

Mitral Valve-in-Ring Leaflet Thrombosis: A Multimodality Imaging Primer



Dena E. Hayes, MD, Daniel Bamira, MD, Alan F. Vainrib, MD, Cezar Staniloae, MD, Hasan Jilaihawi, MD, Mathew Williams, MD, and Muhamed Saric, MD, PhD, *New York, New York*

Transcatheter mitral valve implantation is an emerging therapy for select patients with mitral valve disease, particularly those with high surgical risk. Transcatheter mitral valve implantation may refer to transcatheter treatment of failed surgical or native mitral valves, including mitral valve-in-valve procedure for degenerated surgical bioprostheses, valve-in-ring (ViR) procedure for failed surgical annuloplasty rings and bands, valve-in-mitral annular calcification procedure for degenerated native mitral valves, and transcatheter mitral valve replacement (TMVR) with a prosthesis inside a failed, typically noncalcific, native mitral valve.

Repurposed transcatheter aortic prostheses are used for valve-in-valve, ViR, and valve-in-mitral annular calcification, while dedicated transcatheter prostheses are used for TMVR.

Leaflet thickening and thrombosis of transcatheter aortic valve bioprostheses is now a well-established phenomenon. Repurposed transcatheter aortic valves when placed in the mitral position are prone to the same thrombotic processes as described for aortic bioprostheses. The same processes are expected to occur with the upcoming generation of mitral valve-specific transcatheter bioprostheses. Timely identification of transcatheter heart valve thrombosis (THVT) is essential given the need for anticoagulation and possible reintervention.

Echocardiography and computed tomography (CT) imaging are the primary imaging modalities used to diagnose mitral THVT. Here we discuss a case of a patient who underwent transcatheter mitral valve-in-surgical ring procedure to highlight general echocardiographic and CT findings of THVT.

CASE PRESENTATION

A 38-year-old woman with history of rheumatic mitral valve disease underwent multiple surgical and percutaneous interventions

From the Leon H. Charney Division of Cardiology (D.E.H., D.B., A.F.V., C.S., H.J., M.W., M.S.) and Department of Cardiothoracic Surgery (C.S., H.J., M.W.), New York University Langone Health, New York, New York.

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Correspondence: Dena E. Hayes, MD, Leon H. Charney Division of Cardiology, New York University Langone Health, 560 First Avenue, New York, NY 10016. (E-mail: dena.hayes@nyulangone.org).

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(Table 1). We will focus on intervention 2 (mitral ViR) to illustrate the imaging findings of THVT.

Intervention 1

The patient originally presented to an outside institution with symptomatic rheumatic mitral valve disease with predominant mitral regurgitation (MR). She underwent surgical mitral valve repair using a 28-mm Carpentier-Edwards Physio II rigid complete mitral ring at 38 years of age.

Intervention 2

Several months after the surgical annuloplasty, she presented to our institution with dyspnea on exertion, fatigue, and bilateral lower extremity edema of several weeks' duration. Transthoracic echocardiogram (TTE) and transesophageal echocardiogram (TEE) revealed failure of the mitral valve repair resulting in severe through-the-ring MR that was holosystolic, eccentric, and anteriorly directed (Figure 1, Videos 1 and 2). Available percutaneous and surgical options were discussed with the patient including a redo mitral valve surgery and percutaneous ViR procedure. After being told that her Society of Thoracic Surgeons combined morbidity and mortality score was estimated at 10.4% for a redo surgery, the patient expressed preference for a percutaneous option.

She then underwent successful transcatheter mitral ViR procedure with a 26-mm Edwards Sapien 3 bioprosthetic valve (Edwards Lifesciences, Irvine, CA). Intraprocedural TEE revealed neither transvalvular nor paravalvular MR and demonstrated a mean diastolic mitral valve gradient of 2 mm Hg at a heart rate (HR) of 85 beats per minute (bpm) with rapid E-wave pressure half-time, all indicative of normal prosthetic function (Figures 2 and 3, Videos 3-5).

The patient was then started on warfarin with a recommendation to continue it for the next 3 to 6 months. The patient ultimately remained on warfarin for a total of 8 months, during which time she was in sinus rhythm and had a therapeutic international normalized ratio. After 8 months on warfarin, the patient was instructed by her outpatient cardiologist to stop taking warfarin based on the assumption that current guidelines on the duration of anticoagulation post-implantation of surgical mitral prostheses (3 to 6 months) also apply to transcatheter mitral valves.¹

One month following the cessation of warfarin, the patient presented to the emergency department with progressive dyspnea on exertion and decreased exercise tolerance. Color Doppler TTE imaging revealed no significant MR. Color and spectral Doppler imaging (Figure 4, Video 6) revealed marked flow acceleration across the prosthetic valve and severely elevated mean diastolic mitral valve gradient of 25 mm Hg at a HR of 85 bpm, a markedly elevated peak velocity (V_{max}) of the mitral E wave at 2.9 m/sec, and a prolonged pressure half-time of 240 msec; all indicative of severe bioprosthetic mitral stenosis (Table 2).

