CONTEMPORARY REVIEW

Noncalcific Mechanisms of Bioprosthetic Structural Valve Degeneration

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ABSTRACT: Bioprosthetic heart valves (BHVs) largely circumvent the need for long-term anticoagulation compared with mechanical valves but are increasingly susceptible to deterioration and reduced durability with reoperation rates of ≈10% and 30% at 10 and 15 years, respectively. Structural valve degeneration is a common, unpreventable, and untreatable consequence of BHV implantation and is frequently characterized by leaflet calcification. However, 25% of BHV reoperations attributed to structural valve degeneration occur with minimal leaflet mineralization. This review discusses the noncalcific mechanisms of BHV structural valve degeneration, highlighting the putative roles and pathophysiological relationships between protein infiltration, glycation, oxidative and mechanical stress, and inflammation and the structural consequences for surgical and transcatheter BHVs.

Key Words: bioprosthesis ▪ bioprosthetic heart valve ▪ structural valve degeneration ▪ valve replacement

The prevalence of valvular heart disease is estimated at 2.5% within the US population, with an abrupt increase after the age of 65 years owing to the predominance of degenerative etiologies.1 In parallel, the incidence of degenerative valvular heart disease is expected to increase at a rate commensurate with the expansion of our elderly population. Valvular heart disease remains common in industrialized countries—the decrease in prevalence of rheumatic heart disease has been accompanied by a relative increase in that of degenerative valvular heart disease. In patients with significant native valve insufficiency or stenosis in whom valve repair or reconstruction is not feasible or contraindicated, valve replacement is most commonly offered with either mechanical or bioprosthetic heart valves (BHV).2 Mechanical valves, which are advantageous in settings requiring a diminished profile compared with BHV, require lifelong anticoagulation with an increased risk for bleeding complications and may also be associated with hemolytic anemia.3,4 On the other hand, BHVs largely obviate the need for lifelong anticoagulation, but have reduced durability as a result of BHV failure with reoperation rates of ≈10% at 10 years and up to 30% at 15 years.2,5

BHV tissue components generally consist of glutaraldehyde-fixed heterograft tissues, including porcine aortic valves and pericardium of bovine, porcine, and equine origins.6,7 The most common tissues used in BHVs are bovine pericardium (BP) and intact porcine aortic valves. These tissues have desired viscoelasticity derived from their extracellular matrix (ECM) structures, which are suited to their biomechanically active roles. Type I collagen is the predominant protein in both biomaterials, comprising integrated networks of fiber bundles that provide structural integrity and force dissipation in all directions to withstand the cyclic mechanical loading of valve leaflets.8 Furthermore, structural strength and material durability are imparted by glutaraldehyde treatment, which stabilizes tissue ultrastructure by cross-linking free lysine residues.9 Glutaraldehyde treatment also reduces tissue xenogeneic immunogenicity.10 This method of fixation, however, is imperfect. Glutaraldehyde treatment decreases but does not entirely eliminate the antigenicity of...
bioprosthetic tissue, as animal model studies showed that glutaraldehyde treatment caused humoral and cellular immune responses, including infiltration of xenografts by macrophages, T cells, and eosinophils.\(^1\) In addition, residual aldehydes from this treatment that are chemically bound or adsorbed to the tissue have been shown to contribute to calcification.\(^12,13\) This compounds the inherent susceptibility to calcification of the tissue, which has been shown to derive from phospho-esters in residual nucleic acids and other residual cellular phosphor-lipid membrane components\(^14\) as well as aldehydes intrinsic to the tissue. Susceptibility to tissue alteration in general is fundamentally derived from 2 inherent shortcomings of BHV biomaterials: (1) susceptibility to permeation of molecular and cellular blood components and (2), as with any nonliving tissue, BHV biomaterials lack the ability to turn over and actively remodel ECM to prevent degradation and the accumulation of structural/biochemical alterations. Multiple technologies (mostly aimed at preventing calcification) involving additional chemical modification of BHV tissues after glutaraldehyde treatment have been developed and implemented over the decades.\(^15\) Nonetheless, every valve prosthesis both interacts with blood components and invokes a pathophysiological host response, which impose risks of thromboembolism, prosthetic endocarditis, and nonstructural or structural valve degeneration (SVD) over time.\(^16\)

