Progression of Valvular Pulmonic Stenosis in Adulthood: Never Say Never

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INTRODUCTION

The estimated prevalence of adults living with congenital heart disease (CHD) is 3,000 per million,[1] and valvular pulmonic stenosis (PS) is one of the most common forms of CHD, occurring in 5% to 7% of patients.[2] Patients with mild native valvular PS who do not require an intervention during childhood have a reassuring natural history, with the largest study reporting no increase in gradient over 25-year follow-up.[3] However, as 75% of patients with CHD who are alive at age 18 now live into their 60s,[4] the long-term natural history is still evolving. Here we describe a case of mild PS that progresses in late adulthood, highlighting the importance of lifelong follow-up for adults with CHD.

CASE PRESENTATION

An 80-year-old man was referred to the adult CHD (ACHD) clinic for evaluation of dyspnea on exertion. The patient was diagnosed with valvular PS at age 7 and followed by pediatric cardiology but was lost to follow-up in adulthood. At age 61 they underwent percutaneous coronary intervention for significant coronary artery stenosis, and at age 62 the patient was seen for the first time in an ACHD clinic for dyspnea. Right heart catheterization (RHC) was performed showing mild valvular PS with doming of the leaflets during systole (Videos 1 and 2), although peak-to-peak gradient from the right ventricle (RV) to the pulmonary artery (PA) was only 18 mm Hg (Table 1) with trivial to mild pulmonary regurgitation (PR; Video 2). In addition, there was left PA dilation visualized on the angiograms (Video 3). It was determined the mild valvular PS was not the etiology for the patient's dyspnea at that time, and subsequently they resumed follow-up with their interventional cardiologist.

The patient underwent 2 further coronary angiograms with percutaneous coronary intervention, as well as 2 subsequent RHC and transthoracic echocardiography (TTE) exams at age 67 and 74, showing progression of PS from the mild to the moderate range (Table 1). Contrast-enhanced chest computed tomography (CT) scan (at age 67) was significant for left PA enlargement (measuring 4.3 × 4.2 cm) and a trileaflet pulmonary valve (PV) without calcifications (Figure 1).

The patient did well until age 80, when they developed dyspnea on exertion once again, and repeat coronary angiography showed patent stents and no obstructive coronary disease. However, an outside TTE suggested severe PS; thus, they were referred to the ACHD clinic once again. Physical examination was significant for normal jugular venous pressure and a III/VI systolic murmur at the left sternal border with an early diastolic murmur. ATTE revealed severe PS with a thickened PV and flow acceleration and turbulence across the PV with color-flow Doppler, but no evidence of subvalvular obstruction (Figure 2, Videos 4-8). The peak velocity across the right ventricular

VIDEO HIGHLIGHTS

Video 1: Pulmonary angiogram during cardiac catheterization, left anterior oblique (LAO) projection, showing thickened PV with doming during systole (*yellow arrow*).

Video 2: Right ventricular (RV) angiogram during cardiac catheterization, left anterior oblique (LAO) projection, showing normal RV systolic function, thickened PV with doming in systole (*arrow*), and trivial to mild PR.

Video 3: Pulmonary angiogram during cardiac catheterization, anterior-posterior projection, showing thickened PV with doming during systole (*arrow*) with left PA aneurysmal dilation. *LPA*, Left PA; *RPA*, right PA.

Video 4: Two-dimensional TTE, parasternal short-axis view, with color-flow Doppler on the right, showing a thickened PV (*arrow*), aliasing of flow across the PV, and moderate PR. *AV*, Aortic valve

Video 5: Two-dimensional TTE, parasternal high short-axis view, showing the thickened PV (*yellow arrow*). *Ao*, Aorta

Video 6: Two-dimensional TTE, parasternal high short-axis view, with color-flow Doppler, showing aliasing of flow across the PV (arrow) and moderate PR.

Video 7: Two-dimensional TTE, anterior tilted apical view, showing the thickened PV (*arrow*). *IVS*, Interventricular septum.

Video 8: Two-dimensional TTE, anterior tilted apical view, with color-flow Doppler, showing aliasing of flow across the PV (*arrow*) and moderate PR.

Video 9: Two-dimensional TTE, apical 4-chamber view, showing normal left ventricular systolic function, mildly reduced RV systolic function, and RV hypertrophy. *LA*, Left atrium; *RA*, right atrium.