VIDEO HIGHLIGHTS

Video 1: Intervention 1. Two-dimensional TEE mid-esophageal, 150° view without and with color Doppler imaging demonstrated severe MR several months following surgical mitral annuloplasty.

Video 2: Intervention 1. Three-dimensional TEE transgastric en face short-axis zoomed view without and with color Doppler imaging demonstrated severe MR several months following surgical mitral annuloplasty.

Video 3: Intervention 2. Intraprocedural 2D TEE, 54° long-axis display during native conduction (page 1) and rapid pacing (page 2) is shown to demonstrate the Sapien S3 valve being positioned and deployed within the surgical annuloplasty ring, respectively. The 100° view with color Doppler imaging confirms resolution of the MR and normal function of the ViR (page 3).

Video 4: Intervention 2. Intraprocedural 3D TEE, volume-rendered, zoomed short-axis display without (page 1) and with (page 2) color Doppler imaging demonstrates the Sapien S3 valve is fully deployed inside a surgical annuloplasty ring.

Video 5: Intervention 2. Intraprocedural fluoroscopy demonstrates the ViR procedure.

Video 6: Intervention 2. Follow-up 2D TTE, apical 4-chamber view with color Doppler (page 1) and zoomed color-compare display (page 2) performed several months later demonstrates flow acceleration across mitral ViR indicative of mitral stenosis.

Video 7: Intervention 2. Two- and three-dimensional TEE performed several months post-HALT. Midesophageal 4-chamber view with color Doppler (page 1), 148° view, zoomed color compare display (page 2), transgastric en face short-axis 3D volume-rendered displays with conventional (page 3), advanced glass view (page 4), and color Doppler (page 5) displays demonstrate severe transvalvular MR, which is now seen.

[View the video content online at www.cvcasejournal.com.](http://www.cvcasejournal.com)

Subsequently, contrast-enhanced CT of the chest revealed hypoattenuated leaflet thickening (HALT) in all 3 valve leaflets (Figure 5). There was also restricted leaflet motion (RELM). Due to motion artifacts, accurate grading of RELM in this patient was not possible.

In summary, echocardiographic and CT findings were indicative of THVT and the patient was started on a heparin infusion. Several days after heparin infusion initiation, her symptoms began to improve and she was bridged to warfarin. Twelve days after initiation of

anticoagulation, TTE showed an improved mean diastolic mitral valve gradient of 5 to 6 mm Hg at a HR of 60 to 65 bpm (Table 3). She was discharged home on warfarin with a goal international normalized ratio of 3.0 to 3.5 indefinitely.

One year later and while still on therapeutic warfarin therapy, the patient again reported worsening dyspnea on exertion. Transthoracic echocardiogram demonstrated an elevated mean diastolic gradient of 10 to 12 mm Hg at a HR of 65 bpm but this time with a short pressure halftime of 130 msec. These spectral Doppler findings were indicative of MR rather than stenosis. The severity of MR was assessed according to the guidelines.² Subsequent imaging demonstrated severe transvalvular MR due to bioprosthetic leaflet thickening and partial leaflet retraction seen on three-dimensional (3D) TEE (Figure 6, Video 7) and repeat contrast CT (Figure 7).

Intervention 3

Following the development of severe transvalvular MR of the repurposed Sapien S3 transcatheter valve, the patient was referred to cardiothoracic surgery and underwent mitral mechanical valve replacement with a 25/33 mm On-X valve (On-X Life Technologies, Austin, TX). She was discharged home 3 days after surgery and has experienced complete resolution of her symptoms.

DISCUSSION

In this case report, we describe two complications of a transcatheter mitral ViR bioprosthesis: (1) THVT leading to transient mitral prosthetic stenosis due to HALT with RELM, which improved on warfarin therapy, followed by (2) post-HALT bioprosthetic leaflet degeneration resulting in severe transvalvular MR. Multimodality imaging involving echocardiography and CT was essential in establishing the disease progression.

Discrete leaflet thrombi may or may not be visualized on TTE as thrombi may be too small to be detected. However, the consequences of bioprosthetic leaflet thrombosis, namely, bioprosthetic mitral stenosis and/or MR, are easily recognized by TTE and if present should raise the possibility of THVT in the appropriate clinical setting. Direct visualization of leaflet pathology in the setting of THVT typically requires either TEE or contrast CT imaging with retrospective gating.

