SD, median (interquartile range), or percentages when appropriate. Continuous variables were tested for normality by the Shapiro-Wilk test, and testing of differences was selected accordingly. For normally distributed continuous variables, differences between groups were analyzed with the use of one-way ANOVA followed by the Tukey's post-hoc test for inter-group comparisons. The AVC, AVCi, and AVCd were not normally distributed and were thus presented by median and interquartile range and analyzed by Kruskal Wallis test followed by the Dunn's post-hoc test for inter-group comparisons. We used a squared root transformation to normalize AVC, AVCi, and AVCd; and all linear regression, correlation, and receiver-operating characteristic (ROC) curve analysis used squared-root-transformed levels. After squared-root transformation, these 3 variables were normally distributed with a $p > 0.52$.

Multivariable linear regression analysis was used to identify the independent predictors of MG and Vmax. Results were presented as estimate $\pm$ SE, standardized beta (that represent standardized partial regression weight of each parameter), and p value. Clinically relevant variables with a value of $p \leq 0.05$ on individual analysis were included in the multivariable model. Correlations between echocardiographic stenotic indexes and AVC were assessed with multiple regression models, and the equation providing the best fit was retained. Receiver-operating characteristic curve analysis was used to determine the sensitivity, specificity, and positive and negative predictive values of the various cutoff values of MDCT AVC parameters for the prediction of severe AS. The best thresholds are the ones with the best sum of sensitivity and specificity. The sensitive/specific thresholds are the thresholds with at least 95% sensitivity or 95% specificity. Percentages of correct classification were tested between variables by McNemar's test. A p value $\leq$0.05 was considered statistically significant. Statistical analyses were performed with SPSS (version 20.0, SPSS, Chicago, Illinois) and Table Curve (version 5.01, Systat Software, San Jose, California) software programs.

Results

AS grading. Among the 646 patients included in this study (Mayo clinic: 374; Hôpital Bichat: 165; Institut Universitaire de Cardiologie et de Pneumonogie de Québec: 107), 460 had concordant AS grading (CG), 174 (27%) with CG-moderate AS (AVAi >0.6 cm^2/m^2 and MG <40 mm Hg); 286 (44%) with CG-severe AS (AVA $\leq$0.6 cm^2/m^2 and MG $\geq$40 mm Hg). The remaining 186 patients had DG, 172 (27%) with low MG (AVAi $\leq$0.6 cm^2/m^2 and MG <40 mm Hg, DG-LowMG) and 14 (2%) with high MG (AVAi >0.6 cm^2/m^2 and MG $\geq$40 mm Hg, DG-HighMG) (Table 1).

Baseline characteristics according to AS grading. Overall, we included 258 (40%) women and 388 (60%) men with mean age of 74 $\pm$ 12 years; diabetes prevalence 22%, hypertension 69%, and coronary artery disease 39% (including 21% with history of coronary artery bypass grafting); overall, Vmax was 4.0 $\pm$ 0.9 m/s, MG was

Table 1 Classification of Patients According to Doppler Echocardiographic Assessment of Stenosis Severity

	AVAi $\leq$0.6 cm^2/m^2	AVAi >0.6 cm^2/m^2
MG $\geq$40 mm Hg	286 (44)	14 (2)
MG <40 mm Hg	172 (27)	174 (27)
V_{max} $\geq$4m/s	309 (48)	17 (2)
V_{max} <4m/s	147 (23)	173 (27)

Values are n (%).
AVAi = indexed aortic valve area; MG = mean gradient; Vmax = peak aortic jet velocity.

40 ± 19 mm Hg, AVA was 0.99 ± 0.26 cm^2, AVAi was 0.53 ± 0.14 cm^2/m^2, and LVEF was 64 ± 6%.

Table 2 shows the comparison of baseline characteristics between groups with concordant and discordant AS grading, with highMG and lowMG. Clinical data showed rare differences of small magnitude. A remarkable finding was the trend toward fewer women in the DG-LowMG group with consequent differences in body surface area but without differences in body mass index between CG-severe AS and the 2 DG groups. Doppler echocardiography showed differences in measures of AS severity directly related to the stratification. Some differences warrant emphasizing: the DG-LowMG group was characterized by lower flow as expected. Furthermore, the DG-LowMG was associated with slightly smaller LVOT area indexed-to-body surface area and low aortic compliance, particularly in contrast to the DG-HighMG. By MDCT, AVC, AVCi, and AVCd—overall and stratified by sex—were similar in the 2 DG groups, and these measures of severity of the calcified aortic valve disease were higher in the DG groups than in the CG-moderate AS (Figs. 1A and 1B, Table 2). The AVC, AVCi, and AVCd were also significantly higher in the CG-severe AS group than in all other groups. Among the DG-LowMG group, female sex (67% vs. 72%; $p = 0.64$), AVC (1,659 [976 to 2,531] vs. 1,364 [852 to 2,354] AU; $p = 0.56$), AVCi (887 [571 to 1,349] vs. 657 [382 to 1,182] AU/m^2; $p = 0.51$), and AVCd (417 [281 to 630] vs. 474 [258 to 720] AU/cm^2; $p = 0.82$) were similar in the 147 patients with normal flow (SVi >35 ml/m^2) and in the 25 patients with low flow (SVi $\leq$35 ml/m^2).