Nonstructural BHV degeneration is characterized by valve malfunction that is exclusive of intrinsic biomechanical failure of the prosthesis itself and is secondary to technical issues during implantation or by a host-mediated response that may manifest as pannus formation, suture entrapment, paravalvular leak, valve malpositioning or embolization, and patient–prosthesis mismatch. In comparison, BHV SVD refers to a failure of the intrinsic properties of the BHV biomaterials. Establishment of a comprehensive, uniform, standardized definition of SVD has proven difficult, however, the condition may generally be classified as BHV dysfunction resulting in stenosis, regurgitation, or both, that necessitates reoperation; a 2017 consensus statement from the European Association of Percutaneous Cardiovascular Interventions endorsed by the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery (EACTS) categorized hemodynamic structural aortic valve degeneration as moderate or severe.\(^17\) Moderate SVD was defined as mean trans-prosthetic gradient ≥20 and <40 mm Hg and/or ≥10 and <20 mm Hg change from baseline (before discharge or within 30 days of valve implantation) and moderate intraprosthetic aortic regurgitation, new or worsening (>1+/4+) from baseline. Severe SVD was defined as mean gradient ≥40 and >20 mm Hg change from baseline (before discharge or within 30 days of valve implantation) and severe intraprosthetic aortic regurgitation, new or worsening (>2+/4+) from baseline. Regarding mitral BHVs, a mean gradient ≥6 and <10 mm Hg is suggestive of moderate stenosis, ≥10 mm Hg for severe stenosis, and peak mitral velocity ≥1.9 m/s for prosthetic mitral regurgitation.\(^18\) It should be noted that the EACTS/European Association of Cardiovascular Imaging standardized definitions for SVD do not differentiate between true SVD and prosthesis–patient mismatch. In 2018, the Valve in Valve International Data investigators released a consensus statement whereby SVD was defined as “an acquired intrinsic bioprosthetic valve abnormality defined as deterioration of the leaflets or supporting structures resulting in thickening, calcification, tearing, or disruption of the prosthetic valve materials with eventual associated valve hemodynamic dysfunction, manifested as stenosis or regurgitation.” Notably, infective endocarditis and thrombosis are typically conspicuously excluded from definitions of SVD and will thus not be discussed in this review. Nevertheless, recent studies have suggested that nonstructural degeneration such as bioprosthetic leaflet thrombosis may precede and contribute to the progression of SVD.\(^19\)

Specifically, there was a time-dependent degeneration of transcatheter heart valves by a sequential cascade of thrombus formation within hours, fibrosis after 60 days, and calcification after 4 years, which ultimately contribute to progressive leaflet thickening and SVD, supporting the hypothesis of progressive leaflet thickening over time.\(^19\) In addition, the absence of anticoagulation therapy has been associated with significant increase in transvalvular gradients and accelerated SVD, indicating that valve thrombosis may be a pathologic process promoting SVD.\(^20\)

The difficulty in concisely characterizing BHV SVD is testament to the complex, multifactorial nature of the disease’s histological and clinical manifestations—although the technologies associated with BHV replacement procedures have undergone substantial sophistication, a comprehensive understanding of BHV

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Nonstandard Abbreviations and Acronyms