While the phenomenon of HALT was initially described during trials for transcatheter aortic valve replacement, HALT is similarly observed in surgical bioprosthetic valves in both the aortic and mitral position.³ Originally, HALT was described as a subclinical occurrence associated with normal gradients across the valve. However, HALT is now recognized to be present in cases of thrombosis in which there are clinical manifestations and an increased gradient across the prosthetic valve.

Table 1 Summary of interventions

Intervention no.	Intervention	Device
1	Mitral valve annuloplasty	28-mm Carpentier-Edwards Physio II rigid complete mitral ring
2	Transcatheter mitral ViR	26-mm Edwards Sapien 3 bioprosthetic valve
3	Mechanical mitral valve replacement	25/33-mm On-X valve

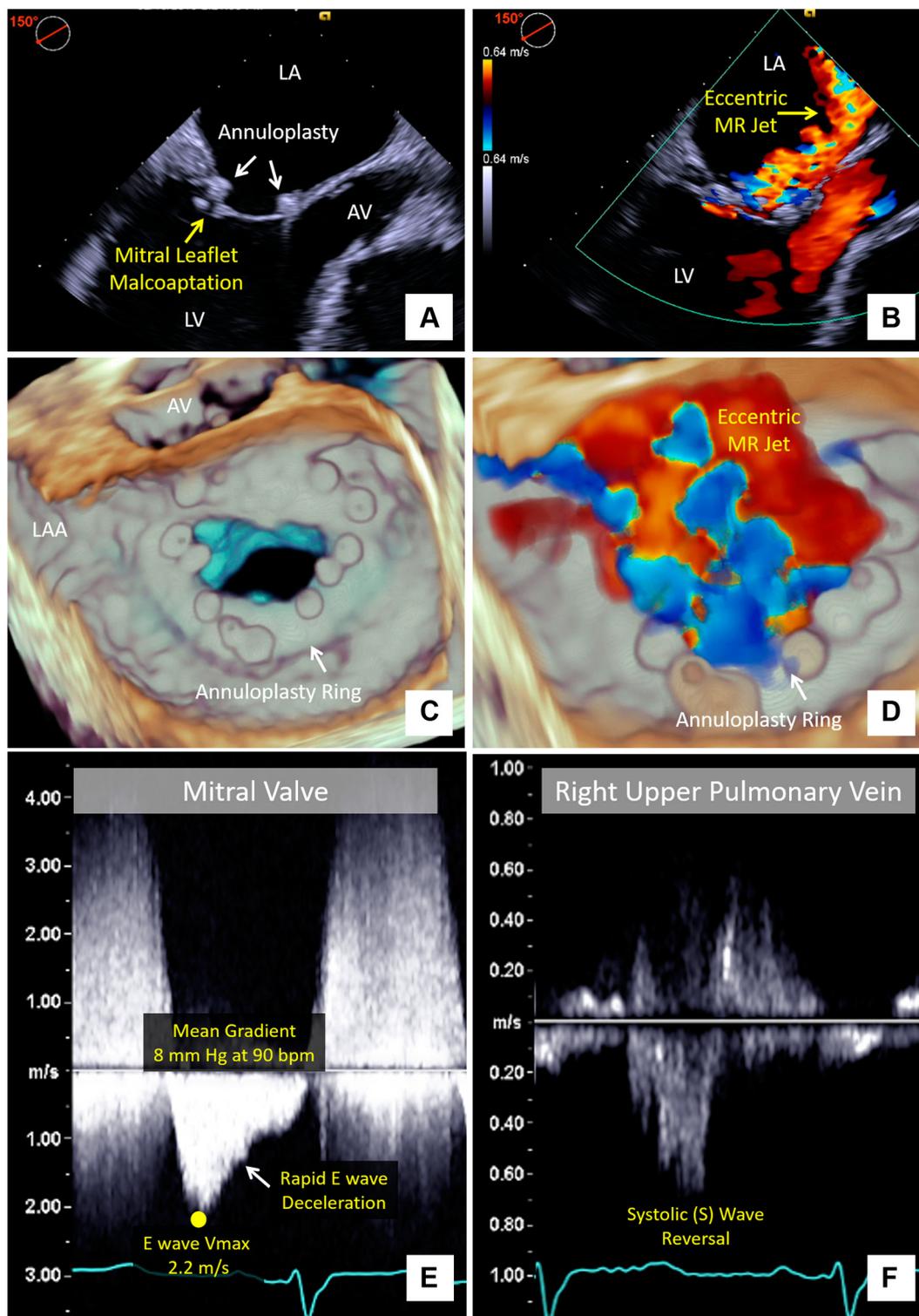


Figure 1 Intervention 1. Midesophageal TEE imaging, two-dimensional (2D) 150° view without (A) and with (B) color Doppler, demonstrated severe MR several months following surgical mitral annuloplasty. Transgastric 3D TEE short-axis orientation and volume-rendered display without (C) and with (D) color Doppler and continuous-wave (E) and pulsed-wave (F) spectral Doppler displays were also obtained. Malcoaptation of the mitral leaflets (A, C) results in