Determinants of MG and Vmax. In univariable analysis, MG and Vmax were associated with age ($p = 0.0004$ and $p = 0.002$, respectively), systolic blood pressure ($p = 0.004$ and $p = 0.007$, respectively), peak aortic flow ($p < 0.0001$ and $p < 0.0001$, respectively), SVi ($p < 0.0001$ and $p < 0.0001$, respectively), systemic arterial compliance ($p < 0.0001$ and $p < 0.0001$, respectively), AVAi ($p < 0.0001$ and $p < 0.0001$, respectively), AVC ($p < 0.0001$ and $p < 0.0001$, respectively), AVCi ($p < 0.0001$ and $p < 0.0001$, respectively), and AVCd ($p < 0.0001$ and $p < 0.0001$, respectively). After adjustment for age and sex, the independent predictors of MG or Vmax were peak aortic flow, systemic arterial compliance, AVAi, and AVCd (Table 3). Models using SVi as a measure of flow and predicting MG or Vmax were equivalent in beta coefficient and p values to those using peak aortic flow, but the latter were preferred to avoid tautological relationship with the compliance presented in Table 3.

Diagnostic value of MDCT for severe AS with CG and normal flow. In the 451 patients with normal flow (SVi >35 ml/m^2) and concordant AS grading (moderate or severe AS), AVC, AVCi, and AVCd were well-associated with all Doppler echocardiographic AS severity measures (i.e., AVAi, Vmax, and MG) (all $|r| > 0.68$ and all $p < 0.0001$) in men and women separately. The ROC curve analyses, in men and women separately, showed that best cutoff values to identify severe AS were AVC $\geq$1,275 AU in women and 2,065 AU in men, AVCi $\geq$637 AU/m^2 in women and 1,067 AU/m^2 in men, and AVCd $\geq$292 AU/cm^2 in women and 476 AU/cm^2 in men (Fig. 2, Table 4). Table 4 also indicates, in men and women separately, the specific or sensitive thresholds that provide either specificity $\geq$95% or sensitivity $\geq$95%, so that all values of AVC load measured can be interpreted in context. The AVCd was associated with the highest area under the ROC curve and percentage of correct classification, rather than AVC and AVCi (correct classification: 87 vs. 86 and 85%, respectively), but these differences did not reach statistical significance (all $p > 0.20$).

AVC load in patients with DG. We then used these cutoff values of AVC, AVCi, or AVCd established in patients with CG and normal flow to corroborate the presence of severe calcified aortic valve disease in patients with DG. Among patients with DG-HighMG AS, most of the patients (71% to 86% of patients, depending on the used criteria) had a high AVC load consistent with severe calcified aortic valve disease. In patients with DG-LowMG AS, at least one-half of the patients (45% to 66% of patients, depending on the used criteria) present high AVC load (Table 5).

Among patients with DG-LowMG, those with and without severe AVCd displayed small statistical differences in age (76 ± 10 years vs. 71 ± 11 years; $p = 0.03$) and systolic blood pressure (128 ± 18 mm Hg vs. 135 ± 18 mm Hg; $p = 0.03$). Hemodynamically, patients with and without severe AVCd had slightly different MG (32 ± 5 mm Hg vs. 27 ± 7 mm Hg; $p < 0.0001$), Vmax (3.7 ± 0.3 vs. 3.4 ± 0.5; $p < 0.0001$), although within the same range (gradient: 15 to 38 mm Hg; Vmax: 2.4 to 4.2 m/s). However, such minimal differences were clinically almost indistinguishable, emphasizing the importance of MDCT as being often the only tool to affirm severe calcific aortic valve disease.

Discussion

The main findings of this multicenter study are that: 1) among patients evaluated in clinical practice for AS, a large percentage present with discordant grading by Doppler; 2) although flow and AVA are major contributors to the observed MG, other factors, arterial compliance, and severity of valvular calcification affect considerably the MG due to AS and can lead to low MG despite severe AS; 3) in patients with concordant-AS grading, specific thresholds of AVC,

Table 2 Clinical, Doppler Echocardiographic, and MDCT Data According to Group Classification

