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# The Complex Nature of Discordant Severe Calcified Aortic Valve Disease Grading

## New Insights From Combined Doppler Echocardiographic and Computed Tomographic Study

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**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 $\leq 0.6$ cm$^2$/m$^2$, MG $\geq 40$ mm Hg), discordant-severity-grading (DG) with low-MG (AVAi $\leq 0.6$ cm$^2$/m$^2$, MG $<40$ mm Hg), or high-MG (AVAi $>0.6$ cm$^2$/m$^2$, MG $\geq 40$ 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 $\geq 0.89$, sensitivity $\geq 86\%$, specificity $\geq 79\%$) 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

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**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).

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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: