Three mechanisms of early failure of transcatheter aortic valves: Valve thrombosis, cusp rupture, and accelerated calcification

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TTE of a distinct mechanism of early TAVR failure: thrombosis.

Central Message

We describe 3 cases of overt, early TAVR failure via 3 distinct mechanisms and review the literature on TAVR degeneration.

See Editorial Commentary page e95.

Video clip is available online.

Transcatheter aortic valve replacement (TAVR) is now a well-established therapy for patients with high or prohibitive surgical risk and severe aortic stenosis. Expanding indications include valve-in-valve treatment of bioprosthetic valve degeneration, predominant aortic regurgitation, and, more recently, treatment of patients at increasingly lower surgical risk and younger ages. Although short and intermediate follow-up studies of early-generation Edwards SAPIEN^{1,2} (Edwards Lifesciences, Irvine, Calif) and SAPIEN XT³ valves consistently have shown that clinically significant early valve degeneration is exceedingly rare, given the continued increase in TAVR volume, clinicians should be aware of the mechanisms for these uncommon presentations. Accordingly, we present 3 clinical cases of early TAVR degeneration from 3 distinct mechanisms.

CASE 1: VALVE THROMBOSIS

A 92-year-old woman presented for evaluation of progressive, mild dyspnea on exertion. She had undergone TAVR 4 years previously with a 23-mm Edwards SAPIEN XT valve for severe, calcific aortic stenosis. To evaluate her symptoms, a transthoracic echocardiogram (TTE) was obtained, which demonstrated a 0.8 × 0.5-cm supravulvar thrombus on the anterior cusp of the bioprosthetic valve (Figure 1 and Video 1). Peak and mean transaortic valvular gradients were elevated at 42 and 22 mm Hg, respectively (peak velocity 3.3 m/s; dimensionless index 0.33).

Moderate aortic regurgitation was noted with a larger central jet and a smaller anterior paravalvular jet. On review of the patient's TTE 1 year previously, the bioprosthetic valve was functioning well with trivial aortic regurgitation, as well as peak and mean transprosthetic aortic valvular gradients of 26 and 15 mm Hg, respectively, compared with gradients of 14 and 8 mm Hg, respectively, immediately post-TAVR. Clinically, she had no features suggestive of infectious endocarditis, and her blood cultures were negative. The patient had been maintained with dual antiplatelet therapy after TAVR. On discovery of valve thrombosis, anticoagulation was started with plans to follow her clinically and with serial echocardiography.

CASE 2: CUSP RUPTURE

A 95-year-old woman presented for evaluation of rapidly progressive dyspnea, initially present with minimal exertion and now with symptoms at rest. She underwent TAVR 3 years previously with a 23-mm Edwards SAPIEN XT valve for severe calcific aortic stenosis. A TTE demonstrated severe aortic regurgitation secondary to a flail posterior prosthetic valve leaflet (Figure 2 and Video 2) that was new compared with the most recent TTE from 1 year previously. Her TTE was otherwise notable for mild left ventricle dilation with mildly reduced systolic function (left ventricular ejection fraction 45%-50%). There were no visible

FIGURE 1. TTE showing 0.8×0.5 -cm supravulvar thrombus (yellow arrow) on bioprosthetic SAPIEN XT (Edwards Lifesciences, Irvine, Calif) valve in parasternal short-axis view (A). TTE with color Doppler during diastole in apical long-axis view demonstrating associated aortic insufficiency (B). TTE with continuous-wave Doppler in apical long-axis view demonstrating mild-moderate aortic insufficiency and increased velocity across the valve (C, peak velocity of 3.3 m/s and peak and mean gradients of 42 and 22 mm Hg, respectively). Correlative TTE images from 1 year previously (3 years post-TAVR) demonstrating the lack of thrombus, valve dysfunction, and lower transvalvular peak velocity and gradients (D-F).

vegetations, she had no systemic or constitutional symptoms, and blood cultures were negative. Severe leaflet calcification was absent, and the mobility of the other leaflets was normal. Therefore, the mechanism was presumed to be structural failure. The patient was managed expectantly on the basis of goals of care discussions.

CASE 3: ACCELERATED CALCIFIC DEGENERATION IN RADIATION-ASSOCIATED HEART DISEASE

A 62-year-old woman presented for evaluation of dyspnea on exertion and orthopnea that had progressed over a 6-month period. She underwent TAVR 5 years previously with a 23-mm Edwards SAPIEN valve for severe aortic stenosis. Her valvular disease developed in the setting of prior mantle radiation for the treatment of Hodgkin's lymphoma at age 15 years. She had several comorbidities, including severe chronic obstructive pulmonary disease, systemic scleroderma, and paroxysmal atrial fibrillation with a prior stroke. A TTE demonstrated new severe mixed bioprosthetic regurgitation and stenosis (peak and mean gradients of 80 and 46 mm Hg, respectively; peak velocity 4.5 m/s; dimensionless index of 0.15), secondary to severely restricted prosthetic valve leaflet motion from accelerated calcific degeneration (Figure 3 and Video 3). There was

also moderate (2-3+) mitral regurgitation and moderate mitral stenosis with thickening of the aorto-mitral intervalvular fibrosa. There was no echocardiographic or clinical findings to suggest prosthetic valve endocarditis. Given the comorbidities and radiation-associated heart disease that limited her surgical candidacy during her native valvular degeneration, she again was deemed suitable for only percutaneous valve therapy and underwent successful transfemoral, valve-in-valve implantation of a 23-mm Edwards SAPIEN XT valve. She had an uneventful postprocedural course, and her symptoms improved to New York Heart Association class I.