	CG AS		DG AS		
	Moderate AS (n = 174) (27%)	Severe AS (n = 286) (44%)	High MG (n = 14) (2%)	Low MG (n = 172) (27%)	p Value
Clinical data					
Age, yrs	72 ± 12	75 ± 12	73 ± 14	73 ± 11	0.06
Female	72 (41)	124 (43)	7 (50)	55 (32)	0.08
Body mass index, kg/m²	27.2 ± 4.8*	28.7 ± 6.5†	27.7 ± 5.9	28.5 ± 5.7	0.04
Body surface area, m²	1.82 ± 0.21‡*	1.89 ± 0.25†	1.78 ± 0.23	1.92 ± 0.23†	0.0003
Systolic blood pressure, mm Hg	131 ± 18§	128 ± 19	116 ± 15†‡	131 ± 18§	0.008
Diastolic blood pressure, mm Hg	71 ± 11	70 ± 10	64 ± 10	71 ± 11	0.06
Heart rate, beat/min	67 ± 12	68 ± 13	70 ± 11	68 ± 12	0.56
Hypertension	121 (70)	192 (67)	10 (71)	124 (72)	0.77
Coronary artery disease	61 (35)	119 (42)	5 (36)	70 (40)	0.60
Diabetes	31 (18)	65 (23)	4 (29)	45 (26)	0.36
Hyperlipidemia	100 (58)	190 (66)	10 (71)	116 (67)	0.29
Previous CABG	30 (17)	69 (24)	5 (36)	31 (18)	0.22
Doppler echocardiographic data					
Vmax, m/s	2.98 ± 0.50‡§*	4.80 ± 0.55†‡§	4.40 ± 0.30†‡*	3.58 ± 0.41†§*	<0.0001
MG, mm Hg	21 ± 7‡§*	57 ± 13†‡§	46 ± 6†‡*	30 ± 7†§*	<0.0001
Dimensionless velocity index	0.35 ± 0.08‡§*	0.22 ± 0.08†‡§	0.29 ± 0.03†*	0.26 ± 0.05†*	<0.0001
AVA, cm²	1.29 ± 0.15‡§*	0.81 ± 0.17†‡§	1.17 ± 0.18†‡*	0.96 ± 0.18†§*	<0.0001
Indexed AVA, cm²/m²	0.71 ± 0.08‡*	0.43 ± 0.07†‡§	0.66 ± 0.04‡*	0.50 ± 0.07†§*	<0.0001
SVi, ml/m²	49 ± 9‡§	50 ± 9‡§	65 ± 11†‡*	43 ± 8†§*	<0.0001
LVOT diameter, cm	2.23 ± 0.23	2.22 ± 0.22	2.31 ± 0.21‡	2.22 ± 0.20§	0.04
LVOT area indexed to body surface area	2.17 ± 0.40	2.09 ± 0.38‡§	2.38 ± 0.26‡*	2.00 ± 0.32§*	<0.0001
LVEF, %	65 ± 5	64 ± 6§	69 ± 7‡*	64 ± 7§	0.03
LV mass index, g/m²	107 ± 26‡*	126 ± 36†‡	126 ± 25	110 ± 29*	<0.0001
SAC, ml/mm Hg/m²	0.88 ± 0.29‡§	0.93 ± 0.34‡§	1.34 ± 0.49†‡*	0.77 ± 0.26†§*	<0.0001
MDCT data					
AVC, AU					
Men	1,240‡§* (720–1,833)	2,695†‡§ (1,878–4,835)	2,617† (1,819–2,819)	1,926†* (1,214–2,695)	<0.0001
Women	487‡§* (251–890)	2,100†‡§ (962–3,096)	1,320†* (747–1,429)	1,145†* (854–1,743)	<0.0001
AVCi, AU/m²					
Men	659‡§* (378–983)	1,837†‡§ (1,316–2,492)	1,465† (1,426–1,875)	965†* (637–1,404)	<0.0001
Women	304‡§* (144–509)	1,174†‡ (875–1,807)	733†* (420–902)	660†* (479–953)	<0.0001
AVCd, AU/cm²					
Men	290‡§* (168–427)	877†‡§ (634–1,114)	575† (508–690)	466†* (312–701)	<0.0001
Women	142‡§* (74–273)	629†‡§ (457–882)	347†* (165–422)	374†* (252–885)	<0.0001

Values are mean ± SD, n (%), or median (interquartile range). Post-hoc Tukey tests: *Different ($p < 0.05$) from CG-severe AS; †different ($p < 0.05$) from concordant gradient (CG)-moderate aortic stenosis (AS); ‡different ($p < 0.05$) from discordant gradient (DG)-Low mean gradient (MG); §different ($p < 0.05$) from DG-High MG.

AU = arbitrary units; AVA = aortic valve area; AVC = aortic valve calcification; AVCd = aortic valve calcification indexed to the cross-sectional area of the aortic annulus; AVCi = aortic valve calcification indexed to body surface area; CABG = coronary artery bypass grafting; LV = left ventricular; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; MDCT = multidetector computed tomography; MG = mean gradient; SAC = systemic arterial compliance; SVi = stroke volume indexed to body surface area; Vmax = peak aortic jet velocity.

AVCi, and AVCd well-identify severe AS, making MDCT an important clinical tool; and 4) among patients with discordant-AS grading, one-half of those with tight AVA but low gradient present with severe AVC load, consistent with severe calcified aortic valve disease.

