Role of Multimodal Cardiac Imaging in Low-Flow, Low-Gradient Aortic Stenosis

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INTRODUCTION

Severe aortic stenosis (AS) is defined as a mean transvalvular aortic gradient (MG) $\geq$40 mm Hg or a peak aortic jet velocity (aortic V_{max}) $\geq$4.0 m/sec, and an aortic valve area (AVA) $\leq$1.0 cm^2.[1] However, >40% of patients with AS have a discordance between MG and AVA,[2] the most frequent cause being the presence of a stenosis with small AVA, low MG and low peak velocity.

The main objective of the present clinical case is to present the multimodal approach used in a patient with paradoxical low-flow, low-gradient (PLF-LG) AS (MG < 40 mm Hg, AVA $\leq$ 1.0 cm^2, left ventricular ejection fraction [LVEF] $\geq$ 50%, and stroke volume [SV] index < 35 mL/m^2).

CASE PRESENTATION

An 88-year-old man with a medical history of permanent atrial fibrillation, dual-chamber pacemaker placement for degenerative conduction system disease, group 3 pulmonary hypertension (obstructive sleep apnea syndrome and chronic obstructive pulmonary disease), and chronic kidney disease (Kidney Disease: Improving Global Outcomes stage IIIb) presented to our emergency department with 2 weeks of fatigue, dyspnea, and progressive lower extremity edema.

On physical examination, blood pressure was 100/60 mm Hg, pulse was 80 beats/min; respiratory rate was 30 breaths/min, and oxygen saturation was 84%. Cardiac auscultation revealed arrhythmic cardiac sounds with a first sound of variable intensity, a second sound with IIP reinforcement, and an ejection murmur in aortic area III/VI with

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Gallavardin's phenomenon in the apex. The lung fields presented bilateral infrascapular crackling rales and bilateral pleural effusion; the patient had a globular abdomen with ascites and edema of the lower extremities.

Electrocardiography indicated that the patient had atrial fibrillation with ventricular paced rhythm and left bundle branch block (Figure 1).

Laboratory investigations revealed high sensitivity troponin I of 83 ng/mL (normal range, 0-15 ng/mL), N-terminal pro–brain natriuretic peptide of 3,764 pg/mL (normal range, 0-125 ng/mL), hemoglobin of 11.8 g/dL, a leukocyte count of 8,100 per μL, a platelet count of 191,000 per μL, glucose of 118.4 mg/dL, creatinine of 2.25 mg/dL, blood urea nitrogen of 60.4 mg/dL, C-reactive protein of 3.43 mg/dL, and procalcitonin of 0.16 ng/dL.

Transthoracic echocardiography (TTE) showed biatrial enlargement, a normal LVEF (58%) using the method of disks, and normal left ventricular global longitudinal strain (−17.2%; Figure 2). Transthoracic echocardiographic evaluation revealed concentric left ventricular hypertrophy, moderate mitral regurgitation with a vena contracta of 0.5 cm, right ventricular systolic dysfunction (fractional area change 30%, tricuspid annular plane systolic excursion 16 mm, tricuspid S velocity 8.5 cm/sec), diastolic dysfunction with increased left ventricular filling pressures (E/e′ ratio = 16.3), a trileaflet aortic valve with severe calcification with extensive thickening resulting in severe restriction of leaflet opening, absence of aortic regurgitation, left ventricular outflow tract (LVOT) diameter of 2.2 cm, and an LVOT velocity-time integral of 12.6 cm resulting in a SV of 48 mL and an SV index (SVi) of 23 mL/m^2. The aortic V_{max} of 2.3 m/sec and MG of 14 mm Hg were discordant with the calculated AVA of 0.96 cm^2 and indexed AVA of 0.47 cm^2/ m^2. Blood pressure at the time of echocardiography was 100/60 mm Hg (Figure 3, Table 1).

Because of the discordance between AVA and MG, transesophageal echocardiography (TEE) was performed. TEE revealed an aortic valve with three calcified and thickened leaflets with severe restriction of the opening, resulting in an AVA by planimetry on three-dimensional multiplanar reconstruction of 0.71 cm^2 (Figure 4, Video 1). Because of the R-R variability that occurs in patients with atrial fibrillation, measurement of the averages of the data assessed by Doppler was performed: aortic V_{max} average = 2.7 m/sec, average MG = 17.9 mm Hg, AVA = 0.95 cm^2, indexed AVA = 0.47 cm^2/m^2, Doppler velocity index (DVI) = 0.23, SV = 57.3 mL, and SVi = 28.1 mL/m^2, without significant differences from the data obtained on TTE (Figure 5, Table 2).

PLF-LG AS was suspected, and the patient underwent multidetector computed tomography, revealing a calcium score of 2,581 Agatston units (AU) and aortic valve calcium density of 955.9 AU/cm^2 (Figure 6).

Echocardiography showed some evidence of restrictive heart disease, such as biatrial enlargement, left ventricular hypertrophy, and increased left ventricular filling pressures. However, no other "red

VIDEO HIGHLIGHTS

Video 1: Two-dimensional TEE, zoomed short-axis view, demonstrating the aortic valve with three calcified leaflets and severe thickening. There is severe restriction of the opening, suggesting severe AS.

Video 2: CMR, stacked steady-state free precession sequences, short-axis views of the tips of the aortic valve leaflets, demonstrating the stenosis with severe restriction of the opening (*red asterisk*). A pacemaker artifact can be seen in the right heart (*yellow asterisk*).

Video 3: CMR, stacked steady-state free precession sequences, three-chamber views of the LVOT, demonstrating AS, mild aortic regurgitation, moderate mitral regurgitation, and a small pericardial effusion. Pacemaker generator and pacer wire artifacts are seen.

View the video content online at www.cvcasejournal.com.

flags" for transthyretin cardiac amyloidosis were observed. Considering the advanced age of the patient and the presence of AS, as well as the association between low-gradient AS and cardiac amyloidosis, we decided to perform cardiovascular magnetic resonance (CMR) and a pyrophosphate scan. The results of the pyrophosphate scan were not consistent with transthyretin cardiac amyloidosis (Figure 7). CMR was performed, revealing an LVEF of 63%, a right ventricular ejection fraction of 43%, AVA of 0.87 cm^2, indexed AVA of 0.46 cm^2, aortic V_{max} of 2.4 m/sec, and an MG of 15 mm Hg (Figure 8, Video 2). Mild aortic regurgitation was present, as was moderate mitral regurgitation, with a mitral regurgitant volume of 39 mL, a mitral regurgitant fraction of 50%, and a small pericardial effusion (Video 3). A late gadolinium enhancement sequence was also not consistent with cardiac amyloidosis (Figure 9). Blood pressure at the time of CMR was 110/60 mm Hg.

The heart team decided to perform transcatheter aortic valve implantation (TAVI), and computed tomographic angiography performed before the procedure corroborated the LVOT area without demonstrating relevant changes with respect to AVA estimation on TEE and TTE (Figure 10, Table 2). TAVI was performed without complications. Postprocedural echocardiography showed normal function of the percutaneous bioprosthesis, with no evidence of paravalvular leaks: MG = 6.7 mm Hg, aortic V_{max} = 1.7 m/sec, AVA = 2.3 cm^2, and SVi = 44 mL/m^2.

After TAVI, the clinical picture of heart failure was improved, and the patient was discharged after 5 days and currently continues with improvement in functional class, tolerating daily activity at 7 METs.

DISCUSSION

Degenerative AS is the most common valvular pathology and the most common indication for valve intervention in high-income countries.[3] A precise evaluation of the severity of AS is crucial for

patient management and risk stratification and to allocate symptoms legitimately to the valvular disease. Currently, the European guidelines for the management of valvular heart disease define four categories of AS[4]:

1. high-gradient AS, in which severity can be assumed independent of cardiac function and flow conditions (AVA ≤ 1.0 cm^2, MG ≥ 40 mm Hg, and aortic V_{max} ≥ 4.0 m/sec);
2. low-flow, low-gradient AS with reduced LVEF (LVEF ≤ 50%, AVA ≤ 1.0 cm^2, MG ≤ 40 mm Hg, and SVi ≤ 35 mL/m^2);
3. low-flow, low-gradient AS with preserved LVEF (LVEF ≥ 50%, AVA ≤ 1.0 cm^2, MG ≤ 40 mm Hg, and SVi ≤ 35 mL/m^2), also known as paradoxical AS; and
4. normal-flow, low-gradient AS with preserved LVEF (LVEF ≥ 50%, AVA ≤ 1.0 cm^2, MG ≤ 40 mm Hg, and SVi > 35 mL/m^2); these patients usually present with moderate AS.

In this case, the patient presented with low-flow, low-gradient AS with preserved LVEF, which corresponds to paradoxical AS. In this scenario, it is important to rule out errors in echocardiographic measurements. An underestimation of the LVOT measurement can result in an underestimation of SV and AVA. To try to reduce these errors, the following steps are recommended:

1. Calculate the DVI; if this measurement is >0.25, an underestimation of the LVOT should be suspected.[5]
2. If possible, SV should be corroborated using another method (two-dimensional Simpson or three-dimensional volume).[6]

In our patient, the DVI was 0.24, which ruled out an underestimation of LVOT measurement. Computed tomographic angiography performed before TAVI corroborated the severity of AS (Table 2). We confirmed a low-flow state with an SVi of 23.0 mL/m^2 and a transvalvular flow rate (Q) of 53.3 mL/sec on TTE and 28.1 mL/m^2 and 63.6 mL/sec, respectively, on TEE.[7]

When transvalvular flow rate is low, the aortic valve may not open sufficiently to represent the true AVA. Hence, AVA at low transvalvular flow rate is not necessarily representative of true AS severity.

The best way to address this issue is to use a quantitative and reliable flow-independent method for the assessment of AS severity, which is the remarkable characteristic of calcium scoring. This method allows an "anatomic" evaluation of AS and not a "hemodynamic" evaluation, as this method does not capture valvular fibrosis, which contributes to AS. Using computed tomography, an aortic valve calcium score ≥2,000 AU in men and ≥1,200 AU in women or an aortic valve density of ≥500 AU/cm^2 in men and ≥300 AU/cm^2 in women corroborates the presence of severe AS.[6] The aortic calcium score in the present case was 2,581.5 AU, suggesting severe AS. Our patient was evaluated using multimodality imaging to verify the diagnosis of discordant AS (Figure 11).

In the diagnostic algorithm of patients with AS with "low flow" behavior, it is important to identify potential causes of this pathophysiology, such as decreased LVEF, restrictive left ventricular physiology, decreased global longitudinal strain, mitral valve disease, decreased right ventricular function, and atrial fibrillation.[6] Our patient fulfilled several of these characteristics, such as decreased right ventricular function, restrictive left ventricular physiology, moderate mitral regurgitation, and the presence of atrial fibrillation. All these factors are causes of reduced
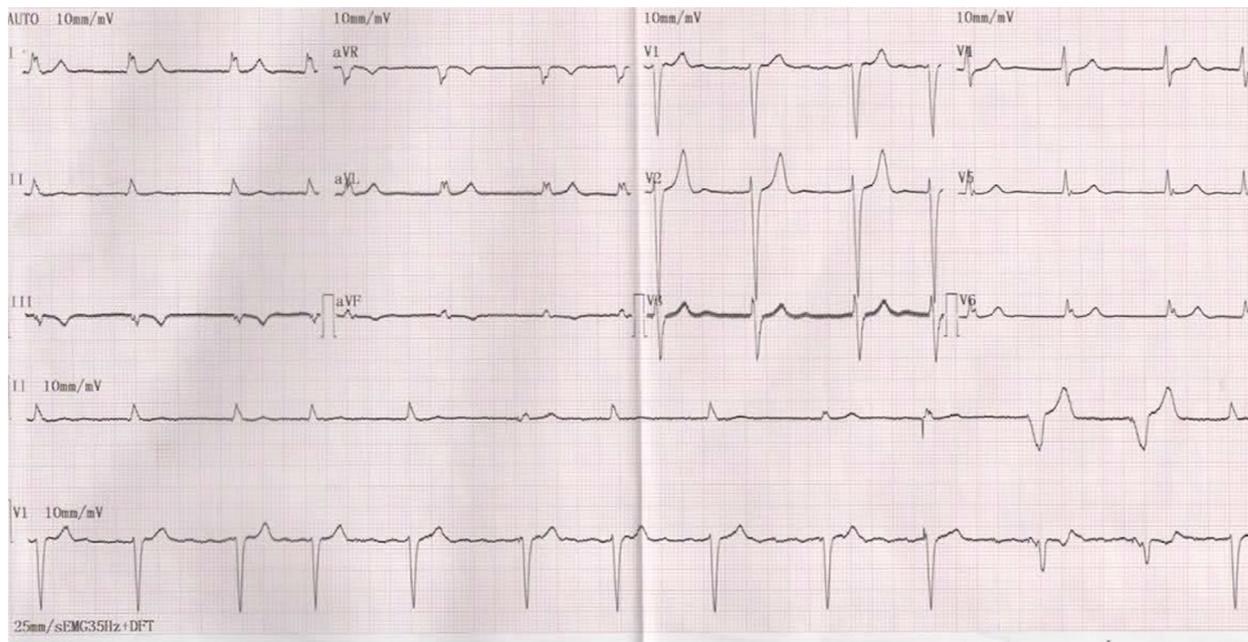
Figure 1 Electrocardiogram showing atrial fibrillation with ventricular paced rhythm and left bundle branch block.
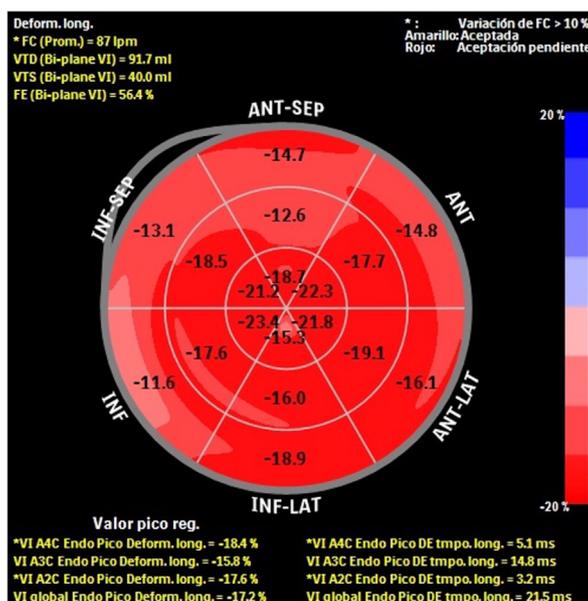
Figure 2 Two-dimensional TTE-acquired left ventricular global longitudinal strain bull's-eye display demonstrating a normal pattern and a normal value of -17.2%.

LVOT diameter: 2.2 cm
SV: 48 mL
SVi: 23 ml/m²
AVA: 0.96 cm²
Index AVA: 0.47 cm²/m²
DVI:0.24
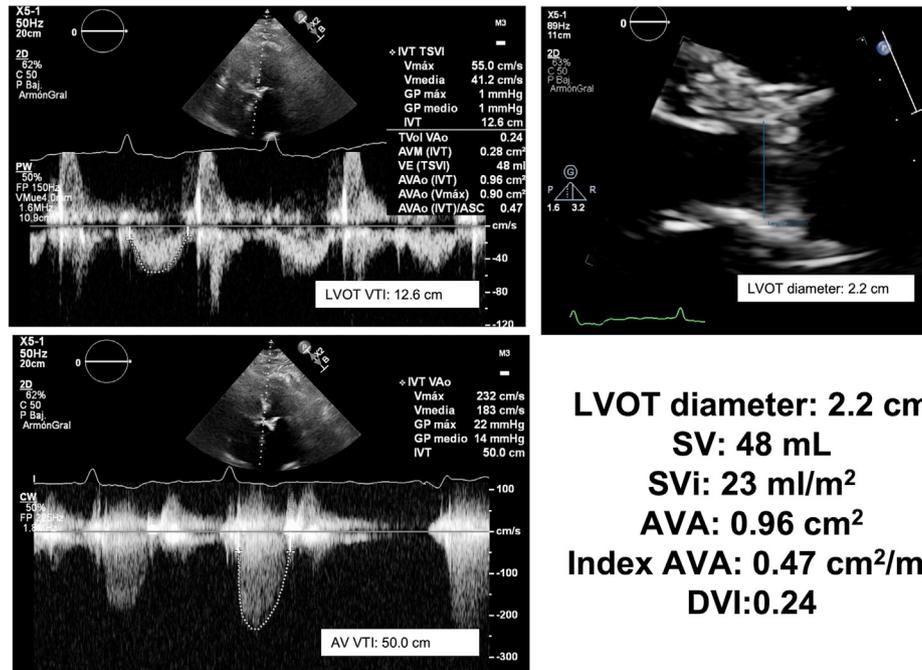
Figure 3 Two-dimensional TTE-guided pulsed-wave (*top left*) and continuous-wave (*bottom left*) Doppler data findings: aortic V_{max} = 2.3 m/sec, MG = 14 mm Hg, AVA = 0.96 cm², indexed AVA = 0.47 cm²/m², SV = 48 mL, SVi = 23 mL/m², and DVI = 0.24. Zoomed parasternal long-axis image of the LVOT diameter (*top right*) demonstrates a maximal diameter of 2.2 cm.

Table 1 Transthoracic echocardiographic measurements

Variable	Value	Normal value
Aortic annulus, cm	2.2	2.6 ± 0.3
Sinuses of Valsalva, cm	2.7	3.4 ± 0.3
Proximal ascending aorta, cm	3.0	2.9 ± 0.3
LVOT VTI, cm	12.6	20.8 ± 2.1
Aortic valve VTI, cm	50	-
LV ejection time, sec	0.9	-
AVA, cm²	0.96	-
AVA index, cm²/m²	0.47	-
DVI	0.24	-
SV, mL	48	-
SVi, mL/m²	23	≥ 35 mL/m²
Transvalvular flow rate (Q), mL/sec	53.3	-
3D AVA, cm²	0.71	-

3D, Three-dimensional; *LV*, left ventricular; *VTI*, velocity-time integral.
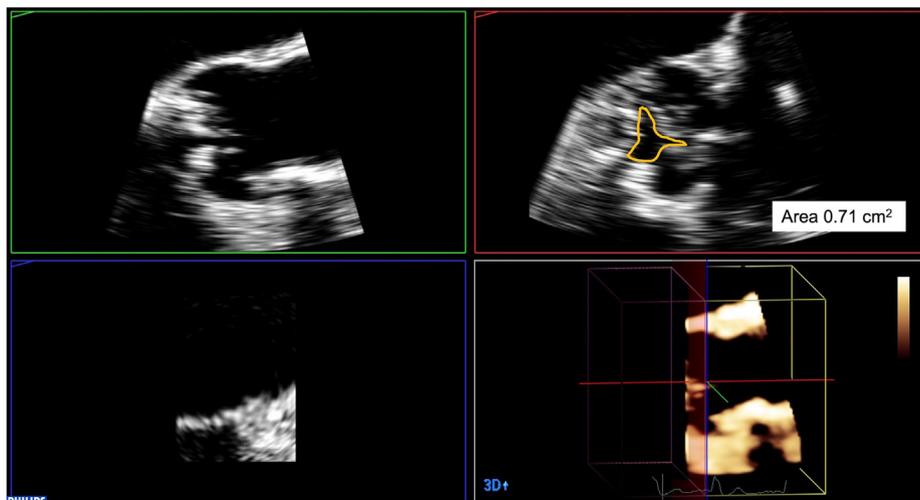
Figure 4 Three-dimensional TEE, multiplanar reconstruction, standard quad display (with long-axis, short-axis cut-planes, and volume-rendered displays), demonstrating aortic valve systolic area of 0.71 cm^2.

Table 2 Comparison among measurements on TTE, TEE, CT, and CMR

Variable	TTE	TEE	CT	CMR
LVOT VTI, cm	12.6	13.8	—	—
Aortic valve VTI, cm	50	60.3	—	—
LV ejection time, sec	0.9	0.9	—	—
LVOT diameter, cm	2.2	2.3	2.1 × 2.6	—
LVOT area, cm^2	3.8	4.15	5.2	—
AVA, cm^2	0.96	0.95	—	0.94
AVA index, cm^2/m^2	0.47	0.47	—	0.46
SV, mL	48	57.3	65.5	78
SVi, mL/m^2	23.41	27.95	32.76	38
Transvalvular flow rate (QR), mL/sec	53.3	63.6	69.4	—

CT, Computed tomography; *LV*, left ventricular; *VTI*, velocity-time integral.

transvalvular flow and decreased transvalvular aortic MG even though the systolic function is preserved.

In our patient, we observed that SVi increased after TAVI. Several studies have demonstrated that TAVI improves ventriculoarterial coupling, resulting in improved cardiovascular efficiency overall in treated patients with AS.

