Mechanisms of Transcatheter Valve Degeneration

A translational perspective.

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Over the past 20 years, transcatheter aortic valve replacement (TAVR) with transcatheter heart valves (THVs) has proven to be a safe and effective alternative to surgical aortic valve replacement (SAVR) with bioprosthetic surgical heart valves (SHVs) or mechanical prostheses.[1] While historically indicated for patients at high surgical risk, improvements in valve durability and design, the growing number of experienced operators, and consideration for patient preference have led to a shift in recommendations toward THV use in younger and lower-risk patients.[2] This broadening of the recipient pool, along with the projected increase in heart valve diseases globally within the aging population, suggests an exponential increase in demand and use of THVs in the coming decades.[3] Thus, studying and improving THV durability is crucial in meeting growing need.

There are four generally accepted modes of valve dysfunction: endocarditis, thrombosis, and nonstructural or structural deterioration.[4-8] The diagnosis of valve endocarditis considers Duke Criteria for infective endocarditis (ie, positive blood culture, vegetation on echocardiography) and can lead to valve degeneration and failure.[9] Subclinical and clinically significant thrombosis includes imaging findings of leaflet thickening and/or reduced leaflet motion with or without symptoms/sequelae of thromboembolic events or hemodynamic deterioration. Nonstructural valve degeneration describes mechanisms of degeneration that are extrinsic to the valve itself. This includes intra- and paraprosthesis regurgitation, pannus formation, valve malpositioning, patient-prosthesis mismatch, and valve embolization. This contrasts with structural valve degeneration (SVD), which encompasses permanent degenerative changes that are intrinsic to the valve leaflets, struts, or stents. Examples include fibrosis,

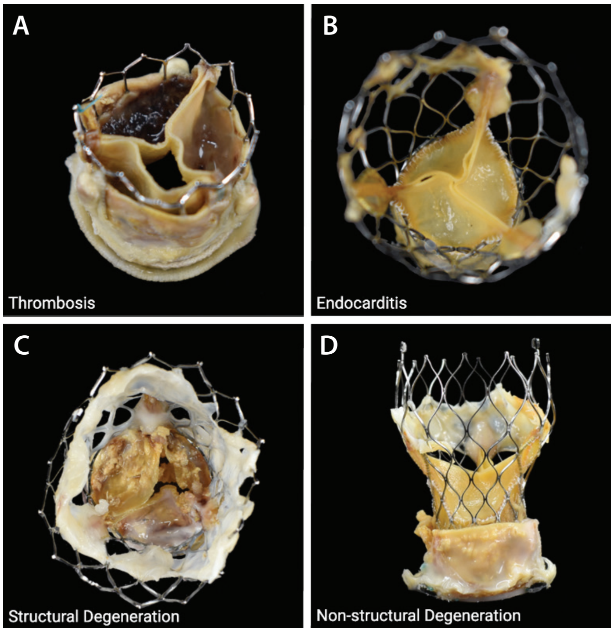

Figure 1. Modes of THV dysfunction: Explanted THV specimens provide insights to THV degeneration and dysfunction, including examples of leaflet thrombosis (A) in a VIV specimen, a THV explanted after endocarditis (B), structural degeneration characterized by expensive leaflet calcification (C), and an example of a VIV explanted due to patient-prosthesis mismatch (D).

wear and tear, disruption, flail, stent fracture or deformation, and calcification.[4-8]

Figure 1 demonstrates examples of these four modes of dysfunction from the bench to provide a translational example beyond typical clinical imaging modalities; Figure 1 shows THVs explanted due to dysfunction that have leaflet thrombosis, demonstrate serve leaflet calcification, or are from patients with prosthesis mismatch or endocarditis.