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

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Table 1 Echocardiographic and catheterization summary over time

Patient age (years)	62	67	74	80
Echocardiographic data				
Left ventricular ejection fraction, %*		65	65	65
Average e' velocity, m/sec		0.09		0.06
E/A		0.76	0.9	0.71
Average E/e'		5.9	9.7	11
RV basal diameter, cm		3.1		4.6
RV end-diastolic area, cm/m^2				13
RV fractional area change, %				30
TAPSE, cm				2.0
RV S', cm/sec				10.2
Pulmonic valve peak velocity, m/sec		2.5	3.5	4.3
Pulmonic valve peak gradient, mm Hg		25	49	74
Pulmonic valve mean gradient, mm Hg		18	30	50
Tricuspid regurgitation velocity, m/sec		2.9	3.0	4.9
RV systolic pressure, mm Hg		34 + RAP	36 + RAP	94 + RAP
Catheterization data				
SVC saturation, %				61
PA saturation, %				63
SpO_2, %				96
RAP, mm Hg	6		3	4
RV pressure, mm Hg	40/6	60/0	74/8	98/8
PA pressure, mm Hg	22/8 (13)	26/9 (17)	27/10 (17)	35/12 (20)
RV-PA peak to peak gradient, mm Hg	18	34	47	63
Pulmonary capillary wedge pressure, mm Hg	6	11	3	7
Systemic BP or aortic pressure	106/57 (77)		119/67 (90)	163/79 (113)
RV pressure % systemic	38		62	63
Cardiac output by FICK, L/min				4.8
Cardiac index by FICK, $L/min/m^2$				2.3
Pulmonary vascular resistance, WU				2.7
Systemic vascular resistance, WU				23

BP, Blood pressure; *RAP*, RA pressure; *SVC*, superior vena cava; *TAPSE*, tricuspid annular planar excursion; *WU*, Woods units.
*Simpson's biplane method of disks.

outflow tract (RVOT) was 4.3 m/sec, mean PV gradient was 50 mm Hg (Figure 3), and estimated right ventricular systolic pressure (RVSP) was 94 mm Hg above the right atrial (RA) pressure (Figure 4). Moderate PR was seen by color and spectral Doppler (Videos 4, 6, and 8, Figure 3). The RV was enlarged (Figure 5) with mildly reduced systolic function by fractional area change of 30% (Figure 6) but preserved longitudinal right ventricular function parameters (Figure 7, Table 1). Although subcostal imaging was inadequate to measure RV wall thickness, the RV free wall appeared thick (Video 9), and there was normal left ventricular size and function, with a biplane left ventricular ejection fraction of 65% (Video 9). A contrast-enhanced chest CT scan demonstrated significant PV calcification and progression of the dilated PA (Figure 8), now measuring 4.9×4.7 cm.

In addition to PS and coronary artery disease, the patient's other medical history was significant for paroxysmal atrial fibrillation, hypertension, hyperlipidemia, chronic kidney disease stage III, osteoarthritis, and lumbar radiculopathy. They were a lifelong nonsmoker and did not have significant lung disease.

Given that PS rarely progresses, to evaluate whether PS was truly the etiology of the patient's symptoms and rule out more common diagnoses such as heart failure with preserved ejection fraction, a RHC was performed. The RHC revealed normal cardiac output and normal RA, PA, and pulmonary capillary wedge pressures, but significant RV hypertension with a peak-to-peak gradient from the RV to the PA of 63 mm Hg (Figure 9, Table 1). The patient's case was discussed in multidisciplinary case management conference with congenital interventional cardiologists and congenital cardiac surgeons. Given their age and comorbidities, surgical intervention to the PV would have significant operative risk and thus was not offered. It was the consensus of the group to consider balloon pulmonary valvuloplasty, recognizing the uncertainty of how a calcified valve would respond, with the potential for worsening of PR. If severe symptomatic PR did occur, it was felt transcatheter PV replacement with a self-expanding prosthesis