DISCUSSION

With increasing indications for TAVR, identifying and understanding associated complications, such as early valvular dysfunction, are increasingly important. Short and intermediate follow-up studies of early-generation Edwards SAPIEN^{1,2} and SAPIEN XT³ valves have consistently shown that clinically significant early valve degeneration is rare and has decreased further with improved valve design in newer-generation valves and with increased experience with TAVR.^{4,5} Nonetheless, distinct, rare causes of early failure have been identified, including structural dysfunction, thrombosis, prosthetic endocarditis, compression, and late migration.⁶

VIDEO 1. TTE demonstrating 0.8×0.5 -cm supravulvar thrombus (yellow arrow) on bioprosthetic SAPIEN XT (Edwards Lifesciences, Irvine, Calif) valve in parasternal short-axis (A) and apical long-axis (C) views. Associated prosthetic valvular insufficiency seen by color Doppler in parasternal short-axis (B) and apical long-axis (D) views. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(16\)31676-2/addons](http://www.jtcvsonline.org/article/S0022-5223(16)31676-2/addons).

FIGURE 2. TTE showing only mild valve thickening, but flail leaflet in parasternal long-axis (A), parasternal short-axis (B), and apical long-axis (C) views. Correlative TTE Doppler views demonstrating severe prosthetic transvalvular regurgitation (D, E). Continuous-wave Doppler demonstrating severe prosthetic valvular insufficiency (F).

VIDEO 2. TTE showing only mild valve thickening, with cusp rupture and flail leaflet in parasternal long-axis (A), apical long-axis (C) and parasternal short-axis (E) views. Correlative TTE color Doppler views demonstrating severe prosthetic valvular insufficiency (B, D, F). Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(16\)31676-2/addons](http://www.jtcvsonline.org/article/S0022-5223(16)31676-2/addons).

In the surgical literature, valve degeneration is invariably defined by the necessity for reoperative valve replacement and occurs infrequently within the first 5 years.^{7,8} Mechanistically, early surgical valve degeneration has been attributed to accelerated bioprosthetic leaflet calcification, subclinical thrombus formation, or pannus ingrowth. However, subclinical valve hemodynamic changes can be detected earlier (up to 20% at 8 years), occur at variable frequencies and rates depending on valve-specific and patient-specific factors, and have been of recent interest because they may be premonitory of overt clinical valve degeneration requiring reoperation.^{9,10}

Recently, in the context of expanding indications and increased life expectancies, much attention has been devoted to questions of percutaneous valve durability, as parallel changes in post-TAVR valve hemodynamics have been observed.¹¹⁻¹⁴ Although 5-year follow-up of the

Placement of Aortic Transcatheter Valves (PARTNER) trial demonstrated no significant changes in mean transvalvular gradients or cases of overt valve failure,¹ other studies have shown small, subclinical changes in valve hemodynamics during the first several years.¹²⁻¹⁴ There has been considerable focus on the potential contributions of subclinical valve thrombosis on both overt, early degeneration and subclinical transvalvular hemodynamic changes for both surgical aortic valve replacement and TAVR.^{15,16}

In the current series of patients, we demonstrate rare cases of overt, early TAVR failure from 3 distinct mechanisms: (1) obstructive valve thrombosis that developed in the interval between 3 and 4 years post-TAVR despite prolonged dual antiplatelet therapy; (2) flail leaflet, likely from inherent structural failure related to cusp rupture; and (3) rapid calcific degeneration in the setting of radiation-associated heart disease.

FIGURE 3. TTE showing severe valve thickening and degeneration in parasternal long-axis (A) and parasternal short-axis (D) views. Associated severe aortic insufficiency demonstrated by color Doppler in apical long-axis (B, C) and parasternal short-axis (E) views. Continuous-wave Doppler demonstrating severe aortic insufficiency (F).