TRANSCATHETER DEGENERATION

Clinical Insights

The study of THV outcomes and durability clinically, including their comparison to SHVs, is challenging. This is in part because of the relative infancy of the use of THVs and the rapidly evolving field of transcatheter valve replacement. This means that longer-term THV studies are limited to earlier-generation transcatheter devices that frequently have been replaced by new technologies. Moreover, rapidly advancing overall operator experience, as well as techniques to optimize factors such as device positioning, sizing, etc, potentially impact durability before long-term outcomes are available. Furthermore, the THV study population continues to evolve from generally older and higher-risk patients to lower-risk populations, resulting in a probable effect on durability and mechanisms of degeneration. Finally, the criteria for defining valve degeneration has evolved; current and recent guidelines focus on the use of imaging and valve functional evaluation.[6-8,10,11] These approaches provide diagnostic but not granular or real-time mechanistic insights to degeneration. However, approaches using positron emission tomography (PET) tracers are beginning to allow such insight to valve degeneration in situ.[12-14] In the 18F-sodium fluoride (18F-NaF) 18F-FAABULOUS study, the radiotracer 18F-NaF is used as a marker of calcific activity to determine SVD in TAVR and SAVR patients.[12,13] Using 18F-NaF PET/CT imaging, this study has found comparable 18F-NaF uptake between TAVR and SAVR, suggesting similar rates of SVD. Furthermore, it has been found that the baseline uptake of 18F-NaF is associated with a resultant change in peak aortic velocity in both TAVR and SAVR and could, therefore, be a predictor and early marker of SVD. Interestingly, the uptake of NaF around the outside of the bioprosthesis suggests continued and active calcific disease progression of the native leaflets after TAVR, a unique feature of THVs that is not considered in SHVs. Interestingly, PET has also recently provided further functional insight to leaflet thrombus formation in surgical and transcatheter valves; 18F-GP-1, targeted to glycoprotein IIb/IIIa, was shown to be specific to activated platelets and targeted to areas of THV leaflet thrombus.[14] This tracer revealed the common and enduring finding of activated platelets, which increased in clinical cases of leaflet thrombosis, did not bind to areas of leaflet fibrosis or calcification, and regressed in clinical thrombosis treated with anticoagulation.

Histopathological Analysis From the Clinic: A Timeline for THV Pathophysiology

Histologic analyses supported by imaging findings propose a likely timeline of pathophysiology of THVs and processes causing degeneration.[15-17] Immediately after THV deployment, the bioprosthesis undergoes covering with the presence of CD31+ cells along the prosthesis, but morphologic analyses of these cells indicate an abnormal pseudostratified columnar hyperplasia phenotype, therefore suggesting prosthesis occupation by dysfunctional endothelial-like cells. This coincides with, or is immediately followed by, thrombus formation of varying degrees that can vary by implant duration, with inflammation a common and early finding of THV pathophysiology. Approximately 2 months after the procedure, fibrosis is found in combination with leaflet thrombus on explants and shows maturation over time, as characterized by morphologic and cellular changes of the matrix and increased decorin expression. Finally, signs of calcification appeared in THVs implanted for 4+ years, with the notable exception of endocarditis, which has been found to include

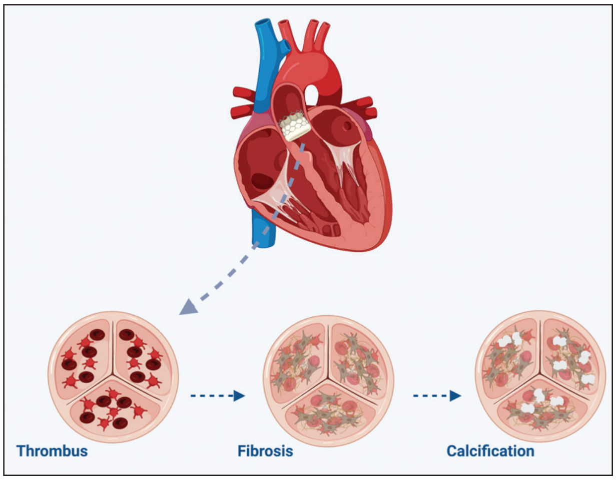

Figure 2. Steps of THV pathophysiology: Biological features of THV pathology contributing to dysfunction and degeneration are still being elucidated but include thrombus formation, fibrosis, and calcification for which timelines have been established by histopathology. This figure was made with Biorender.