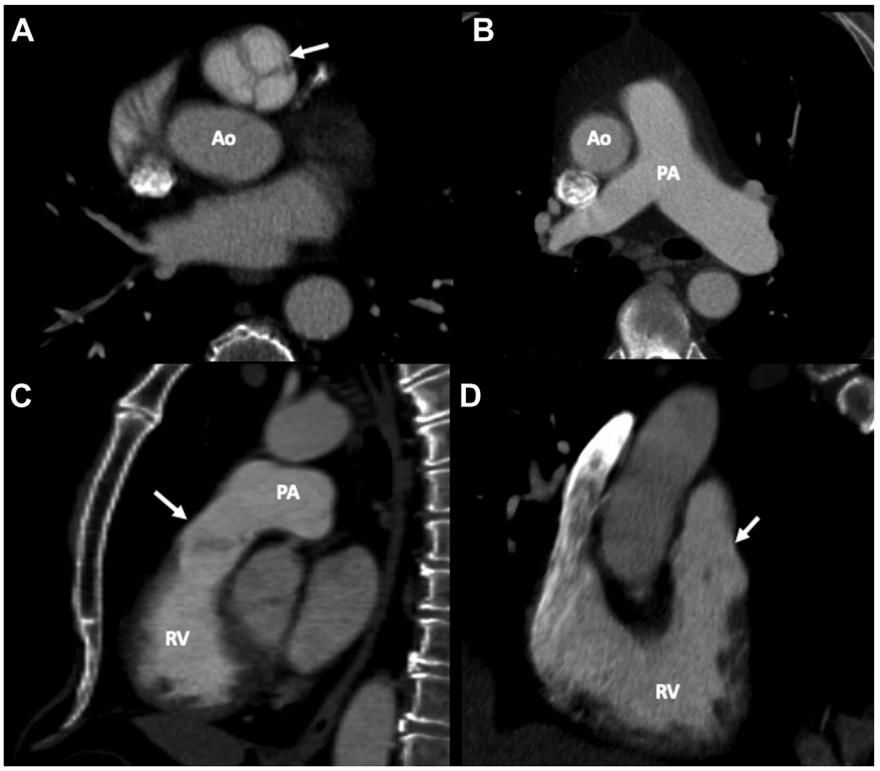

Figure 1 Contrast-enhanced CT of the chest. **(A)** Axial slice at the level of the PV (*white arrow*) showing a trileaflet valve without calcifications. **(B)** Axial slice at the level of the PA showing PA dilation. **(C)** Sagittal and **(D)** coronal sections demonstrating no PV calcifications. *Ao*, Aorta.

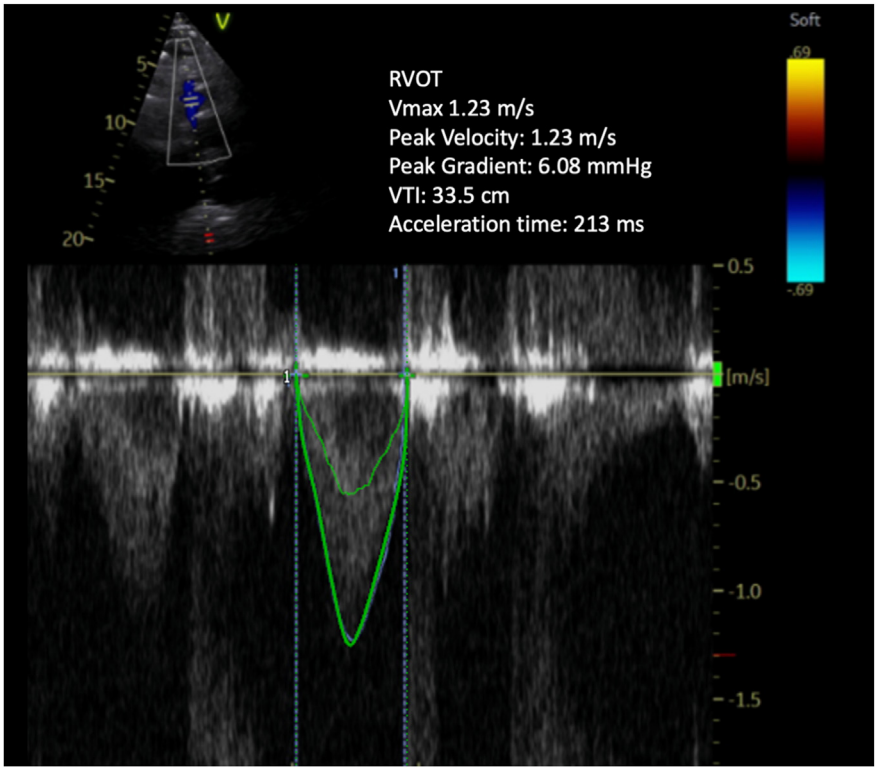

Figure 2 Two-dimensional TTE pulsed-wave Doppler tracing, parasternal short-axis view, demonstrates a normal RVOT velocity, indicating no subvalvular obstruction in the area interrogated.