Finally, it is important to keep in mind that the association of low-flow AS and cardiac amyloidosis is relatively frequent, so it is necessary to consider the "red flags" for this entity, such as advanced age, male sex, deafness, carpal tunnel syndrome, disproportionate heart failure symptoms, and lumbar spinal stenosis.[8] Studies in patients with AS reported a prevalence of transthyretin cardiac amyloidosis of 4% to 29%.[8] Accordingly, we performed a pyrophosphate scan and CMR, with negative results for the presence of cardiac amyloidosis in the present case.

CONCLUSION

The diagnosis of "discordant" AS is a challenge, causing uncertainty about AS severity. Therefore, a comprehensive echocardiographic evaluation combined with multimodal imaging is essential for accurate diagnosis. Furthermore, it is important to diagnose cardiac amyloidosis in patients with low-flow, low-gradient AS, as pharmacologic therapies may improve their survival.

ETHICS STATEMENT

The authors declare that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.
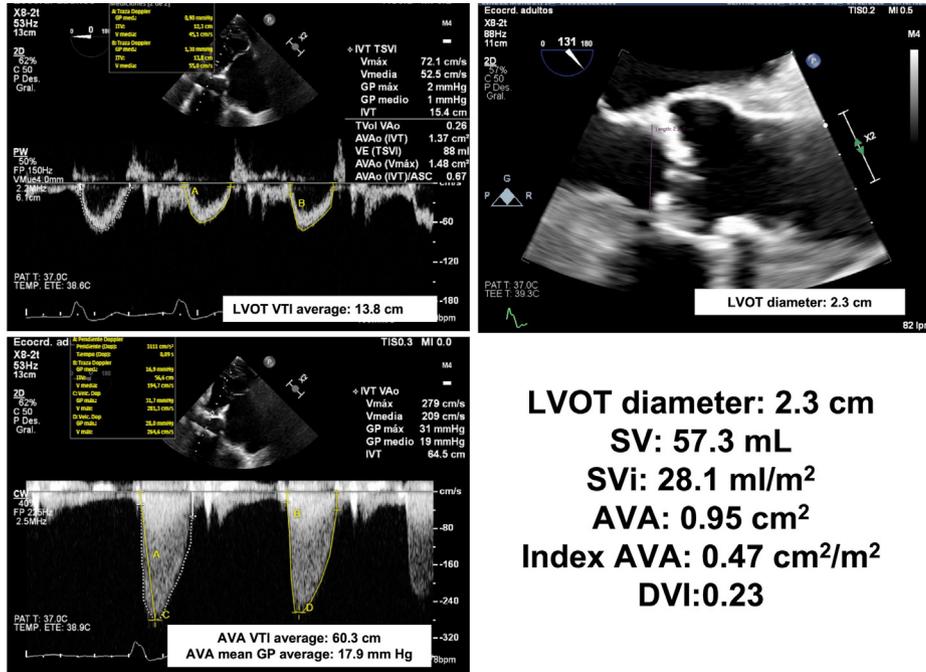
Figure 5 Two-dimensional TEE-guided pulsed-wave (*top left*) and continuous-wave (*bottom left*) Doppler findings demonstrate average aortic V_{max} of 2.7 m/sec, average MG of 17.9 mm Hg, AVA of 0.95 cm^2, indexed AVA of 0.47 cm^2/m^2, DVI of 0.23, SV of 57.3 mL, and SVi of 28.1 mL/m^2. Zoomed apical long-axis image (131°) of the LVOT diameter (*top right*) demonstrating a maximal diameter of 2.3 cm.

