JACC: CASE REPORTS VOL. 2, NO. 14, 2020

CASE REPORT

INTERMEDIATE

CLINICAL CASE SERIES

Subthreshold Aortic Valve Calcium Scores in Severe Aortic Stenosis and Transthyretin Cardiac Amyloidosis

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ABSTRACT

We have clinically observed that some patients with transthyretin cardiac amyloidosis and severe aortic stenosis may have lesser degrees of calcification than one might expect. We report a case series of 3 patients with transthyretin cardiac amyloidosis and severe aortic stenosis despite discordant aortic valve calcium scores. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2020;2:2205–9) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Use of computed tomography (CT) to confirm severity of aortic stenosis (AS) is advocated in patients with low-flow low-gradient (LFLG) AS, including patients with transthyretin (TTR) cardiac amyloidosis (CA) (1). Sex-specific aortic valve (AV) CT calcium scores (CSs) from the 2017 European Society of Cardiology (ESC) Valvular Heart Disease Guidelines state severe AS is considered likely with a score of ≥2,000 AU in males and ≥1,200 AU in females (2). Furthermore, these guidelines say that significant AS is unlikely with a score of <1,600 AU in males and <800 AU in females (2).

LEARNING OBJECTIVES

- Aortic valve calcium scores may not always be applicable in patients with severe aortic stenosis and cardiac amyloidosis, as stated in the sex-specific ESC guidelines.
- Assessment of aortic stenosis severity in patients with cardiac amyloidosis should never rely on 1 parameter alone; rather, such decisions should be based upon a composite, weighted average of the best available clinical and multimodality imaging data.

These authors have clinically observed that some patients with TTR CA and severe AS may have lesser degrees of calcification than one might expect. This paper reports a case series of 3 patients with TTR CA and severe AS, despite discordant AV CSs.

TTR CA was diagnosed as follows: confirmatory endomyocardial biopsy or a grade 2- or 3-positive 99m-technetium-labeled pyrophosphate (^{99m}Tc-PyP) and a negative monoclonal gammopathy screen (enabling TTR CA to be diagnosed reliably without the need for histology) (3). LFLG severe AS was diagnosed as follows: clinical symptoms and signs consistent

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Case Reports* author instructions page.

Manuscript received July 21, 2020; revised manuscript received September 29, 2020, accepted October 5, 2020.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2020.10.002

ABBREVIATIONS AND ACRONYMS

^{99m}Tc-PyP = technetium-99m pyrophosphate
AS = aortic stenosis
AU = Agatston units
AV = aortic valve
CA = cardiac amyloidosis
CS = calcium score
CT = computed tomography
LFLG = low-flow low-gradient
TTR = transthyretin

with severe AS along with echocardiographic parameters as follows: AV area <1 cm^2 and dimensionless index <0.25. LFLG severe AS was diagnosed with a stroke volume indexed to body surface area <35 ml/m^2 and a mean gradient of <40 mm Hg. LFLG was subdivided into paradoxical (left ventricular ejection fraction [LVEF] ≥50%) and classical ([LVEF <50%] subtypes). To further evaluate classical LFLG, severe AS (and exclude pseudostenosis), dobutamine stress echocardiography was performed as has been previously recommended (4–6). All patients had noncontrast CT performed from which AV CSs were retrospectively measured using Syngo.Via software (Siemens, Erlangen, Germany).

PRESENTATION

PATIENT 1. An 85-year-old male with a medical history of atrial fibrillation, hyperlipidemia, and heart failure was referred for further evaluation of heart failure. Echocardiography findings were consistent with severe classical LFLG AS versus pseudostenosis (Table 1). Dobutamine stress echocardiography was performed which confirmed the former. Echocardiography strain imaging was notable for apical sparing, and CA was suspected. Scanning with ^{99m}Tc-PyP was performed, which revealed increased uptake (grade 3) in the myocardium, thus confirming diagnosis of TTR CA. AV CS score was found to be 1,095 AU (Figure 1), less than the sex-specific ESC threshold (Figure 2). The patient was managed medically as he was too declined for either surgical aortic valve replacement or transcatheter aortic valve replacement (TAVR) according to the high-risk AVR team, based upon surgical risk and anatomy. He died 20 months later, after CA diagnosis.

PATIENT 2. A 79-year-old female was referred for TAVR evaluation because of congestive heart failure and severe AS. Her medical history was also notable for atrial fibrillation and immunoglobulin G monoclonal gammopathy with prominently increased left