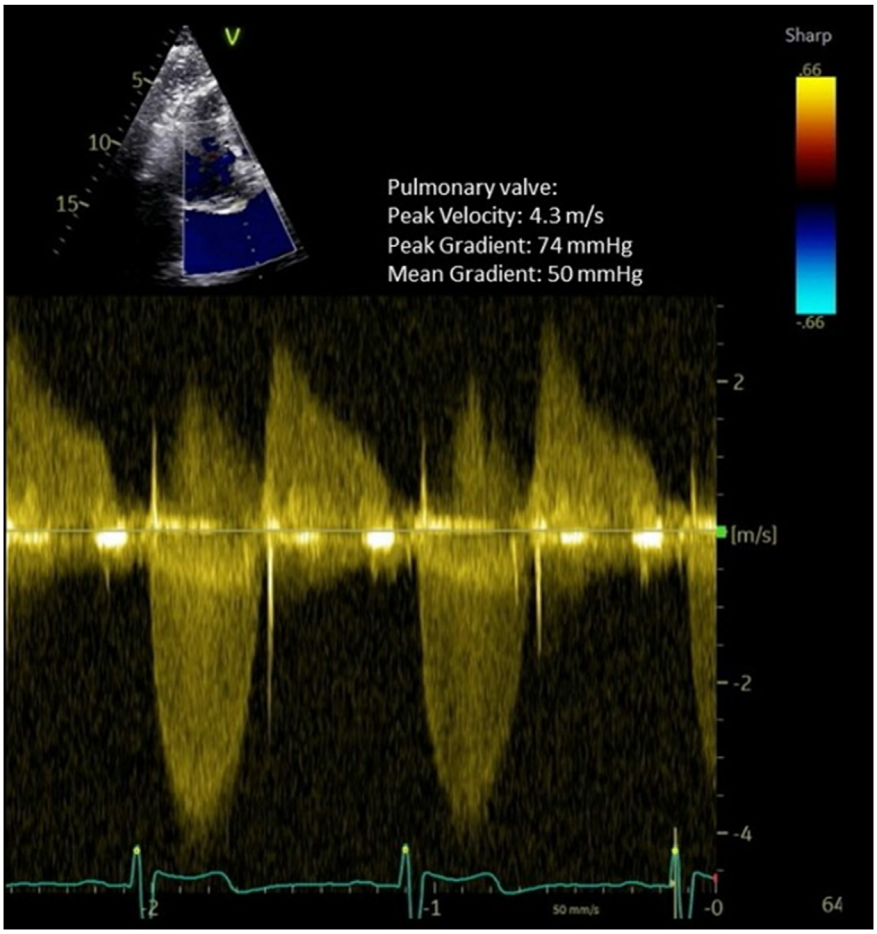

Figure 3 Two-dimensional TTE continuous-wave Doppler tracing, anterior tilt apical 5-chamber view, demonstrates severe PS and moderate PR.

may be an option based on evaluation of the CT images. However, after discussing the risks and benefits with the patient and their family, they elected not to proceed with balloon valvuloplasty and continue conservative follow-up.

DISCUSSION

Historic data on valvular PS are based on cohorts from the 1970s to the 1990s, with multiple studies indicating that mild valvular PS in children and adults does not progress.[3,5,6] The largest of these studies included 580 patients, with at most 25 years of follow-up.[3] However, since that time the demographic of CHD patients has changed, with more adults than children now alive with CHD and an increasing number of patients living into their 60s and beyond.[4,7]

With the increasing age of CHD patients, additional comorbidities may develop, and other etiologies for symptoms should be investigated. While our patient had a significant history of coronary artery disease, they did not have new obstructive disease as the cause of their symptoms. Furthermore, heart failure with preserved ejection fraction is common in patients with comorbidities such as coronary artery disease, systemic hypertension, and atrial fibrillation, although our patient's left-sided filling pressures were normal. As such, the consensus from our multidisciplinary team was that the PS was the most likely reason for the dyspnea.

Valvular PS should be differentiated from other causes of RVOT obstruction, including subvalvar PS (caused by double-chambered RV or infundibular stenosis) and supravalvar PS with narrowing in the main or branch pulmonary arteries; in these lesions, the PV morphology and mobility are typically normal. In valvular PS, Doppler ultrasound through the RVOT and branch pulmonary arteries shows an area of discrete stenosis at the level of the valve. Grading of PS (and other causes of RVOT obstruction) is based on the highest velocity obtained by continuous-wave Doppler across the RVOT, with a peak gradient <36 mm Hg across the valve considered mild, 36 to 64 mm Hg considered moderate, and >64 mm Hg considered severe.[8,9] Unlike assessment of aortic stenosis, calculation of the valve area for PS by the continuity equation is not typically performed and has not been validated.[9]

Valvular PS is most often an isolated lesion, with a dome-shaped PV and preserved mobility at the base of the valve, similar to what was seen in our patient (Video 1). Dysplastic valves with poor mobility and myxomatous thickening can cause more severe stenosis early in life and are less common, although frequently seen in patients with Noonan syndrome.[10] In addition, in patients with valvular PS, PA dilation can occur independent of the severity of valvular disease, as seen in our patient (Figures 1 and 8).[10] However, the incidence of PA dissection is extremely low and only seen in patients with concomitant pulmonary hypertension.[11]