eccentric, anteriorly directed holosystolic MR jet (B, D) with an effective regurgitant orifice area of 0.56 cm². A mean gradient of 8 mm Hg with rapid E-wave deceleration (E) and reversal of the S wave in the pulmonary vein (F) are indicative of severe MR. AV, Aortic valve; LAA, left atrial appendage; LA, left atrium; LV, left ventricle. [Video 1](#) corresponds to panels A and B; [Video 2](#) corresponds to panels C and D.

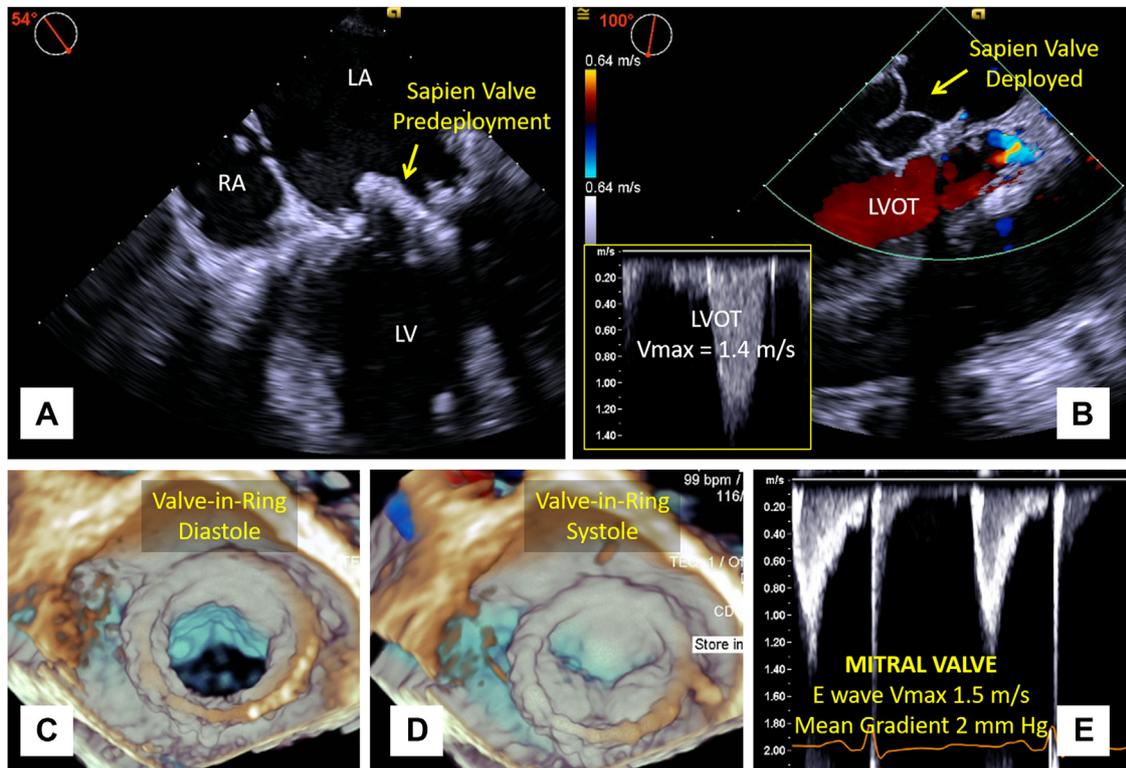


Figure 2 Intervention 2. Intraoperative TEE, midesophageal, 54° view without (A) and 100° view with (B) color Doppler; 3D short-axis orientation, volume-rendered display in diastole (C) and systole (D); and spectral Doppler displays (B, insert, and E). The Sapien S3 valve in the process of being deployed (A) and subsequently fully deployed with no evidence of LVOT obstruction as judged by laminar flow in LVOT (B) and a normal LVOT Vmax (B, insert). Three-dimensional TEE shows a normally functioning implanted transcatheter valve (so-called surgical view of the mitral valve in C, D) with a mean gradient of 2 mm Hg and E-wave Vmax of 1.5 m/sec (E). LA, Left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; RA, right atrium. Video 3 corresponds to panels A and B; Video 4 corresponds to panels C and D.