Figure 6 Multidetector computed tomography with aortic valve calcium score of 2,581 AU and aortic valve calcium density of 955.9 AU/cm^2.
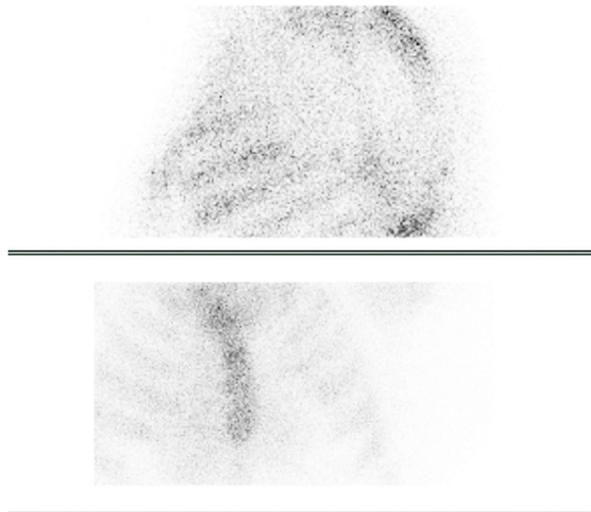
Figure 7 Nuclear pyrophosphate planar scans, sagittal (*top*) and frontal (*bottom*) displays, demonstrating no cardiac uptake.
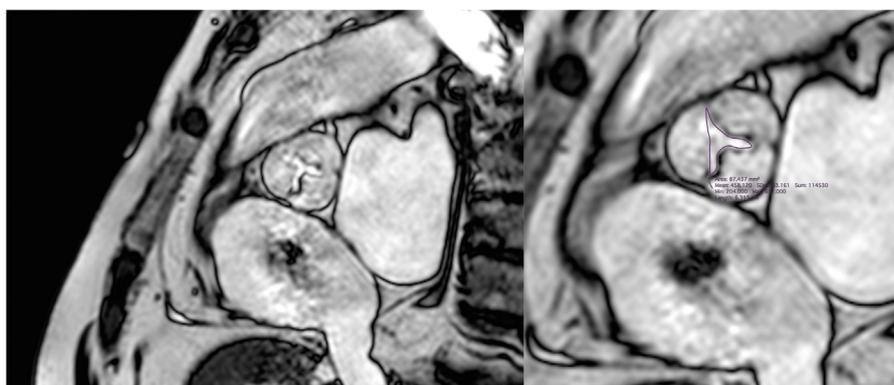
Figure 8 CMR, steady-state free precession sequence, sagittal display (*left*) and zoomed systolic image (*right*), demonstrating AS with a planimetered AVA of 0.87 cm^2 (indexed AVA 0.46 cm^2).
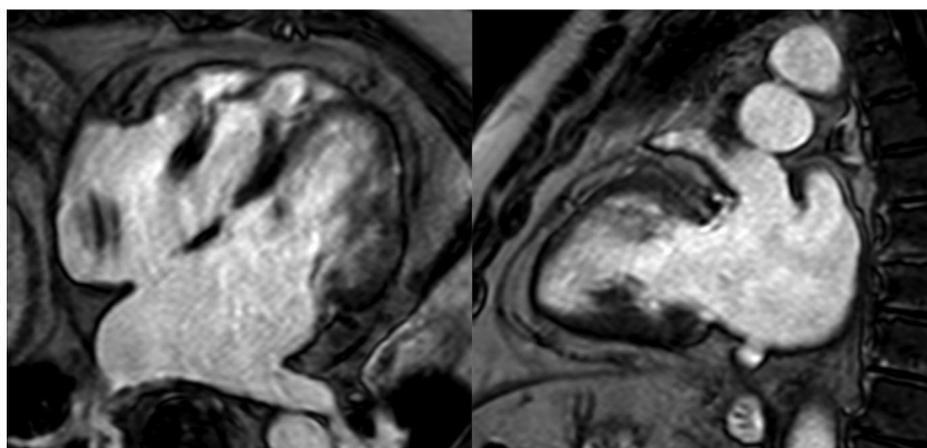
Figure 9 CMR, late gadolinium enhancement (LGE) sequence, four-chamber (*left*) and two-chamber (*right*) display, demonstrating biatrial enlargement and a normal LGE pattern without evidence of myocardial fibrosis, scarring, or findings that suggest cardiac amyloidosis.
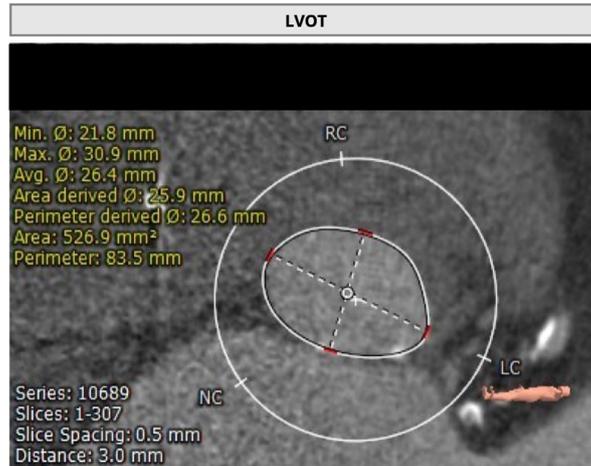