In current American clinical guidelines (1), there is no specific recommendation for the management of patients with DG-LowMG. In recent European guidelines (2), aortic valve replacement should be considered in symptomatic low-flow DG-LowMG AS after careful confirmation of AS severity. However, this subset of DG-LowMG patients is frequent, between 30% and 70% of diagnosed AS (5,12), and is challenging in terms of diagnosis and management. Indeed, a recent study (12) reported similar outcomes with DG-LowMG and with CG-moderate AS (better than with CG-severe AS) and thus should be followed under conservative management. However, other outcome studies reached different conclusions, suggesting that patients with AS and discordant grading, characterized by tight AS and low gradient, are at

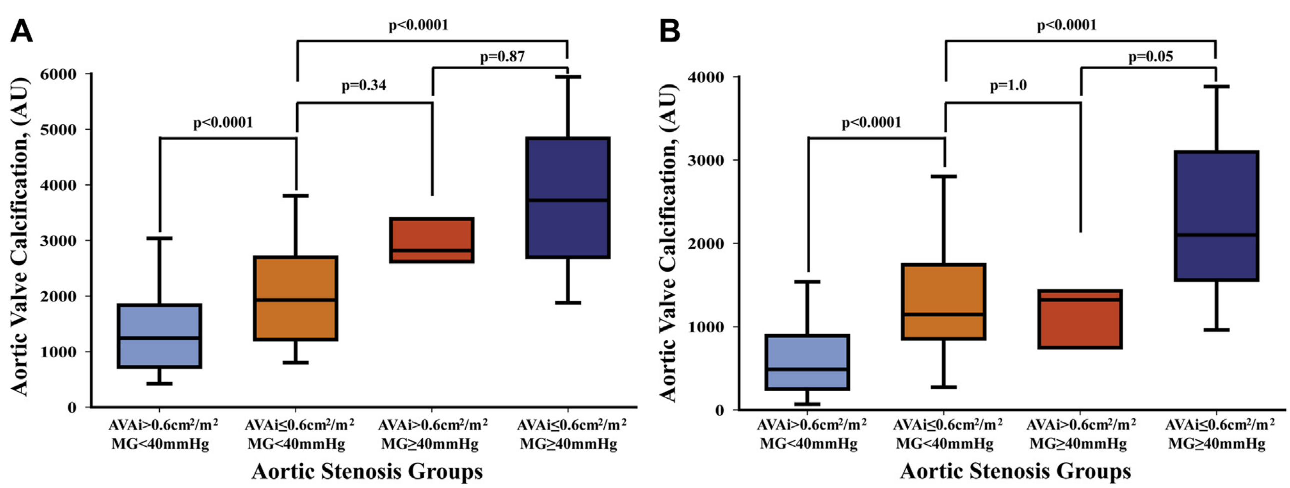

Figure 1 **Distribution of Aortic Valve Calcification by Sex in the Various AS Groups**

Concordant grading-moderate aortic stenosis (AS), discordant grading with low mean gradient (MG), discordant grading with high MG, and concordant grading-severe AS; x-axis in box-plot format, whereby the box indicates the 25th to 75th percentiles, the line within the box indicates the median, and the vertical bar indicates the 95% range. The y-axis indicates the aortic valve calcification load. **(A)** Data in men; **(B)** data in women. Of note, among patients with low MG, the overlap of aortic valve calcification between patients with severe AS (small AVA) and moderate AS (larger AVA) is more prominent in men than in women. AU = arbitrary units; AVAi = aortic valve area indexed to body surface area.

high risk for complications and mortality (4,5,17) and should be considered as having severe AS and be treated with aortic valve replacement (18–21). Thus, the nature of this syndrome of DG-LowMG AS has not been resolved by available outcome studies warranting novel analysis that takes into account the valvular lesion for which MDCT can provide new insights.

Indeed, since the early description of degenerative AS, the importance of valvular calcification has been emphasized as the main disease mechanism (22), for initiation (23) as well as progression (24). Thus, the magnitude of the calcified aortic valve disease defines the valve lesion (13,14,25) but also demonstrates the complexity of the AS hemodynamic status. The link between valve area and gradient, once thought to be purely related to flow, is shown by our study to be far more complex (26). Indeed, the presence of a relatively low gradient due to low flow (low SV) is much less frequent than low gradient with normal flow (27). Different studies suggested that reduced aortic compliance tends to be associated with decreased MG (28,29). Our multicenter clinical cross-sectional study is coherent with these observations, because reduced aortic compliance was found to independently determine lower gradient for any given flow and valve area. Moreover in the present study we showed that the association between systemic arterial compliance and gradient/velocity was as strong as that between flow and gradient/velocity (by similar standardized partial weight [beta] in the correlation models). This component of AS hemodynamic status is important (30) and might explain discordances between invasive hemodynamic status and Doppler in the context of hypertension and emphasizes the interest of measuring the total LV impedance in the context of AS (31). Another component of gradient variability is related to the AVC load. Patients with the largest load tend to present with the highest gradient independently of AVA and flow, probably in relation to differences in valvular inertia or shape (32), which might affect the C coefficient linking these variables in the Gorlin formula (33,34). Although errors in the Doppler