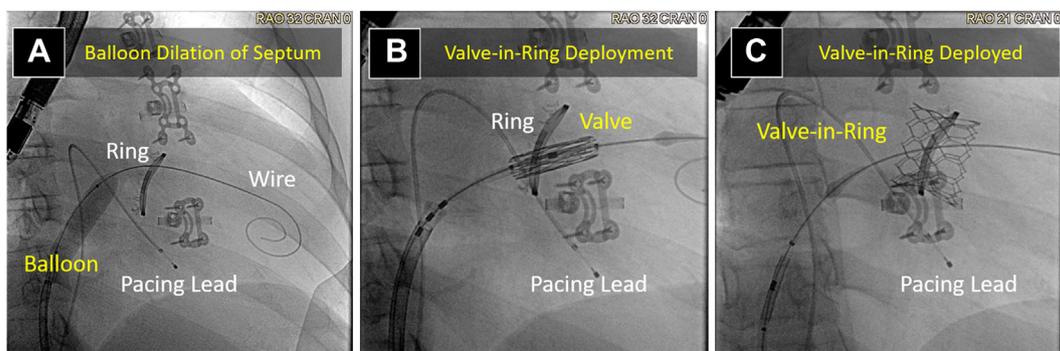


Figure 3 Intervention 2. Intraoperative fluoroscopy (performed during critical time points of the ViR procedure and serially displayed from A to C) demonstrates the ViR procedure. Video 6 corresponds to this figure.

A good CT acquisition of a surgical or transcatheter bioprosthetic valve is a prerequisite for HALT and RELM assessment using previously published protocols. The CT acquisition protocol to evaluate for HALT should use retrospective electrocardiogram gating, minimal contrast, 1-mm slice thickness, and the highest resolution possible. Assessment starts with establishing whether HALT is present or not during the appropriate part of the cardiac cycle (diastolic phase for aortic and systolic phase for mitral prostheses). HALT is defined as

hypoattenuated leaflet thickening and is the hallmark of leaflet thrombosis. In the next step, one determines the presence and the extent of RELM. Percentage of RELM (% RELM) is defined as $\% \text{ RELM} = (W \div \frac{1}{2} * D) * 100\%$, where W is the base-to-tip width during maximal leaflet opening and D is the diameter within the stent frame.⁴

HALT and RELM can also be either suspected or directly visualized by echocardiography. A sudden and otherwise unexplained increase in transvalvular velocities and gradients (>50% over baseline values)