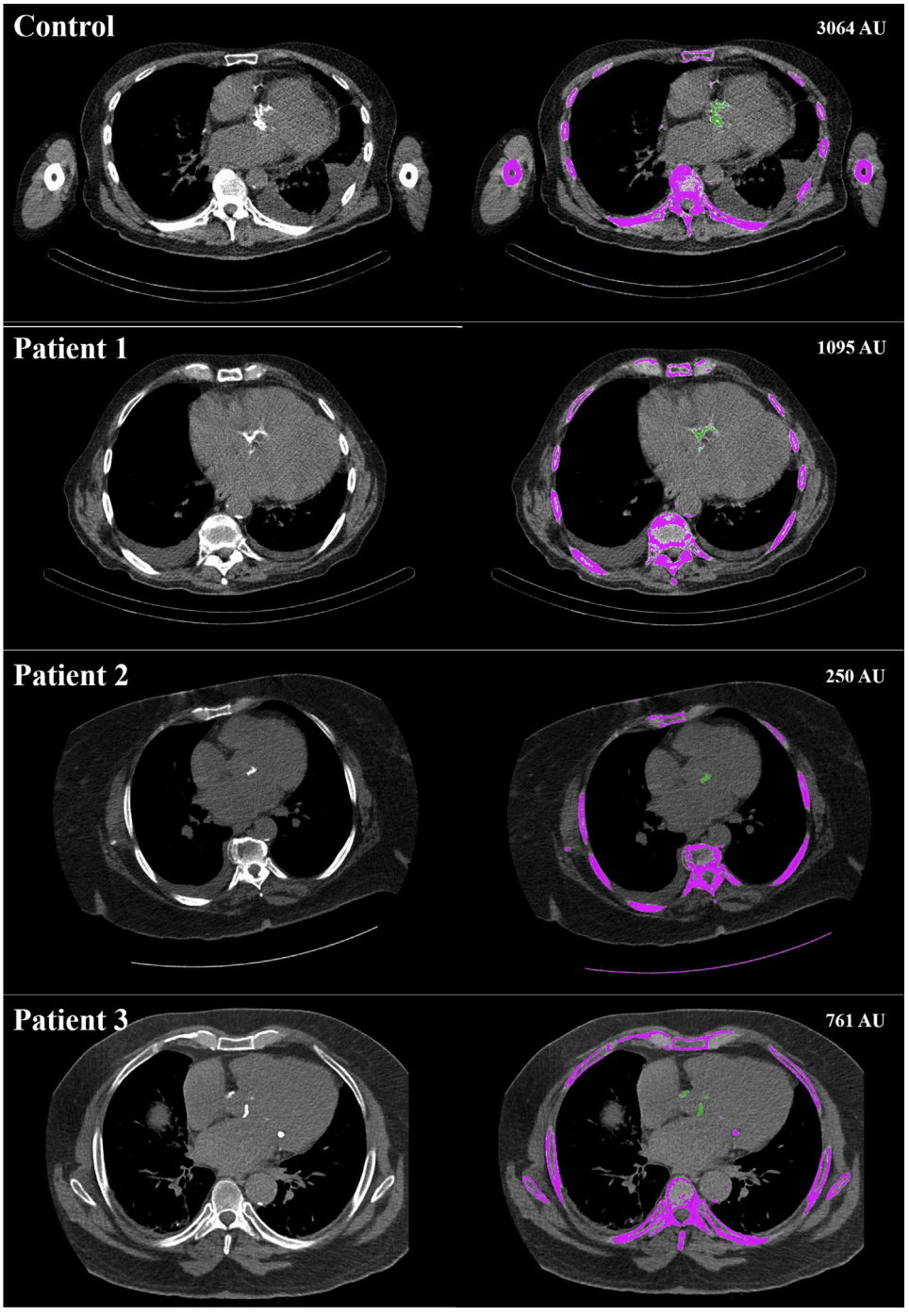
TABLE 1 Patient Characteristics

	Patient 1	Patient 2	Patient 3
Age, yrs	85	79	83
Sex	M	F	M
Race	African American	African American	White
CV risk factors			
Hyperlipidemia	+	+	+
Hypertension	0	+	+
Diabetes mellitus	0	+	0
Current/previous smoker	0	+	0
CT findings			
Aortic valve calcium score, AU	1,095	250	761
Aortic valve calcium density, AU/cm^2*	238	89	217
Hybrid aortic valve area, cm^2†	0.92	0.98	0.90
Echocardiography findings			
LFLG AS type	Classical	Paradoxical	Paradoxical
Left ventricular ejection fraction, %	40	64	52
Stroke volume index, ml/m^2 (low flow) <35 ml/m^2	32	23	24
Aortic valve area, cm^2 (severe = <1 cm^2)	0.96	0.89	0.82
Aortic valve area indexed to body surface area, cm^2/m^2 (severe = <0.6 cm^2/m^2)	0.50	0.40	0.36
Peak/mean aortic valve gradients, mm Hg (severe = mean >40 mm Hg)	35/25	31/17	43/18
Dimensionless index (severe = <0.25)	0.21	0.23	0.24
Acceleration time, ms	113	102	106
Acceleration time/ejection time (severe = >0.36)	0.38	0.38	0.47
Cardiac amyloid diagnosis	Clinical + diagnostic ^{99m}TC-PyP	Cardiac biopsy	Cardiac biopsy
Intervention	Medical management	TAVR	TAVR
Short-term outcome, 30 days	Alive	Alive	Alive
Survival time from Dx to death‡	20 months	2.5 months	19 months

*Aortic valve calcium density = calcium score over left ventricular outflow tract area by echocardiography (Male > Female). †Hybrid aortic valve area (LVOT area by CT and flow by echocardiography). ‡Dx = diagnosis; Time zero = time of diagnosis (^{99m}Tc-PyP scan date for patient 1; cardiac biopsy dates for Patients 2 and 3).