Valve Thrombosis

Significant bioprosthetic valve thrombosis occurs infrequently in surgically implanted valves with a frequency of 0.36% to 1.26%.¹⁷ Temporally, overt thrombus is known to occur more frequently shortly after surgery, and many patients are consequently treated with systemic anticoagulation for several months after surgery. The incidence, clinical significance, and proper antithrombotic prophylaxis for valve thrombosis are less well-established post-TAVR. Valve thrombosis was not reported in the PARTNER trials, and only a single case (0.8% of 130 patients) was identified in the PARTNER EU trial.^{1,18} In a large multicenter retrospective study of more than 4200 patients, bioprosthetic valve thrombosis (SAPIEN AND SAPIEN XT valves) was identified in only 26 patients (0.61%), with an associated increased mean transvalvular gradient (41 ± 14 mm Hg) within 2 years postprocedure.¹⁹ Many of these events may be clinically silent because symptoms were not identified in 31% of these patients. Likewise, a study using sensitive multidetector computed tomography scanning in 140 patients up to 3 months after SAPIEN XT TAVR identified only 5 patients (4%) with valve thrombosis, all asymptomatic without a change in valve hemodynamics.²⁰ In a multicenter registry of more than 1500 patients, the lack of anticoagulation at discharge was independently predictive of hemodynamic deterioration

(>10 mm Hg transprosthesis gradient increase).¹⁵ Other than this report, there have been only 10 published reports (15 individual cases) of overt valve thrombosis involving the SAPIEN or SAPIEN XT valves, and a large proportion of these were nonobstructive, subclinical thrombi.²⁰ The current case demonstrates an obstructive thrombus (mean transvalvular gradients >20 mm Hg) with associated symptoms of acute decompensated heart failure that occurred during an intermediate time interval after TAVR. In prior studies, the use of anticoagulation in patients with subclinical valve thrombi with increased transvalvular gradients has resulted in gradient reduction, and likewise, this patient is currently being treated with initial anticoagulation therapy.¹⁹

Cusp Rupture

Cusp rupture and associated flail leaflet without a clear cause, such as from prosthetic valve endocarditis, trauma, or calcific degeneration, have not been reported in SAPIEN valves. In the largest post-TAVR meta-analysis of 70 prior studies, only 3 prior cases of structural valve failure with severe transaortic prosthetic regurgitation were identified.⁶ Only 1 of these was presumed to be due to cusp rupture and occurred in a 29-mm CoreValve device (Medtronic, Minneapolis, Minn).²¹ In this case, Pagnotta and colleagues²¹ presumed that postdilation of the valve resulted in tearing of the valve leaflet, inducing severe transvalvular

VIDEO 3. TTE showing severe valve thickening and degeneration in apical long-axis views (A, C) and parasternal short-axis view (E). Correlative color Doppler demonstrating severe aortic insufficiency (B, D, F). Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(16\)31676-2/addons](http://www.jtcvsonline.org/article/S0022-5223(16)31676-2/addons).

aortic regurgitation several days after the initial implantation. Zegdi and colleagues²² demonstrated that postdilation causes microscopic leaflet injury, but progression to overt valvular failure and regurgitation must be exceedingly rare given how frequently postdilation is performed. In the surgical literature, gross pathology studies of degenerated bioprosthetic valves more than 10 years after implantation have shown high rates of cusp tears or perforations (80%), primarily attributed to calcific degeneration.²³ This case demonstrates an extremely rare cause of early valve failure with cusp rupture and flail leaflet with associated severe transvalvular aortic regurgitation. This failure occurred between 2 and 3 years post-TAVR without a clear cause, presumably related to primary structural failure.

Accelerated Calcific Degeneration in Radiation-Associated Heart Disease

The long-term survival of patients with radiation-associated heart disease who undergo cardiothoracic surgery is known to be significantly lower than of the general population, but data on TAVR durability in this population are scarce.²⁴ Only 3 patients (0.9%) enrolled in PARTNER A and 15 patients (8.4%) in PARTNER B had documented deleterious effects from prior mediastinal radiation.^{25,26} In 5-year follow-up of the initial PARTNER trial, there was no association of prior chest radiation with worse outcomes or concerns of valve durability, although the numbers were small.^{1,2} The PARTNER 2 trial did not specifically collect data on prior mediastinal radiation.³ In a study comparing standard TAVR cases with TAVR cases with prior

radiation-induced valvular heart disease (9.6% of the study's cohort of 198 patients), there were no differences in valve hemodynamics or function at 6 months, but studies specifically devoted to longer-term follow-up have not been performed.²⁷ The current case demonstrates the first report of accelerated calcific degeneration in the setting of prior radiation-associated heart disease. In the surgical literature, it is known that patients with radiation-associated heart disease who undergo cardiothoracic surgery have significantly worse perioperative and long-term survival, with approximately 40% mortality at a mean of approximately 7.5 years.²⁴ The mechanism of increased mortality is unclear, but aorto-mitral curtain thickness appears to be independently predictive.²⁸ Although the mechanism for early valve failure in this patient is uncertain, we postulate that the extent and location of severe pre-TAVR calcifications related to prior mantle radiation may have contributed to unique and subtle but deleterious hemodynamic stress from incomplete circumferential deployment that accelerated recalcification of this first generation SAPIEN valve.

CONCLUSIONS

In this series of patients, we demonstrate 3 cases of overt, early TAVR failure from 3 distinct mechanisms. Although this is rare, with increased use of TAVR, it is important for clinicians to recognize the clinical presentations and mechanisms of early TAVR degeneration.

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