| Abbreviation | Definition |
|--------------|------------|
| AGE          | advanced glycation end-products |
| BHV          | bioprosthetic heart valve |
| BP           | bovine pericardium |
| DM           | diabetes mellitus |
| ECM          | extracellular matrix |
| HSA          | human serum albumin |
| MMP          | matrix metalloproteinase |
| SAVR         | surgical aortic valve replacement |
| SVD          | structural valve degeneration |
| TAVR         | transcatheter aortic valve replacement |
| VIV          | valve-in-valve |
SVD remains elusive. Our current understanding of calcific BHV SVD has improved considerably; however, currently no strategies for mitigation of BHV mineralization have achieved the desired result. The risk of structural failure is related to patient age, particularly in the case of individuals <35 years old who undergo valve replacement with BHVs. Children and adolescents have the highest rate of early primary tissue failure; BHVs implanted in patients <35 years old demonstrate nearly uniform valve failure at 5 years, whereas only 10% of BHVs implanted in patients >65 years old fail within 10 years.21 In a recent risk analysis stratified by age group, Bourguignon et al22 demonstrated that a 65-year-old patient has only a 5% probability of requiring reintervention for mitral BHV degeneration after 9 years of implant duration, whereas that probability for a 40-year-old patient is increased to 25%. Similarly, Frasca et al23 reported that in the rat subcutaneous implantation model, higher calcium content was found in BP implanted in juvenile rats compared with BP in adult rats. In addition, the mechanism(s) underlying age-dependent SVD is known to be a multifaceted process comprising an induced immunologic host response to the bioprostheses, leading to calcification in the majority of cases.5,24 Of note, however, more than 25% of BHV reoperations attributed to SVD occur with no or minimal leaflet mineralization.25,26 A proportion of the remaining 75% of degenerated BHVs may be subject to underappreciated, noncalcific mechanisms in which mineralization is a consequence rather than an active mediator of SVD. Adding an additional level of complexity, the natural histories of BHV SVD at the aortic and mitral positions, for example, are not equivalent; mitral valve BHVs are subject to dissimilar hydrodynamic stress, and the consequent SVD is characterized by earlier onset and is overall less robustly studied.27 Pivotal risk factors for BHV calcification include young age,28 renal failure,29 and diabetes mellitus (DM);30,31 although the importance, mechanisms, and approaches to the prevention of BHV calcification have been widely investigated, noncalcific mechanisms have been largely neglected in research and development efforts.25,32 The purpose of this article is to review noncalcific modes of BHV SVD, highlighting the need for further development of preventive and therapeutic strategies.

NONCALCIFIC MECHANISMS OF SVD Protein Infiltration
A major deficit of BHV biomaterials, in contrast to any native cardiovascular tissue, is the lack of any active barrier functionality against the infiltration of body fluids and biomolecules circulating therein. As a result, BHVs are highly susceptible to the infiltration of biomolecular components of the blood and the modifications to the tissue matrix. Indeed, the infiltration phenomenon underlies calcification, the most prominent feature of SVD. Pathologic mineralization leading to dystrophic calcification, and the formation of calcium phosphates, such as hydroxyapatite, involves disruption of calcium and inorganic phosphate balance attributed to local disease-related events interacting with calcium infiltration and alkaline phosphatase hydrolysis of phosphoesters. Beyond small molecule precursors for mineralization, it has long been established that both infiltrated circulating proteins and proteins derived from infiltrated cell membranes deposit in BHV tissue and influence mineralization. A battery of studies from the early 1980s confirmed the accumulation of low levels of osteocalcin, a bone-specific protein, and potentially other Gla-containing calcium-binding proteins in clinically implanted and animal-implanted porcine BHV tissues as well as validated the mechanism of noncellular diffusive infiltration in vitro.33–35 Furthermore, these studies indicated that osteocalcin accumulation correlated with calcification, suggesting that the properties of infiltrated proteins—in this case calcium binding—can mechanistically contribute to SVD. More than a decade later, osteopontin accumulation in BHVs and a similar association to calcification were also shown.36 Later, the same group used electrophoresis to observe an additional, 14-kDa protein preferentially accumulated in calcified, explanted clinical BHVs as well as 3 infiltrated proteins exclusively accumulated in noncalcified valves, providing the first indication that protein infiltration may contribute to noncalcific SVD.37 Furthermore, lipid complexes have been widely shown to infiltrate into BHV and may contribute to failure38–41 to the point that plasma lipoprotein levels correlate with BHV SVD.42,43 These findings establish that not only small molecules but also biological macromolecules and complexes relatively freely diffuse into BHV biomaterial.