calcification at much earlier time points. Figure 2 depicts major features of this timeline.[15-17]

TISSUE MECHANISMS OF DEGENERATION

Leaflet Structure and Mechanical Degradation

The native heart valve is a complex and bioactive structure capable of responding to its environment, performing self-repair, and maintenance. This is in stark contrast to the decellularized and uniform tissue used in surgical and transcatheter bioprosthetic heart valves (BHVs). Some of these differences are thought to explain why BHVs degenerate much faster than native heart valves.[18] For instance, the lack of an active/functional barrier allows for the accumulation of micro- and macro-molecules, including calcium, calcium-binding proteins, lipid complexes, fibrin/fibrinogen and plasminogen, alkaline phosphatase, matrix metalloproteinases (MMPs), and serum albumin. The deposition of these molecules leads to changes in the landscape of the prosthesis by providing new ligand-binding domains and, through the continued functionality of various enzymes, can directly remodel collagen fibers.[19]

The extracellular matrix (ECM) structure of BHVs itself can lead to increased mechanical stress. Compared to native valves that utilize a complex arrangement and rearrangement of ECM components throughout the cardiac cycle, BHV leaflets have an overly rigid and simplistic collagen arrangement that does not adapt to the cardiac cycle.[18,20] In diastole, the very low pressures cause the native heart valve leaflets to be stretched closed, collagen is aligned and uncrimped, and elastin is stretched to avoid leaflet prolapse. In systole, the opposite occurs, the native leaflets are bent open, collagen is crimped and unaligned, and elastin is relaxed and recoiled. In BHV leaflets, the collagen arrangement is locked in a "closed valve" position. This results in increasingly rigid leaflets, which reduces their ability to absorb strain.[18,21]

During tissue preparation, most BHVs are treated with glutaraldehyde, a cross-linking agent that improves stability and reduces antigenicity while maintaining the viscoelastic properties of collagen. However, glutaraldehyde cross-linking also results in a stiffer, more rigid tissue matrix and residual aldehydes from the treatment can become attractive nuclei for calcification.[22] Furthermore, elastin, glycosaminoglycans (GAGs), and proteoglycans (PGs) are often lost or damaged in the treatment process. Not only does this alter the elastic and structural properties of the matrix to reduce extensibility and increase stiffness, but PGs in particular are known to block certain areas of collagen fibers called "hole zones." In the absence of PGs, calcium phosphates (CaPs) are known to grow from these collagen fiber hole zones.[21]