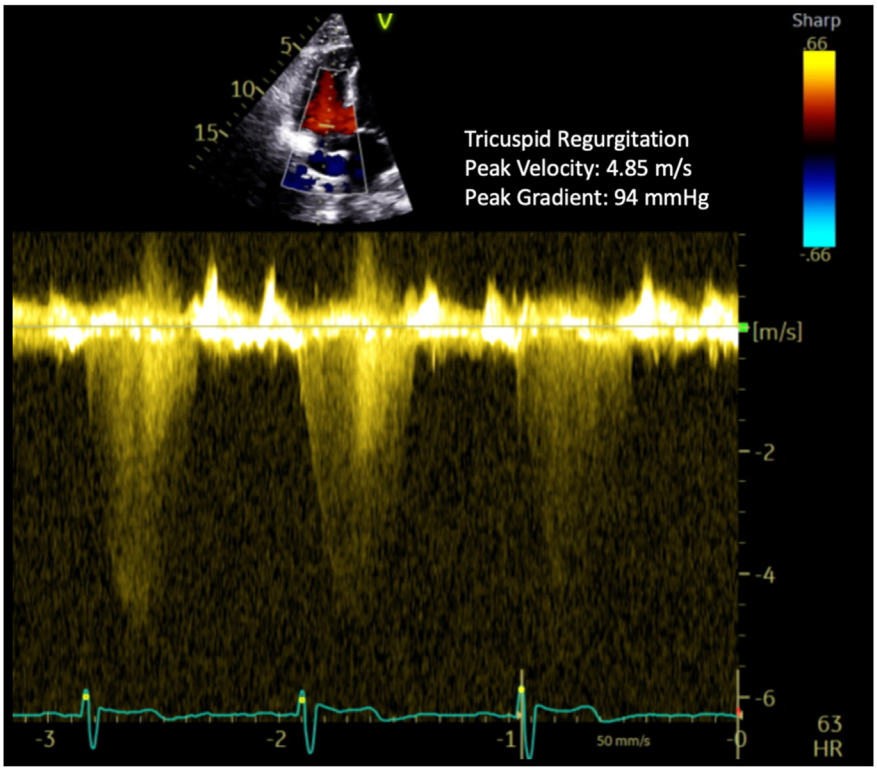

Figure 4 Two-dimensional TTE continuous-wave spectral Doppler tracing, apical 4-chamber view, demonstrates trace TR, which estimates an elevated RVSP (94 mm Hg above the RA pressure).

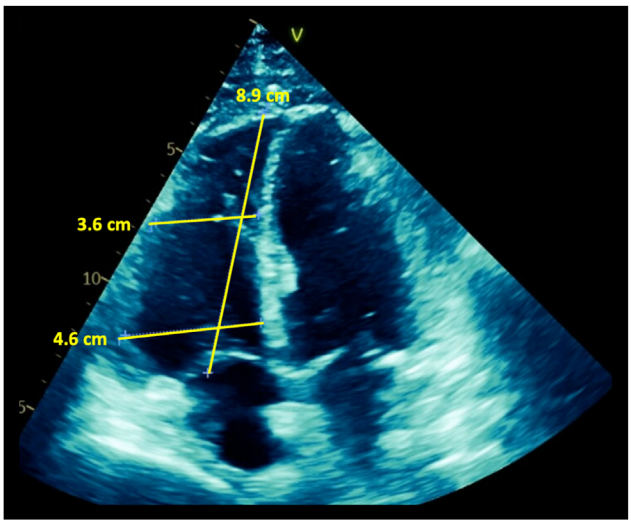

Figure 5 Two-dimensional TTE with B-mode colorization, RV-focused apical 4-chamber view, end diastole, demonstrates RV enlargement.

Patients with significant PS generally have elevated RVSP, as assessed by the tricuspid regurgitation (TR) velocity (Figure 4), and could be thought to have pulmonary hypertension if there is not careful evaluation for RVOT obstruction as the cause of elevated RVSP. In addition to the above two-dimensional and Doppler assessment of the RVOT and PV, PS can be distinguished from pulmonary arterial hypertension by the RVOT pulsed-wave spectral Doppler envelope. In pulmonary arterial hypertension, the RVOT acceleration time is generally shorter (less than 105 ms) and may have midsystolic notching,[11] which are not seen in PS (Figure 2).

While our patient's PV was abnormal with doming in systole, they did not develop significant stenosis until the development of valvular calcification, making this the most likely etiology for progression of PS. Prior studies have shown that the development of PV calcification in patients without prior valve manipulation is rare.[12,13] Those reports included patients who were younger (ages 21-59 years) and all had severe PS, many with other concomitant forms of CHD, hypothesizing that both long-standing elevated RV pressure and potentially healed endocarditis were the etiology of valve calcification. However, there is 1 prior report of a 77-year-old woman who developed calcific PS and underwent a balloon valvoplasty, although longitudinal data on the severity of PS were not available.[14] Our patient did not have significant valvular calcification until after age 67 (Figures 1 and 8) or severe stenosis until after age 74 (Table 1). One potential etiology for the development of valvular calcification is age-related calcification, similar to the abovementioned case report as well as what is seen in patients with calcific aortic stenosis. In addition, it is possible that renal dysfunction contributed to the development of valvular calcification in our patient. Perhaps these conditions, combined with the congenitally abnormal valve, led to calcification on the valve, which would not occur with a normal PV. Cases such as these should be taken into consideration as the ACHD population ages and support the