The suggestion from these observations that the inherent properties of circulating proteins, such as calcium or lipid-binding capability, remain intact after infiltration into the tissue carries significant general implications for noncalcific SVD mechanisms. In 1992, Hilbert et al38 employed transmission electron microscopy to visualize extensive insudation of plasma proteins into Ionescu-Shiley bovine pericardial prostheses (particularly in areas of tissue delamination and around calcifications), specifically indicating fibrin infiltration. This group concluded that protein deposition is largely responsible for tissue thickening, a hallmark SVD characteristic. Accumulation of fibrinogen as well as plasminogen in explanted BHVs was confirmed recently.44 It was suggested that increased fibrinogen in BHVs versus native valves may contribute to the formation of fibrin thrombi, thus contributing to bioprosthetic valve
thrombosis. Similarly, the authors suggested that plasminogen contributes to inflammation and calcification in BHV and native valves. The separate identification of both fibrinogen and fibrin fibers in BHV tissue suggest that infiltrated fibrinogen retains its ability to be enzymatically cleaved and its resultant polymerization functionality in the tissue (Figure 1). Also with respect to enzymes, alkaline phosphatase and matrix metalloproteinases (MMPs) retaining procalcific and ECM-degrading enzymatic activity, respectively, have been shown both to persist in BHV tissues through glutaraldehyde treatment and to infiltrate into clinically or experimentally implanted BHV tissue. Such degradative enzymatic activities compound the negative effects of the tissue’s inherent inability to turn over/remodel its ECM. A recent work reported both the deposition of the most abundant circulating protein, human serum albumin (HSA), in explanted clinical BHV and the uniform diffusive infiltration of albumin throughout bovine pericardial BHV tissue in vitro within 24 hours of exposure to physiologic concentrations of HSA. Furthermore, given the multiple indications that protein properties are retained in BHV tissue and the noted contributions of body fluid insudation to BHV SVD, serum albumin may especially contribute to collagen misalignment and tissue thickening/mass increase because of its high hygroscopicity and outsized contribution to oncotic pressure. It may also significantly modify tissue affinity for circulating molecules because of its promiscuous ligand-binding capabilities.

Inflammation and Oxidative Stress in Noncalcific Structural Valve Disease

Oxidative stress has been identified as an important, understudied contributor to material failure in all
biological grafts or prostheses, regardless of the tissue composition or the site of implantation. All implantable biological and synthetic materials invariably elicit host immune reaction, termed the foreign body reaction. The foreign body reaction is macrophage-mediated and foreign body giant cell–mediated and is characterized by acute and chronic inflammation involving a localized response characterized by the migration of activated inflammatory cells to the surface of the material; active inflammatory cells produce reactive oxygen and nitrogen species as well as MMPs that play key roles in tissue remodeling under both physiologic and pathologic conditions by degrading extracellular matrix proteins such as collagen, elastin, and fibronectin. The contribution of oxidative damage to BHV failure has been most rigorously studied in the context of pathologies associated with increased oxidative stress. DM, for example, is characterized by hyperglycemia and a resultant increase in the production of highly reactive oxygen species. Significantly shorter implant duration was found in patients with DM compared with patients without DM by Lee et al.

Lee et al. further demonstrated that elevated concentrations of oxidized amino acids and calcium in BHV leaflets correlate with BHV dysfunction requiring reoperation (Table 1). Specifically, this work identified dityrosine (a protein cross-linking oxidized amino acid) most prominently within the central region of the BHV cusps. Localization to the central region of the cusp (the most prominent site of collagen architecture disruption in failed BHVs) suggests an important association between mechanical stress, oxidative damage, and BHV failure. Indeed, all explanted cusps demonstrated a lower degree of collagen fiber alignment in the vicinity of the nodulus of Arantii, accompanied frequently by a band extending from the nodulus down toward the basal attachment; the same result was achieved also in in vitro tests, suggesting the change in leaflet curvature during the cardiac cycle gives rise to bending stresses, shearing, or buckling. Notably, calcium concentrations alone did not necessarily predict implant duration, suggesting that oxidized amino acids may play a significant role in a calcium-independent mechanism of BHV SVD.