Table 3 **Univariable and Multivariable Analysis of Predictors of MG or Vmax**

	MG			Vmax		
	Estimate ± SE	β	p Value	Estimate ± SE	β	p Value
Age, yrs	−0.009 ± 0.04	0.005	0.82	−0.05 ± 0.18	−0.006	0.80
Female	6.66 ± 0.90	0.17	<0.0001	32.48 ± 4.16	0.17	<0.0001
Peak aortic flow, ml/s	2.39 ± 0.31	0.18	<0.0001	14.41 ± 1.57	0.19	<0.0001
SAC, ml/mm Hg/m^2	12.13 ± 1.40	0.21	<0.0001	60.25 ± 6.47	0.21	<0.0001
AVAi, cm^2/m^2	−75.30 ± 3.98	−0.55	<0.0001	−404.04 ± 18.54	−0.60	<0.0001
AVCd, AU/cm^2	0.78 ± 0.07	0.35	<0.0001	3.49 ± 0.33	0.32	<0.0001

AVAi = aortic valve area indexed to body surface area; β = standardized partial regression weight; other abbreviations as in Table 2.

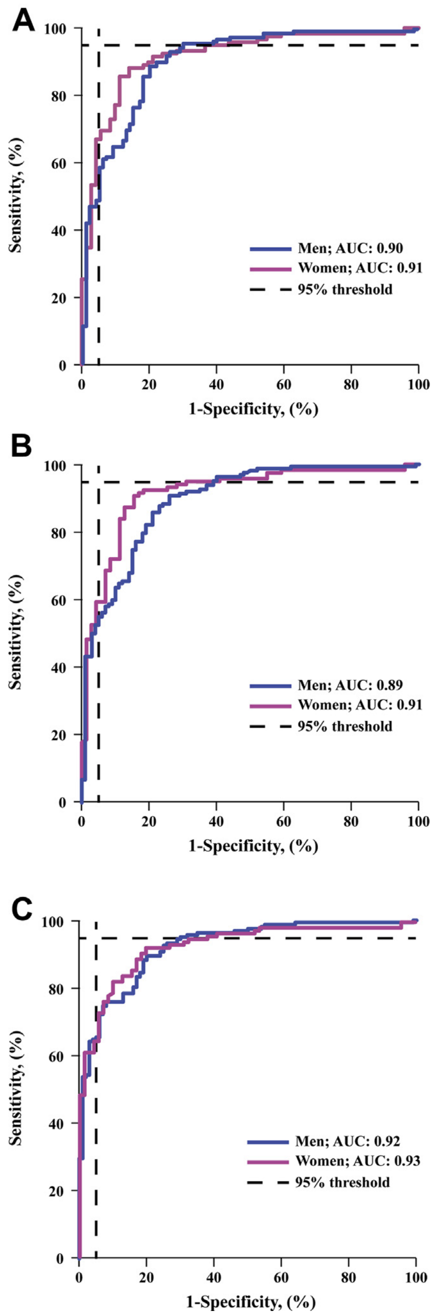

Figure 2 **Receiver-Operating Characteristic Curves to Identify Severe AS**

Receiver-operating characteristic curves to identify severe aortic stenosis (AS) in the subset of 451 patients with normal flow (stroke volume indexed to body surface area [SVi] >35 ml/m^2) for the different multidetector computed tomography indexes. Aortic valve calcification **(A)**, aortic valve calcification indexed to body surface area **(B)**, and aortic valve calcification indexed to cross-sectional area of left ventricular outflow tract **(C)**. The **dashed lines** represent 95% specificity **(vertical)** or 95% sensitivity **(horizontal)**. AUC = area under the curve.

echocardiographic measurements (i.e., underestimation of SV and AVA) might play a role in discordant grading (12,35), the strong link between echocardiographic AVA and survival (5) and in the present study the larger AVC load with DG-LowMG compared with CG-moderate AS suggest that errors should not be universally blamed for DG AS and that the diagnosis should be carefully individualized with appropriate tools and in particular with MDCT. Thus, our study underscores the complexity of the determinants of transvalvular gradient in the adult with AS and emphasizes the importance of MDCT as a clinical tool to assess the severity of the calcified aortic valve disease in the DG-low gradient patients that represent a conundrum in clinical practice.

Our large multicenter study provided the opportunity to analyze AVC thresholds separating most effectively moderate versus severe AS in a relatively pure subset with CG and normal SVi. We were thus able to define thresholds coherent with severe AS, particular to men and women, and also providing a sensitive, specific, and most accurate detection of severe AS, allowing fine-tuning for clinical interpretation. These criteria applied to patients with DG, particularly to those with low gradient, showed that one-half of these patients had evidence of severe calcified aortic valve disease on the basis of AVC load measured by MDCT, much more frequently than in patients with CG moderate AS. Hence, this large series provides evidence that patients with DG-Low MG should be comprehensively evaluated for AS, particularly by MDCT. An important finding is that the range of AVC load in patients with DG is wide, suggesting that this group is heterogeneous. Those with DG-LowG and low calcification might be the result of possible measurement errors (36), asymmetry of LVOT (37), inaccuracy of indexation to body size (particularly in obese patients), or low flow leading to pseudo-severe AS (38).