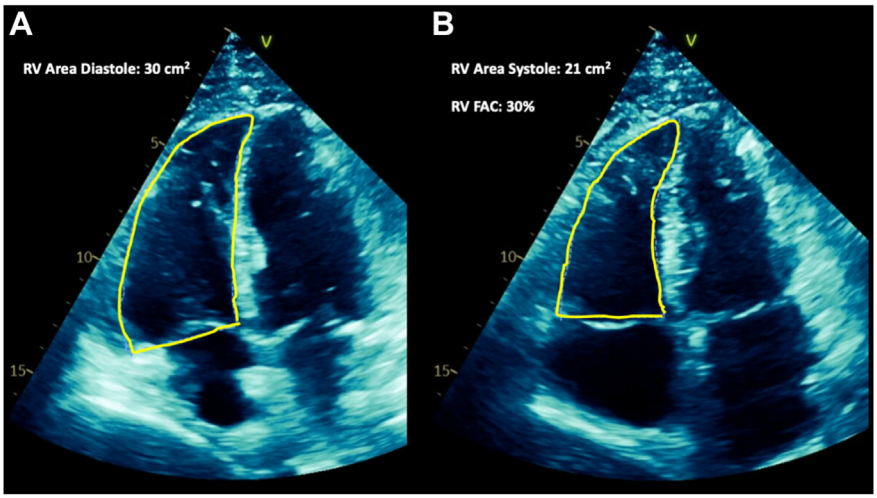

Figure 6 Two-dimensional TTE with B-mode colorization, RV-focused apical 4-chamber view in **(A)** end diastole and **(B)** end systole, demonstrates RV enlargement and mildly reduced systolic function by fractional area change (FAC).

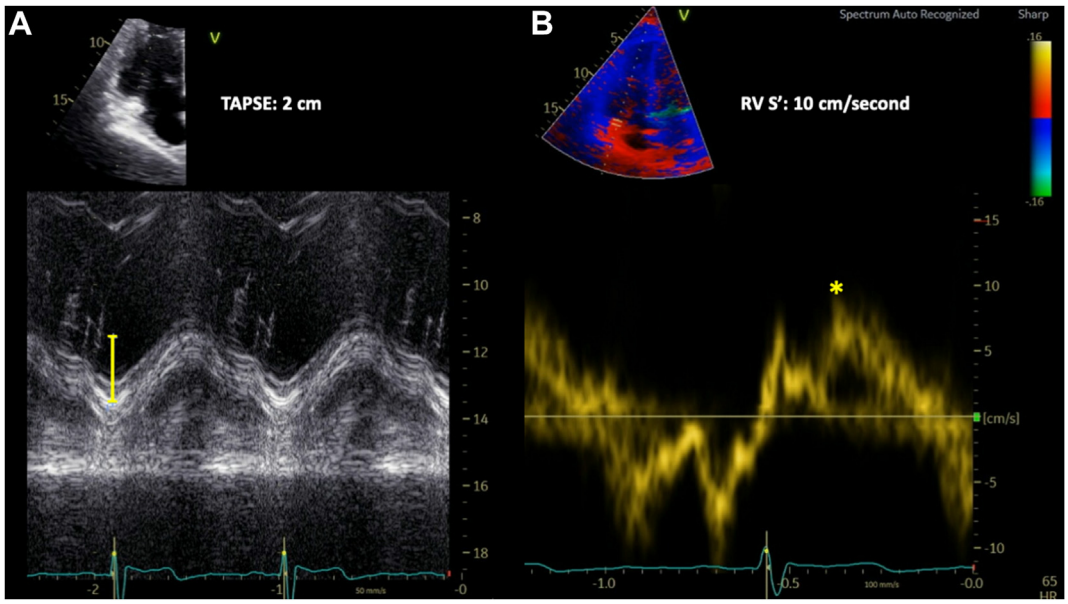

Figure 7 Two-dimensional TTE, RV-focused view with **(A)** M-mode assessment of tricuspid annular planar systolic excursion (TAPSE) and **(B)** tissue Doppler S′, demonstrates preserved RV longitudinal systolic function.

recommendation for lifelong follow-up,[8,10] even for simple CHD such as valvular PS.

Adult CHD guidelines recommend intervention for PS in patients with moderate or severe isolated PS and symptoms of heart failure or exercise intolerance, with balloon valvuloplasty as the first-line intervention in the absence of a hypoplastic annulus or dysplastic valve. In patients with severe stenosis, intervention can be performed in the absence of symptoms.[8,10] Guidelines from the European Society of Cardiology make further recommendations that in the presence of severe valvular PS, intervention is indicated with decreasing RV function, progression of TR to the moderate range, and RVSP >80 mm Hg.[10] Additionally, if an atrial-level shunt is present and there is right-to-left shunting, intervention is also indicated.[10] Pulmonary regurgitation can develop after intervention for PS and was already present in our patient; due to right ventricular volume loading this can also cause right ventricular dilation. Similar guideline recommendations exist for intervention on PR, with intervention indicated for symptomatic patients with moderate or more regurgitation and RV dilation.[8]

Transthoracic echocardiography has a key role in the serial assessment of patients with valvular PS, with guideline recommendations for follow-up every 12 to 60 months depending on severity.[8] In