Christian et al. investigated the effects of oxidative stress on bovine BHVs using clinical pathologic BHV explants as well as experimental models: increased levels of the oxidized amino acids such as ortho-tyrosine, meta-tyrosine, and di-tyrosine were present in explanted valves compared with nonimplanted BHV. In vitro modeling demonstrated that exposure to oxidizing conditions results in significant collagen deterioration, loss of glutaraldehyde cross-links, and increased susceptibility to collagenase degradation leading to matrix stiffening. The role of oxidative stress in BHV SVD has also been investigated by Lee et al. in both BP and porcine BHVs: one third of the explanted BHVs had little to no detectable leaflet calcium content, even if the relatively noncalcified BHV explants had implant durations that did not differ significantly from calcified explants. Thus, they observed di-tyrosine was significantly increased in all explanted BHVs compared with unimplanted BHVs.

Bottio et al. instead observed lipid insudation and monocyte infiltrates in the cuspal tissue of explanted porcine BHVs even in the absence of mineralization. Another study by Shetty et al. suggested that active cellular and inflammatory mechanisms triggered by oxidized lipids could contribute to SVD: a high proportion (72%) of explanted BHV had a significant accumulation of oxidized low-density lipoprotein (ox-LDL) within their leaflets, dense cellular inflammatory infiltrates, foam cells, expression of MMP-9, and disruption of collagen fibers. It should indeed be emphasized that MMP-9 was highly expressed by infiltrating inflammatory cells and that the active form of the enzyme was also present within the BHV leaflets. It is well known that foam cells and macrophages activated by ox-LDLs produce and release MMPs.

The lipidic-inflammatory pathway has been supported by studies suggesting high lipid levels as a risk factor for BHV SVD. Mahjoub et al. noticed higher plasma levels of low-density lipoprotein cholesterol, non–high-density lipoprotein cholesterol, and apoB (apolipoprotein B) as well as higher apoB/apoA-I (apolipoprotein A-I) and total cholesterol/non–high-density lipoprotein cholesterol ratios are significantly associated with increased risk of valve degeneration. A similar result was investigated by Nsabilia et al., suggesting an elevated ox-LDL/high-density lipoprotein ratio and a high blood plasma concentration of PCSK9 (proprotein convertase subtilisin/kexin 9) protein highly expressed in the liver, where it decreases the expression of the LDL receptor, as risks of SVD. Indeed, metabolic syndrome, a cluster of atherogenic-inflammatory-atherothrombotic abnormalities, which are largely a result from overweight/obesity and sedentary lifestyles, was found to be associated with accelerated SVD. Future investigations to experimentally demonstrate mechanistic effects of the lipidic-inflammatory pathway on SVD are warranted.

**Nonenzymatic, Posttranslational Protein Glycation of BHV Biomaterials**

Glycation comprises a complex constellation of chemical reactions between saccharide, such as glucose and fructose, or sugar-derived reactive carbonyl species, such as glyoxal, methylglyoxal, and 3-deoxyglucosone, with nucleophilic groups in protein N-termini and side chains (predominantly those of lysine and arginine residues). Glycation may proceed via multiple
distinct and/or interrelated pathways to the generation of biologically permanent advanced glycation end-products (AGE). Some hexose-dependent pathways also proceed through longer lived, biologically significant intermediates, such as Amadori products. Glycation is strongly established as degenerative to various native tissues in diverse disease contexts via 2 general pathways: (1) biochemical modification of tissue ECM, including cross-linking and leading to biomechanical stiffening and structural dysfunction, and (2) stimulation of inflammatory responses and immune cell activity via receptor signaling such as the receptor for the AGE signaling pathway. In particular, glycation has been shown to degenerate collagogenous native tissues, with glycation-instigated stiffening of vessel walls and resultant dysfunction of tissue microvasculature being understood to underlie many of the organ dysfunction complications of DM.