This heterogeneity underscores the importance of integrating all the information available. Although, in patients with low LVEF, dobutamine echocardiography is an important tool—allowing detection of pseudo-severe AS (39–41)—it is unclear how useful the test is in patients with preserved LVEF that might be in a low-flow state (4,17,38,42). In this context, AVC load is important, because it provides direct evidence of the aortic valve lesion severity in patients that cannot be recognized by any other clinical or rest echocardiographic mean. Higher AVC load is also associated with worse outcome (13,43), so that higher AVC load is a marker not just of hefty calcified aortic valve disease but also of future complications warranting—in addition to the other markers of severity of AS—consideration for aortic valve replacement. Our results suggest that AVC density (indexed to the area of the aortic annulus) provides the highest diagnostic value to corroborate AS severity, and AVC density ≥292 AU/cm^2 in women and 476 AU/cm^2 in men provide the highest sum of sensitivity and specificity to identify severe AS. Further studies are needed to assess the impact of AVC and AVC density on clinical outcome.

Study limitations and strengths. Doppler echocardiography has limitations in evaluating AS severity, but it is now the basis of guidelines for clinical management of AS. The reference grading by Doppler echocardiography was

Table 4 Accuracy of AVC, AVCi, and AVCd to Identify Severe AS

Sex	AUC	Threshold	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
AVC						
Women	0.91					
	Specific threshold	1,681*	69	95	95	65
	Best threshold	1,274*	86	89	93	79
	Sensitive threshold	791*	95	63	81	88
Men	0.90					
	Specific threshold	3,381*	59	95	95	59
	Best threshold	2,065*	89	80	88	82
	Sensitive threshold	1,661*	95	70	84	90
AVCi						
Women	0.91					
	Specific threshold	1,071†	59	95	96	59
	Best threshold	637†	91	85	91	85
	Sensitive threshold	476†	95	69	84	89
Men	0.89					
	Specific threshold	1,733†	55	95	95	57
	Best threshold	1,067†	86	79	87	77
	Sensitive threshold	776†	95	61	80	88
AVCd						
Women	0.93					
	Specific threshold	580‡	73	95	96	68
	Best threshold	292‡	92	81	87	86
	Sensitive threshold	228‡	95	68	83	89
Men	0.92					
	Specific threshold	727‡	65	95	95	63
	Best threshold	476‡	90	80	88	82
	Sensitive threshold	402‡	95	70	84	90

Accuracy of AVC, AVCi, and AVCd to identify severe AS in patients (n = 451) with preserved LVEF, normal flow (SVi >35 ml/m^2) and concordant AS grading at Doppler echocardiography according to sex. *AU; †AU/m^2; ‡AU/cm^2.
AUC = area under the curve; NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Table 2.

based on the purest set of patients, combining concordant grading by AVAi and MG, with normal flow and LVEF, leaving little room to doubt the AS severity.

The MDCT measurements were done in each institution, and this international collaboration was challenging for the exchange of images between centers. However, the training for calcium measurement was common and standardized in the 3 centers, and we arranged an inter-center investigator visit to address inter-observer variability as previously published (15). Moreover, all centers displayed similar relationships between hemodynamic AS severity and AVC load (the main aim of the present study) by covariance analysis (p = 0.42). The MDCT was used as a global AVC load, without specifying the spatial distribution of this load. In that regard, it is possible that future studies analyzing valve tissue versus annular and leaflet versus commissural calcification load might provide additional information on AS pathophysiology, but the present large study of global AVC load is the first to provide specific criteria allowing integration of MDCT into clinical practice management of AS in men and women.

Table 5 Prevalence of Patients With Evidence of Severe Stenosis on the Basis of AVC or AVCd Criteria

AVC Showing Severe AS	Patients With CG: Moderate AS (n = 174)	Patients With CG: Severe AS (n = 286)	Patients With DG: High MG (n = 14)	Patients With DG: Low MG (n = 172)
Absolute AVC				
Best cutoff	28 (16)	251 (88)	10 (71)	77 (45)
Sensitive cutoff	56 (32)	272 (95)	12 (86)	110 (64)
AVCd				
Best cutoff	33 (19)	260 (91)	10 (71)	91 (53)
Sensitive cutoff	53 (30)	272 (95)	12 (86)	114 (66)

Values are n (%).
Abbreviations as in Table 2.

The use of indexed AVA to classify AS severity was justified by the obvious link between body size and cardiac size, particularly aortic valve size, and hence AVA. Although AVAi might influence the group distribution, use of non-indexed AVA would overestimate stenosis severity in small patients and would introduce a bias between sexes and potentially limit the relevance of AVC threshold values. This approach did not lead to overestimate the DG-LowMG syndrome, which has been proven to be of high frequency in community studies (5,27).