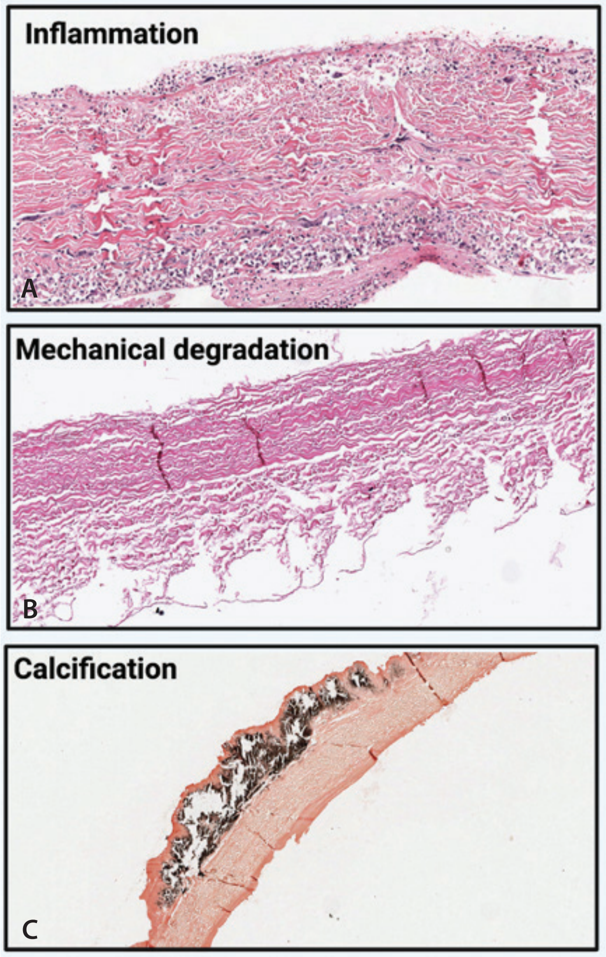

Figure 3. Histopathologic features of THV degenerative mechanisms: Features of degeneration mechanisms of THVs can be appreciated on histopathology and include inflammation (A), mechanical damage (B), and calcification (C).

Beyond leaflet structure, of which there are many shared features between pericardial surgical and transcatheter valves, some mechanisms of leaflet damage that can contribute to degeneration are specific to THVs. These include (1) trauma from crimping, loading into a delivery catheter; (2) damage due to balloon expansion; and (3) noncircular or suboptimal deployment.[23-25] While bench studies can look at the mechanisms and extent of this damage, examine their impact of biological response using in vitro systems or animal models, and assess potential wear over time using accelerated wear testing, studies linking these to long-term causes of SVD in patients are still needed.

Immune Response

A common response to the implantation of bioprostheses, including THVs, is the innate foreign body

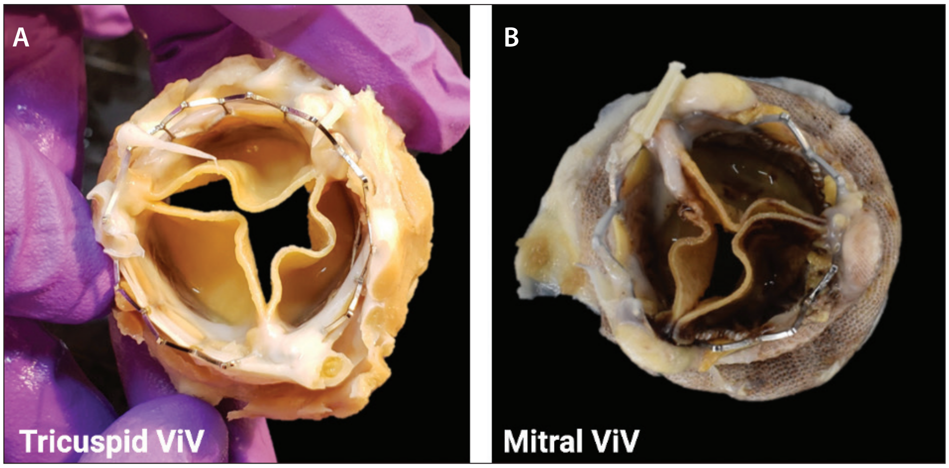

Figure 4. Nonaortic THV degeneration: Specimens from nonaortic positions are beginning to provide insights features of degeneration, including those from VIV implants including the tricuspid (A) and mitral (B) positions.

immune response. This response is generally triggered by damage to the surrounding tissue during implantation and is quickly followed by adsorption of serum protein and leukocyte adhesion, leading to thrombosis and inflammation at the implant site. Fibroblasts eventually attempt to seal off the foreign device from the rest of the body and so encapsulate it in excessive ECM.[20,26-28]