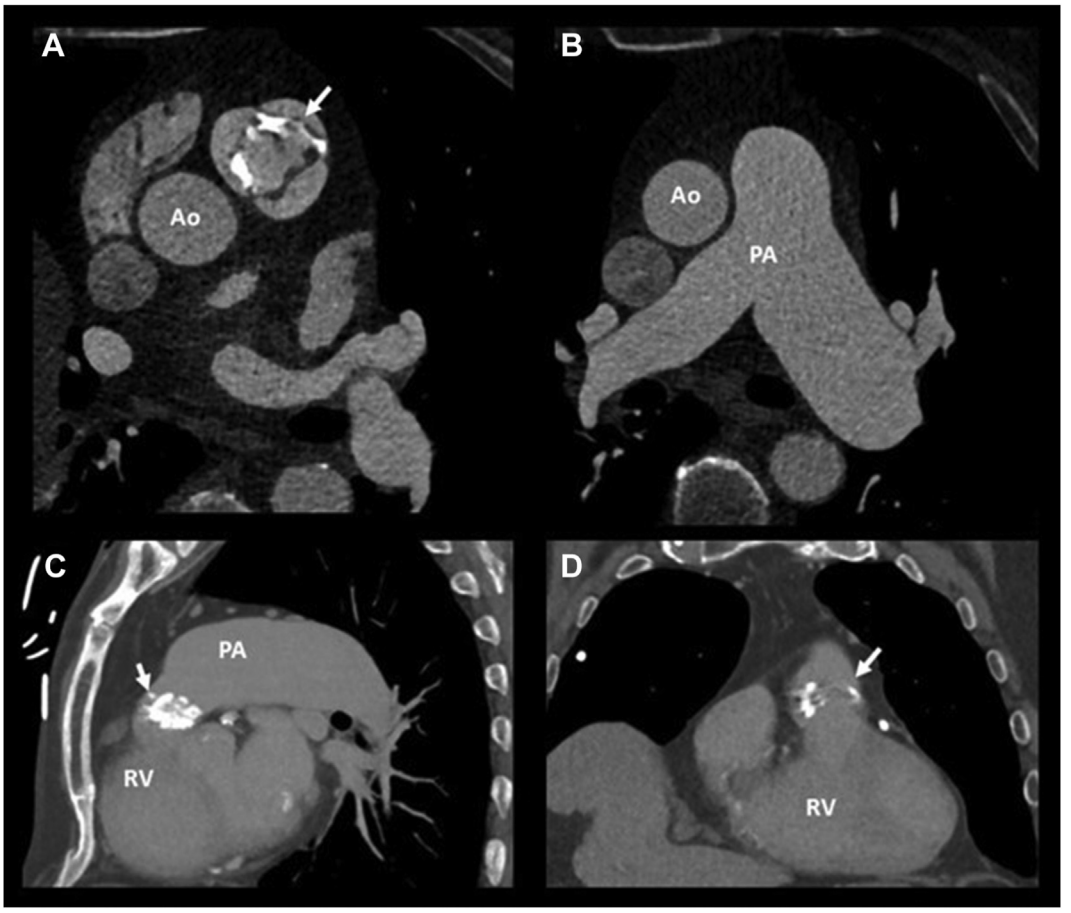

Figure 8 Contrast-enhanced CT of the chest. **(A)** Axial slice at the level of the PV (*white arrow*) showing valvular calcifications. **(B)** Axial slice at the level of the PA showing PA dilation. **(C)** Sagittal and **(D)** coronal sections demonstrating valvar calcifications (*white arrow*). *Ao*, Aorta.

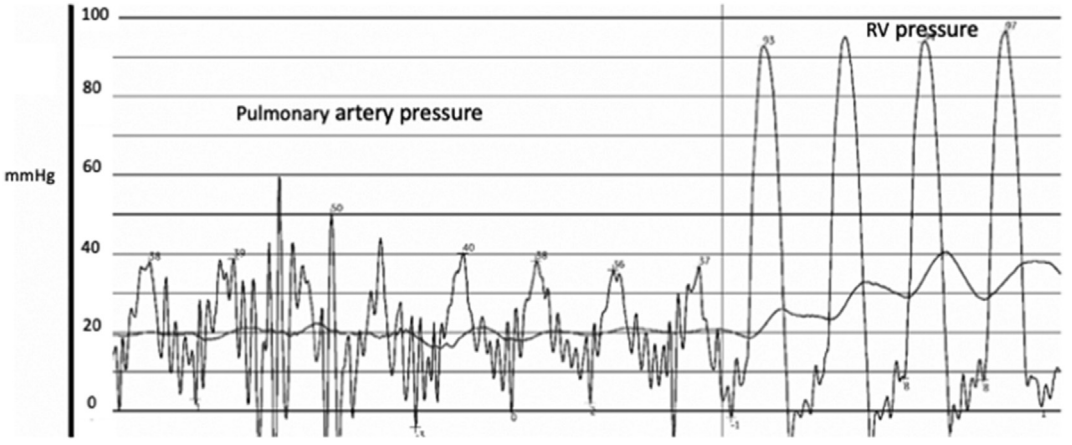

Figure 9 Hemodynamic tracing from RHC showing pressure difference on PA to RV pullback.