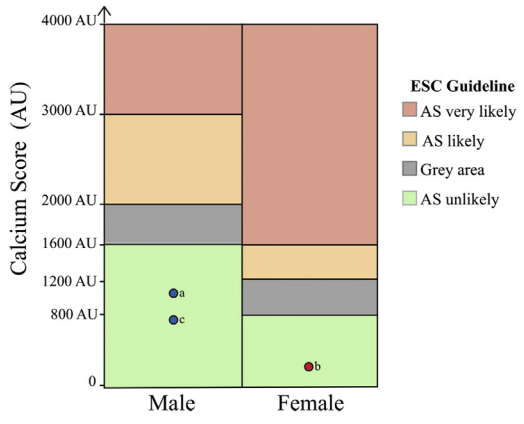
+ = presence of finding; 0 = absence of finding; AS = aortic stenosis; AU = Agatston units; CT = computed tomography; CV = cardiovascular; LFLG = low-flow low-gradient; LVOT = Left ventricular outflow tract; TAVR = transcatheter aortic valve replacement; ^{99m}Tc-PyP = technetium 99m-labeled pyrophosphate.

FIGURE 1 **Noncontrast Computed Tomography With Markup of Aortic Valve Calcium**



Noncontrast computed tomography images with markup of aortic valve calcium in Syngo.Via software for each patient in this case series. The control illustration represents a male patient pre-transcatheter aortic valve replacement with severe aortic stenosis. Aortic valve calcium markup represented in **green**. Any calcium uptake is shown in **pink**.

FIGURE 2 CT Aortic Valve Calcium Score for Each Patient Plotted Relative to the ESC Guideline for Severe Aortic Stenosis



a = Patient 1; b = Patient 2; c = Patient 3. AS = aortic stenosis; CT = computed tomography; ESC = European Society of Cardiology.

ventricular wall thickness. Echocardiography findings were consistent with severe paradoxical LFLG AS (Table 1). AV CS score was found to be 250 AU (Figure 1), less than the sex-specific ESC threshold (Figure 2). The patient successfully underwent TAVR. Concomitant myocardial biopsy taken during the procedure was positive for TTR CA. The patient was alive at 30 days post-TAVR without major complications and doing well in a nursing home but unfortunately died in hospice 2.5 months after valve replacement.

PATIENT 3. An 83-year-old male was referred for TAVR evaluation because of New York Heart Association (NYHA) functional class III heart failure and severe AS. His medical history was also notable for coronary artery disease, atrial fibrillation, hypertension, and hyperlipidemia. Echocardiography confirmed severe paradoxical LFLG AS (Table 1). AV CS score was found to be 761 AU (Figure 1), less than the sex-specific ESC threshold (Figure 2). The patient underwent successful TAVR. Concomitant myocardial biopsy taken during the procedure was positive for TTR CA. The patient was alive at 30 days post-TAVR without major complications. He died 19 months later, after valve replacement.

DISCUSSION

This clinical case series reports 3 patients with severe AS and concomitant CA, all of whom had AV CSs lower than the ESC threshold for severe AS (indeed, all 3 had AV CSs in the range in which AS would be considered unlikely).

These cases illustrate the fact that there exists a subcohort of CA patients who may develop severe AS in the absence of severe calcification (with calcium scores that, according to conventional guidelines, would even make a diagnosis of significant AS unlikely). For the cohort of patients in this series, strict adherence to conventional guidelines could lead to failure to recognize severe AS, which may have implications for quality of life and functional status (5,6). Perhaps for such patients, the remodeling may reflect more infiltrative changes with resultant restricted valve opening and valve stiffening and relatively less calcification. There are reports of high prevalence of localized amyloid deposition in AS which may be due to atheroinflammatory or hemodynamic function at the AV (7). This may indicate that AV CSs may be less applicable in a subset of patients with CA cohort to assess severity of AS or outcomes such as cardiac event rate, need for surgery and mortality (8,9). In the present case series, 2 patients underwent aortic valve interventions despite lower than threshold AV CS, highlighting how such decision making should never rely on 1 parameter alone but rather be based upon a composite, weighted average of the best available clinical and multimodality imaging data.

From a technical perspective, 1 point to note is that the median slice thickness in this study was 1 mm (CT guidelines for CS measurement recommend a slice thickness of 3 mm). Given that thinner slices result in higher CSs, the CSs reported here may even be overestimated, which would serve to simply strengthen our results (10).

CONCLUSIONS

This study is the first to report lower than expected AV CT CSs in a subcohort of CA patients with LFLG AS. These novel findings raise the question of why the AV CS may be lower in some patients with CA and caution against adjudication of severe AS on the basis of AV CS alone in these patients.

AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS aortic valve calcium score, cardiac amyloidosis, low-flow low-gradient aortic stenosis, severe aortic stenosis