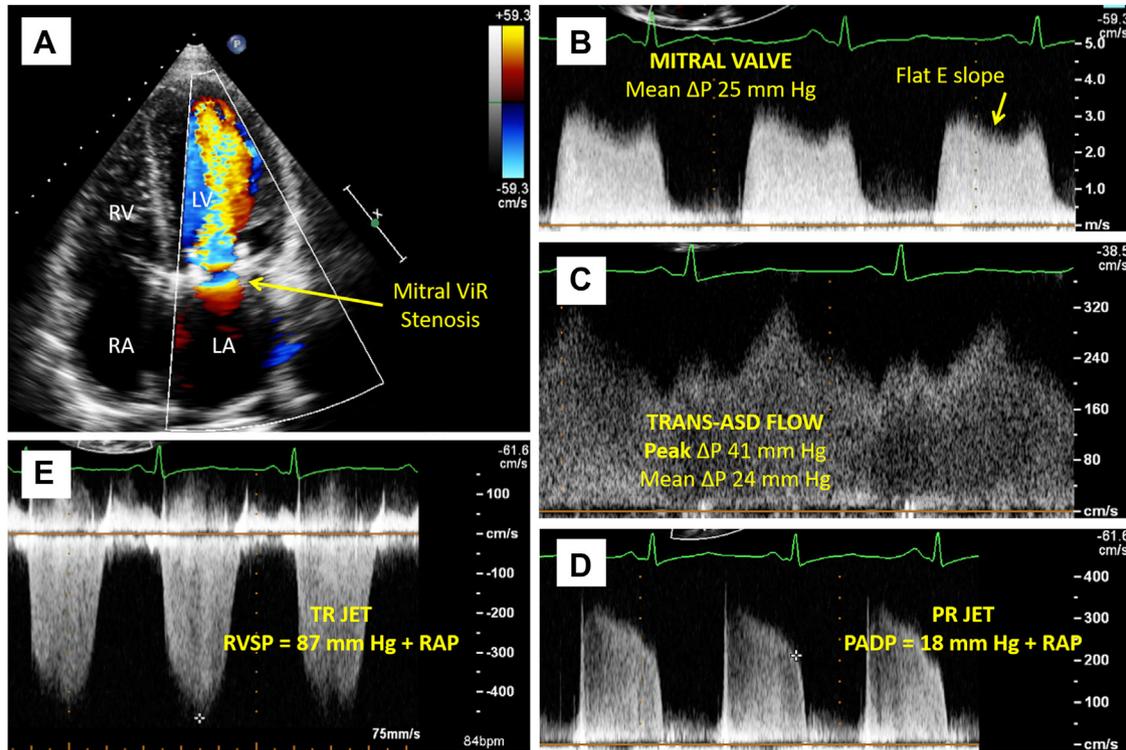


Figure 4 Intervention 2. Follow-up TTE several months after intervention 2. **(A)** Two-dimensional TTE, apical 4-chamber view, color Doppler TTE display revealed flow acceleration across mitral ViR indicative of mitral stenosis. **(B)** Continuous-wave spectral Doppler display demonstrated a mean gradient of 25 mm Hg and with a flat E slope and elevated RVSP **(E)** and PADP **(D)**. **(C)** Pulsed-wave spectral Doppler display confirmed elevated pressures across the iatrogenic ASD. ASD, Atrial septal defect; LA, left atrium; LV, left ventricle; PADP, pulmonary artery diastolic pressure; RA, right atrium; RAP, right atrial pressure; RV, right ventricle. **Video 7** corresponds to panel A.

Table 2 Echocardiographic guidelines for diagnosis of prosthetic mitral stenosis

Parameter	Normal range	Possible MS	Significant MS
Mean pressure gradient, mm Hg	≤5	5-10	>10
Peak velocity, m/sec	<1.9	1.9-2.5	≥2.5
Effective orifice area, cm ²	>2.0	1.0-2.0	<1.0
Pressure halftime, msec	<130	130-200	>200

and typically indicative of moderate or severe valvular stenosis should raise the possibility of HALT and RELM. Echocardiographically, there is RELM with leaflet thickening in the absence of calcifications or pannus formation. HALT and RELM should be differentiated from structural deterioration of prosthetic leaflets where leaflet calcification and pannus formation are prevalent. Moreover, HALT and RELM typically occur earlier after valve implantation (<5 years) than structural degeneration (often 5-10 years after implantation).

This case raises the question of what constitutes an appropriate anticoagulation duration following TMVR in patients who remain in sinus rhythm. A recent study demonstrated that THVT following TMVR is relatively common, occurring in 12.3% of the population studied, with the majority of cases occurring in the first 3 months following valve implantation and in patients not receiving therapeutic anticoagulation.⁵ Studies have shown that THVT is more likely to

occur in the mitral position than in the aortic position, largely due to hemodynamic factors, as well as hemostatic and surface factors.^{6,7} Additionally, patients who underwent valve-in-valve and ViR procedures may be more likely to develop THVT compared to those with a bioprosthetic valve in a native valve due to altered flow dynamics.^{8,9}

The case of late-stage central transvalvular regurgitation in our patient is uncertain. Transcatheter valves are known to be at risk of central regurgitation if overexpanded during implantation.¹⁰ However, in our case, there was no transvalvular regurgitation at the time of implantation and 12 months thereafter. The patient developed HALT with RELM some 9 months post-implantation and MR occurred a year later. We speculate that post-HALT scarring may have been responsible for leaflet degeneration and development of late-stage MR.