Table 2 Recommended echocardiography imaging in patients with valvular PS

Area of focus	Specific techniques
RV size	• Assessment of size in the RV-focused view • 3D RV volumes • RV free wall thickness in the subcostal view
RV function	• TAPSE • RV S′ • Fractional area change • 3D RV ejection fraction • RV free wall strain
Severity of PS/PR	• Color-flow Doppler of the RVOT* • Pulsed-wave Doppler through RVOT and in branch pulmonary arteries* • Continuous-wave Doppler through the RVOT*
Estimation of RVSP	• Continuous-wave Doppler of the TR jet to assess RV to RA pressure difference • Assessment of inferior vena cava size and collapsibility to assess RA pressure
Severity of TR	• Interrogation of the tricuspid valve with color and continuous-wave Doppler • If regurgitation present, obtain quantitative measures including vena contracta area
Presence of an atrial-level shunt	• 2D and color Doppler interrogation of the interatrial septum in multiple views • Bubble study with agitated saline performed at least once

2D, Two-dimensional; *3D*, three-dimensional; *RV*, right ventricular; *TAPSE*, tricuspid annular planar systolic excursion.
Refer to guidelines[9,15] for comprehensive explanations of above techniques.
*Obtain in short-axis and modified apical 5-chamber views if possible.

addition to Doppler measures of the severity of valvular stenosis and regurgitation, echocardiography is essential in the evaluation for estimation of RVSP by the TR velocity. Furthermore, quantitative measures of RV size and function should be obtained with serial echocardiography for ventricular dilation or dysfunction, ideally incorporating three-dimensional TTE imaging if possible.[15] If the RV is not well seen or there is discordant information, cardiovascular magnetic resonance imaging should be used to further evaluate the right ventricular size and function.[8] Comprehensive assessment of valvular stenosis and ventricular size and function is outlined in guidelines,[9,15] with the authors' consensus of specific areas for focus in PS outlined in Table 2.

CONCLUSION

While historical data suggest that valvular PS does not progress, we report a patient with progression from mild to severe valvular PS leading to dyspnea. Thus, as the ACHD population ages, this case exemplifies the importance of lifelong follow-up for patients with all forms of CHD and exemplifies how multimodality imaging with TTE, CT, and invasive cardiac catheterization are complementary in the assessment of CHD, including valvular PS.

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.

CONSENT STATEMENT

Complete written informed consent was obtained from the patient for the publication of this study and accompanying images.

FUNDING STATEMENT

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DISCLOSURE STATEMENT

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2023.12.007.

REFERENCES

1. van der Bom T, Bouma BJ, Meijboom FJ, Zwinderman AH, Mulder BJM. The prevalence of adult congenital heart disease, results from a systematic review and evidence based calculation. Am Heart J 2012;164:568-75.
2. Shuler CO, Black GB, Jerrell JM. Population-based treated prevalence of congenital heart disease in a pediatric cohort. Pediatr Cardiol 2013;34:606-11.
3. Hayes CJ, Gersony WM, Driscoll DJ, Keane JF, Kidd L, O'Fallon WM, et al. Second natural history study of congenital heart defects. Results of treatment of patients with pulmonary valvar stenosis. Circulation 1993;87(2 Suppl):I28-37.
4. Dellborg M, Giang KW, Eriksson P, Liden H, Fedchenko M, Ahnfelt A, et al. Adults with congenital heart disease: trends in event-free survival past middle age. Circulation 2023;147:930-8.
5. Rowland DG, Hammill WW, Allen HD, Gutgesell HP. Natural course of isolated pulmonary valve stenosis in infants and children utilizing Doppler echocardiography. Am J Cardiol 1997;79:344-9.
6. Gielen H, Daniëls O, van Lier H. Natural history of congenital pulmonary valvar stenosis: an echo and Doppler cardiographic study. Cardiol Young 1999;9:129-35.
7. Baumgartner H. Geriatric congenital heart disease: a new challenge in the care of adults with congenital heart disease? Eur Heart J 2014;35:683-5.
8. Stout KK, Daniels CJ, Aboulhosn JA, Bozkurt B, Broberg CS, Colman JM, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. J Am Coll Cardiol 2019;73:1494-563.

9. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. J Am Soc Echocardiogr 2009;22:1-23.
10. Baumgartner H, De Backer J, Babu-Narayan SV, Budts W, Chessa M, Diller GP, et al. 2020 ESC Guidelines for the management of adult congenital heart disease. Eur Heart J 2021;42:563-645.
11. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2022;43:3618-731.
12. Dinsmore RE, Sanders CA, Harthorne JW, Austen WG. Calcification of the congenitally stenotic pulmonary valve. N Engl J Med 1966;275:99-100.
13. Roberts WC, Mason DT, Morrow AG, Braunwald E. Calcific pulmonic stenosis. Circulation 1968;37:973-8.
14. Ayad RF, Johnston SB, Grayburn PA, Schmidt TT, Choi JW. Congenital pulmonic stenosis in a 77-year-old woman successfully treated with percutaneous balloon valvuloplasty. Proc (Bayl Univ Med Cent) 2010; 23:21-3.
15. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of echocardiography and the European Association of cardiovascular imaging. J Am Soc Echocardiogr 2015;28:1-3914.