Conclusions

This large multicenter series of patients with AS diagnosed in clinical practice shows that discordant grading of AS by

AVA and gradient is frequent. The combination of Doppler and MDCT with AVC measurement provides unique pathophysiologic insights into the determinants of discordant low gradients. Although flow and AVA are major contributors to the observed MG, other factors, arterial compliance, and severity of valvular calcification affect considerably the MG due to AS and can lead to low MG, despite severe AS. Hence, patients with discordant AVA-gradient at echocardiography require particular attention and might need additional diagnostic tests to confirm stenosis severity. To this effect, AVC quantification by MDCT might be helpful to identify patients with severe AS, specifically with AVC $\geq$1,274 AU in women and 2,065 AU in men or with AVC density (indexed to annulus cross-sectional area) $\geq$292 AU/cm^2 in women and 476 AU/cm^2 in men. Hence, among patients with discordant-AS grading, with tight AVA but low gradient, heavy AVC load—consistent with severe calcified aortic valve disease—is present in one-half of the patients, underscoring the potential of MDCT as an important clinical tool. However, the new thresholds of AVC proposed in the present study need to be validated by longitudinal studies with outcome data.

Reprint requests and correspondence: Dr. Maurice Enriquez-Sarano, Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic, 200 First Street Southwest, Rochester, Minnesota 55905. E-mail: sarano.maurice@mayo.edu.

REFERENCES

1. Bonow RO, Carabello BA, Kanu C, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol 2006;48:e1–148.
2. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J 2012; 33:2451–96.
3. Minners J, Allgeier M, Gohlke-Baerwolf C, Kienzle RP, Neumann FJ, Jander N. Inconsistencies of echocardiographic criteria for the grading of aortic valve stenosis. Eur Heart J 2008;29:1043–8.
4. Hachicha Z, Dumesnil JG, Bogaty P, Pibarot P. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. Circulation 2007; 115:2856–64.
5. Malouf J, Le Tourneau T, Pellikka P, et al. Aortic valve stenosis in community medical practice: determinants of outcome and implications for aortic valve replacement. J Thorac Cardiovasc Surg 2012;144:1421–7.
6. Bach DS, Cimino N, Deeb GM. Unoperated patients with severe aortic stenosis. J Am Coll Cardiol 2007;50:2018–9.
7. Ambler G, Omar RZ, Royston P, Kinsman R, Keogh BE, Taylor KM. Generic, simple risk stratification model for heart valve surgery. Circulation 2005;112:224–31.
8. Pellikka PA, Sarano ME, Nishimura RA, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. Circulation 2005;111:3290–5.
9. Iung B, Cachier A, Baron G, et al. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? Eur Heart J 2005;26:2714–20.
10. Harrison MR, Gurley JC, Smith MD, Grayburn PA, DeMaria AN. A practical application of Doppler echocardiography for the assessment of severity of aortic stenosis. Am Heart J 1988;115:622–8.
11. Barasch E, Fan D, Chukwu EO, et al. Severe isolated aortic stenosis with normal left ventricular systolic function and low transvalvular gradients: pathophysiologic and prognostic insights. J Heart Valve Dis 2008;17:81–8.
12. Jander N, Minners J, Holme I, et al. Outcome of patients with low-gradient "severe" aortic stenosis and preserved ejection fraction. Circulation 2011;123:887–95.
13. Messika-Zeitoun D, Aubry MC, Detaint D, et al. Evaluation and clinical implications of aortic valve calcification measured by electron-beam computed tomography. Circulation 2004;110:356–62.
14. Cueff C, Serfaty JM, Cimadevilla C, et al. Measurement of aortic valve calcification using multislice computed tomography: correlation with haemodynamic severity of aortic stenosis and clinical implication for patients with low ejection fraction. Heart 2011;97:721–6.
15. Aggarwal SR, Clavel MA, Messika-Zeitoun D, et al. Sex differences in aortic valve calcification measured by multidetector computed tomography in aortic stenosis. Circ Cardiovasc Imaging 2013;6:40–7.
16. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–32.
17. Lancellotti P, Magne J, Donal E, et al. Clinical outcome in asymptomatic severe aortic stenosis: insights from the new proposed aortic stenosis grading classification. J Am Coll Cardiol 2012;59:235–43.
18. Tarantini G, Covolo E, Razzolini R, et al. Valve replacement for severe aortic stenosis with low transvalvular gradient and left ventricular ejection fraction exceeding 0.50. Ann Thorac Surg 2011;91:1808–15.
19. Belkin RN, Khalique O, Aronow WS, Ahn C, Sharma M. Outcomes and survival with aortic valve replacement compared with medical therapy in patients with low-, moderate-, and severe-gradient severe aortic stenosis and normal left ventricular ejection fraction. Echocardiography 2011;28:378–87.
20. Pai RG, Kapoor N, Bansal RC, Varadarajan P. Malignant natural history of asymptomatic severe aortic stenosis: benefit of aortic valve replacement. Ann Thorac Surg 2006;82:2116–22.
21. Clavel MA, Dumesnil JG, Capoulade R, Mathieu P, Senechal M, Pibarot P. Outcome of patients with aortic stenosis, small valve area, and low-flow, low-gradient despite preserved left ventricular ejection fraction. J Am Coll Cardiol 2012;60:1259–67.
22. Monckeberg J. Der normale histologische bau und die sklerose der aortenklappen. Virschows Arch Pathol Anat 1904;176:472–514.
23. Otto CM, Kuusisto J, Reichenbach DD, Gown AM, O'Brien KD. Characterization of the early lesion of 'degenerative' valvular aortic stenosis. Histological and immunohistochemical studies. Circulation 1994;90:844–53.
24. Messika-Zeitound D, Bielak LF, Peyser PA, et al. Aortic valve calcification: determinants and progression in the population. Arterioscler Thromb Vasc Biol 2007;27:642–8.
25. Cowell SJ, Newby DE, Burton J, et al. Aortic valve calcification on computed tomography predicts the severity of aortic stenosis. Clin Radiol 2003;58:712–6.
26. DeGroff CG, Shandas R, Valdes-Cruz L. Analysis of the effect of flow rate on the Doppler continuity equation for stenotic orifice area calculations: a numerical study. Circulation 1998;97:1597–605.
27. Dumesnil JG, Pibarot P, Carabello B. Paradoxical low flow and/or low gradient severe aortic stenosis despite preserved left ventricular ejection fraction: implications for diagnosis and treatment. Eur Heart J 2010;31: 281–9.
28. Kadem L, Dumesnil JG, Rieu R, Durand LG, Garcia D, Pibarot P. Impact of systemic hypertension on the assessment of aortic stenosis. Heart 2005;91:354–61.
29. Cramariuc D, Cioffi G, Rieck AE, et al. Low-flow aortic stenosis in asymptomatic patients: valvular-arterial impedance and systolic function from the SEAS Substudy. J Am Coll Cardiol Img 2009;2:390–9.
30. Briand M, Dumesnil JG, Kadem L, et al. Reduced systemic arterial compliance impacts significantly on left ventricular afterload and function in aortic stenosis: implications for diagnosis and treatment. J Am Coll Cardiol 2005;46:291–8.