Figure 10 Multidetector computed tomographic angiography, zoomed short-axis display of the aortic valve and LVOT, demonstrating pre-TAVI measurements.
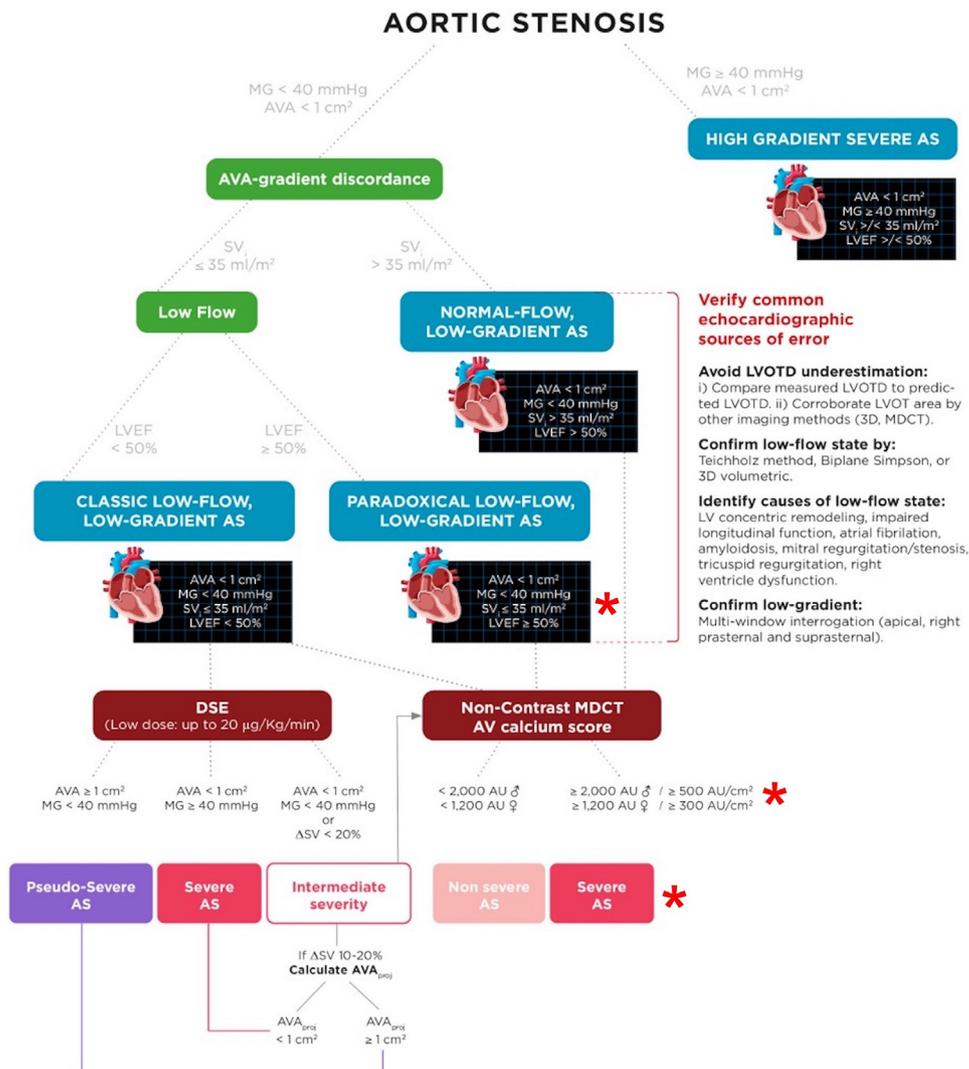
Figure 11 Algorithm for AS severity. *AVA_proj*, Projected aortic valve area; *ΔSV*, SV increment. *Represents findings in our patient. Adapted with permission from Silva I, Salaun E, Côté N, Pibarot P. Confirmation of aortic stenosis severity in case of discordance between aortic valve area and gradient. *J Am Coll Cardiol Case Rep*. 2022;4:170-177.

CONSENT STATEMENT

Complete written informed consent was obtained from the patient (or appropriate parent, guardian, or power of attorney) for the publication of this study and accompanying images.

FUNDING STATEMENT

DISCLOSURE STATEMENT

The authors report no conflict of interest.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.case.2023.03.003.

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