THV leaflets derived from porcine or bovine tissue contain two notable carbohydrates: galactose-alpha-1,3-galactose (α-Gal) and N-glycolylneuraminic acid (NeuGC). α-Gal and NeuGC are found in most mammalian membranes but are absent in humans. Furthermore, given their lack of amino groups or lack of accessible amino groups, these carbohydrates can evade cross-linking by glutaraldehyde. So, although glutaraldehyde treatment reduces antigenicity, it does not completely absolve it; the exposed antigens can attract immune cells, such as macrophages, which have a specific receptor for α-Gal, triggering an adaptive immune response.[20,29-31] Several studies of BHV explants have identified occupation of the prosthetic valves. Furthermore, studies of THVs have identified some of the cell types to infiltrate THV leaflets,[15-17] including analysis of enzymes expressed, which may contribute to THV degeneration. For example, MMPs have been noted in THVs and surgical bioprosthetic valves[15,32] and are hypothesized to play a role in both tissue response and leaflet degradation.

Mechanisms of Calcification

Mechanisms of calcification can be classified in different ways, but two general groupings are passive and recipient-related calcification. Passive calcification describes the gradual deposition of CaP on cell debris, fibrosis, and degraded collagen fibers.[33] Recipient-related calcification considers patient-specific factors that can accelerate calcification. This includes higher than average concentrations of serum calcium-binding proteins or CaP or low concentrations of fetuin A, conditions that can affect calcium metabolism such as hyperparathyroidism, end-stage renal disease, or growth spurts, as well as the recipients' own cells[34-37]—for instance, macrophage mineralization through apoptosis or the creation of new calcification nuclei brought about by the iron released from recipient red blood cells that goes on to oxidize cell debris and ECM components.[38]

Figure 3 demonstrates some histopathologic findings of leaflet inflammation, mechanical leaflet damage, and leaflet calcification.

FUTURE DIRECTIONS

Research that aims to uncover mechanisms of valve degeneration and seeks new methods to improve durability is paramount. As our knowledge continues to grow, an important future direction will be the consideration of the use of THVs in positions other than the aortic valve; it will be critical to consider if timelines and mechanisms of degeneration in these implants and patient populations differ. While no current analyses have provided insights on mechanisms of degeneration in a large cohort, case series and reports do provide some insights on tricuspid and mitral prostheses,[39,40] including use of aortic THVs for valve-in-valve (VIV) procedures. Figure 4 shows features of some such VIV explants.

Much work also remains to improve aortic transcatheter valve durability. Given what we know about the mechanisms of THV degeneration, there would appear to be three general categories of research to improve durability: (1) targeting and reducing mechanical stress and improving leaflet structure, (2) methods to prevent and slow calcification processes, and (3) evading and suppressing the recipient's immune response.

An important difference between BHV leaflets and native leaflets is a lack of cellularity and an overly static tissue matrix configuration that can make BHV leaflets unable to respond to their environment or self repair and maintain their structural integrity. This issue is being addressed by some groups working to produce more bioactive BHV leaflets that are better able to adapt and respond to their environment and the cardiac cycle.[41,42] Furthermore, there is ongoing research into new methods of cross-linking and preparing BHV leaflet tissue. These include the use of diepoxides or genipin instead of glutaraldeyde.[43-45] These methods seek to reduce mechanical stress, improve tissue structure and longevity, reduce affinity for CaP deposition, and better evade immune rejection.

Studies into methods to prevent and slow calcification include various anticalcific treatments such as FREE and Resilia (Edwards Lifesciences) that work to reduce exposed phospholipids, aldehydes, and other chemical groups that are known to promote CaP deposition.[46,47] Furthermore, methods to improve decellularization of leaflet material are being explored. As retained cells and cellular debris can initiate immune reactions that can lead to calcification and SVD, this is a potentially impactful line of investigation.[41]

To reduce immunogenicity of THV implants, some groups are looking into the use of genetically modified porcine or bovine tissues—specifically, the use of strains of pigs and cows in which α-Gal and/or NeuGC is knocked out while often simultaneously increasing expression of various human proteins.[48-50] Similarly, other research considers the use of various immunosuppressants, including steroid therapies, to evade and suppress the recipient's immune response.[51] ■

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