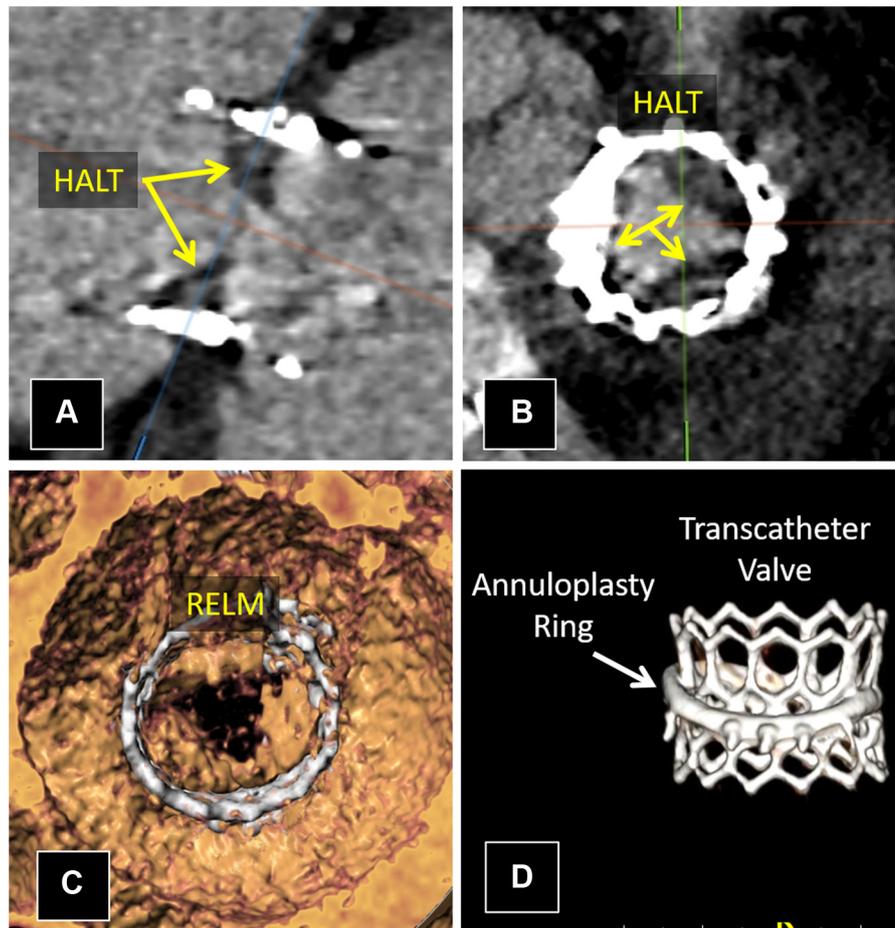


Figure 5 Intervention 2. Contrast-enhanced cardiac CT scan, multiplanar reconstruction in a zoomed long-axis (A) and short-axis (B) orientation, 3D volume-rendered en face view (C) and tissue-extracted, window-level modified (D) prosthetic material-only view performed several months postintervention demonstrates HALT of the prosthetic valve with RELM. Panel D demonstrates a normal ViR frame apparatus.

Table 3 Evolution of mitral bioprosthetic transvalvular gradients

Event	Months post-mitral ViR	Mean MV gradient, mm Hg
Mitral ViR performed (intervention 2)	4.6	2
		7
HALT, warfarin started	8.7	25
	8.8	26
	8.8	14
	9.1	5
Progressive development of transvalvular MR	10.2	7
	12.1	6
	22.6	11
Surgical MVR (intervention 3)	24.2	2