31. Hachicha Z, Dumesnil JG, Pibarot P. Usefulness of the valvuloarterial impedance to predict adverse outcome in asymptomatic aortic stenosis. J Am Coll Cardiol 2009;54:1003–11.
32. Gilon D, Cape EG, Handschumacher MD, et al. Effect of three-dimensional valve shape on the hemodynamics of aortic stenosis: three-dimensional echocardiographic stereolithography and patient studies. J Am Coll Cardiol 2002;40:1479–86.
33. Gorlin R, Gorlin S. Hydraulic formula for calculating the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. An Heart J 1951;41:1–29.
34. Cannon SR, Richards KL, Crawford M. Hydraulic estimation of stenotic orifice area: a correction of the Gorlin formula. Circulation 1985;71:1170–8.
35. Otto CM, Pearlman AS. Doppler echocardiography in adults with symptomatic aortic stenosis. Diagnostic utility and cost-effectiveness. Arch Int Med 1988;148:2553–60.
36. Michelena HI, Margaryan E, Miller FA, et al. Inconsistent echocardiographic grading of aortic stenosis: is the left ventricular outflow tract important? Heart 2013;99:921–31.
37. Messika-Zeitoun D, Serfaty JM, Brochet E, et al. Multimodal assessment of the aortic annulus diameter: implications for transcatheter aortic valve implantation. J Am Coll Cardiol 2010;55:186–94.
38. Clavel MA, Ennezat PV, Marechaux S, et al. Stress echocardiography to assess stenosis severity and predict outcome in patients with paradoxical low-flow, low-gradient aortic stenosis and preserved LVEF. J Am Coll Cardiol Img 2013;6:175–83.
39. Blais C, Burwash IG, Mundigler G, et al. Projected valve area at normal flow rate improves the assessment of stenosis severity in patients with low-flow, low-gradient aortic stenosis: the multicenter TOPAS (Truly or Pseudo-Severe Aortic Stenosis) study. Circulation 2006;113:711–21.
40. Clavel MA, Burwash IG, Mundigler G, et al. Validation of conventional and simplified methods to calculate projected valve area at normal flow rate in patients with low flow, low gradient aortic stenosis: the multicenter TOPAS (True or Pseudo Severe Aortic Stenosis) study. J Am Soc Echocardiogr 2010;23:380–6.
41. Nishimura RA, Grantham JA, Connolly HM, Schaff HV, Higano ST, Holmes DR Jr. Low-output, low-gradient aortic stenosis in patients with depressed left ventricular systolic function: the clinical utility of the dobutamine challenge in the catheterization laboratory. Circulation 2002;106:809–13.
42. Adda J, Mielot C, Giorgi R, et al. Low-flow, low-gradient severe aortic stenosis despite normal ejection fraction is associated with severe left ventricular dysfunction as assessed by speckle-tracking echocardiography: a multicenter study. Circ Cardiovasc Imaging 2012;5:27–35.
43. Rosenhek R, Binder T, Porenta G, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. N Engl J Med 2000;343:611–7.

Key Words: aortic valve calcification ▪ aortic valve stenosis ▪ Doppler echocardiography ▪ multidetector computed tomography.