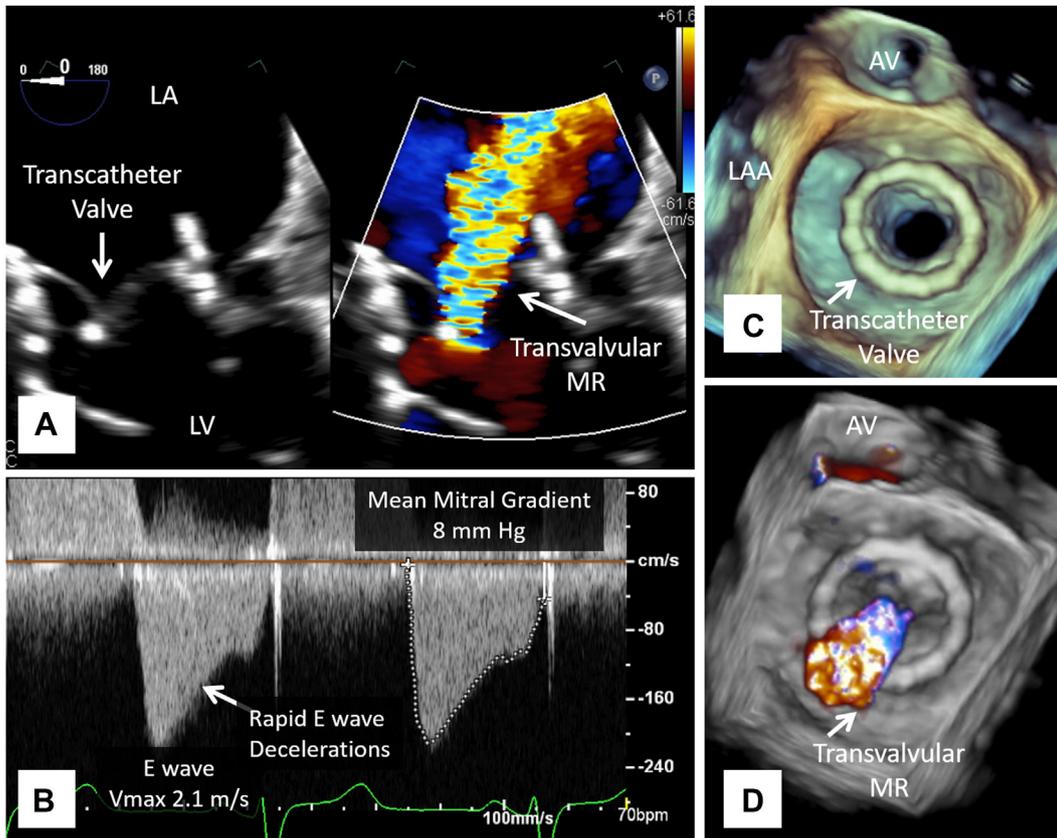


Figure 6 Intervention 2. Transesophageal echocardiogram performed several months after recognition and treatment of HALT. **(A)** Midesophageal, 0° orientation, zoomed image display without and with color Doppler demonstrated transvalvular MR. **(B)** Continuous-wave spectral Doppler display showed a mean gradient of 8 mm Hg, Vmax of 2.1 m/sec, and rapid E-wave decelerations consistent with MR. Three-dimensional volume-rendered display, surgical view, without **(C)** and with **(D)** color Doppler, confirms a normal diastolic ViR appearance and transvalvular MR in systole. AV, Aortic valve; LA, left atrium; LAA, left atrial appendage; LV, left ventricle. [Video 7](#) corresponds to this figure.

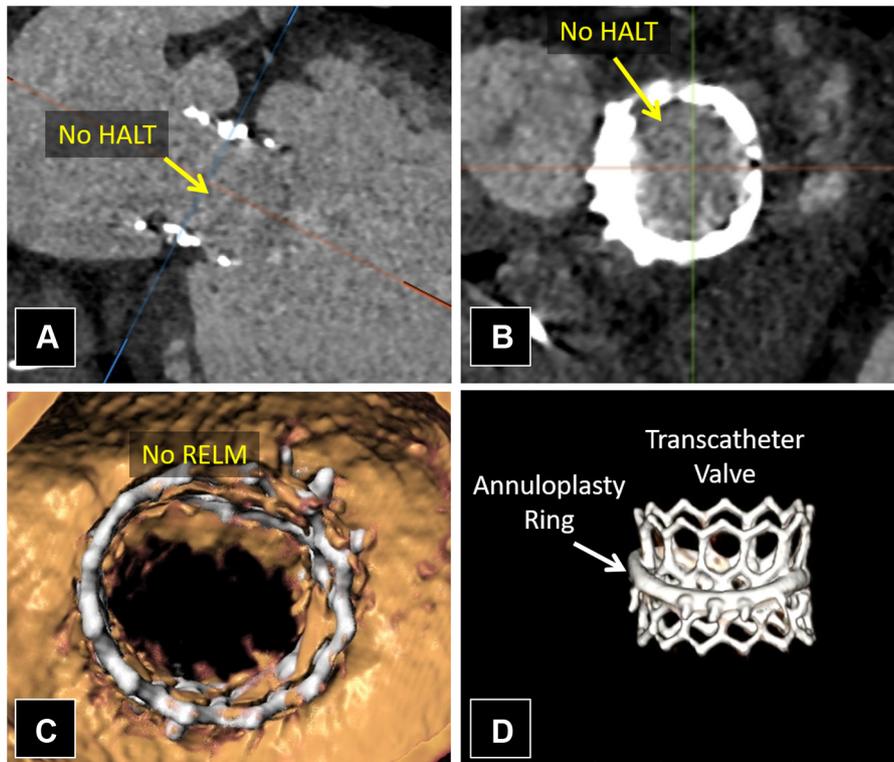


Figure 7 Intervention 2. Contrast-enhanced cardiac CT scan, multiplanar reconstruction in a zoomed long-axis **(A)** and short-axis **(B)** orientation; 3D-volume rendered en face view **(C)** and tissue-extracted, window-level modified **(D)** prosthetic material-only view performed several months after recognition and treatment of HALT confirms the lack of HALT and RELM. Panel **D** demonstrates a normal ViR frame apparatus.

CONCLUSION

THVT is a possible complication of transcatheter mitral valve implantation. This case illustrates that multimodality imaging involving echocardiography and contrast-enhanced, gated CT imaging is important for accurate and timely diagnosis of mitral THVT. Moreover, this case underscores the notion that the adequate duration of anticoagulation to prevent THVT of bioprosthetic mitral valves remains unknown.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.case.2022.05.009>.

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