It was recently reported that AGE deposition was observed in a series of 45 clinical BHV explants with SVD and was not detectable in unimplanted BHV leaflets (Figure 2). Various AGEs were observed by immunohistochemistry to be diffusely accumulated in all 45 valves. In vitro, AGE accumulation is sufficient to induce structural and functional degeneration in clinical-grade BHVs. In vitro glycation of BHV progressively deteriorated clinical-grade BHV performance with respect to effective orifice area, mean pressure gradient, peak ejection velocity, and energy loss to degrees equivalent to clinically significant SVD during International Organization for Standardization (ISO)-5840–compliant cardiac pulse duplication testing. These results are in accordance with previous observations of the effects of glycation on the structure and biomechanical functionality of collagen type I–based biomaterials.

The interaction of glycation with other factors involved in SVD has also been studied. In vivo experiments using the established rat subcutaneous BHV tissue implantation model with juvenile and adult rats showed that glycation is accelerated in younger animals. Therefore, glycation may contribute to the dramatically reduced BHV durability seen in younger (particularly pediatric) patients. The involvement of glycation in clinical SVD may also provide a mechanism explaining recent observations that DM may be a strong risk factor for early and more common SVD.

The recent study of glycation in BHV SVD further indicated multiple aspects of interaction between glycation and serum protein (eg, HSA) infiltration. In vitro coinubation of glutaraldehyde-fixed BP with HSA and glyoxal increased the accumulation of N-carboxymethyl lysine, the most-studied AGE and a highly established proinflammatory signal, in BP compared with treated with glyoxal alone. This derives from the fact that many tissue lysines are occupied by glutaraldehyde cross-links, whereas lysine residues belonging to infiltrated proteins are available for glycation; thus, blood protein infiltration relatively enriches lysines versus other glycation sites in BHV tissue. This indicates that infiltration of blood proteins alters the biochemical landscape of BHV tissue and influences related physicochemical modifications during implantation. In addition, HSA exacerbated the effects of glyoxal on collagen network disruption in BP and functional degeneration of BHV in physiologic pulse duplication testing.

Taken together, these observations suggest that glycation may be a fundamental mechanism driving functional degeneration in both noncalcific and calcific SVD.

**Structural Changes in Noncalcific SVD**

One of the principal processes that account for limited BHV durability is noncalcific leaflet damage such as leaflet tears and perforations, resulting from mechanical fatigue and remodeling of ECM proteins. As early as 1977, Spray et al demonstrated fibrin deposition via plasma insudation and enzymatic degradation by opening up pathways within the chemically treated tissue matrix. The authors used small angle light scattering to reveal substantial noncalcific structural damage in 42 clinical explanted BHV cusps. In the calcified cusps, structural damage was consistently spatially distinct from the calcification deposits and in a distribution similar to that noted in porcine BHVs subjected to in vitro durability testing. These results indicated that BHV structural change is independent of calcification. Furthermore, it was envisioned that mechanically induced structural damage may also enhance BHV degeneration via plasma insudation and enzymatic degradation by opening up pathways within the chemically treated tissue matrix.

Cyclic fatigue is known to contribute to the mechanical failure of BHV. Vesely et al reported the reduced extensibility of explanted porcine
bioprostheses compared with unimplanted tissue in both radial and circumferential directions. An in vitro accelerated fatigue study by Vyavahare et al\textsuperscript{75} proved that cyclic fatigue caused a progressive loss of collagen helicity and glycosaminoglycans content in the leaflets of glutaraldehyde-fixed porcine aortic valves.

In addition, Mirnajafi et al\textsuperscript{76} used a customized fatigue tester to control cyclic flexural loading on porcine BHV tissue: it was shown that cyclic flexural loading induced collagen delamination and that flexural rigidity was significantly reduced during fatigue loading. These studies suggest that the mechanical function
of BHVs facilitates biomaterial degeneration and damage within BHV tissues. In addition to collagen-mediated BHV deterioration, damage to elastin leads to a passive elongation of the tissue, a reduction in extensibility, and an increase in stiffness; if the elastin network of BHV is damaged over time (by elastase or otherwise), the mechanical changes that occur will subject collagen fibers to greater shock loading, ultimately increasing the rate of material fatigue.\(^7\)

Recently, second harmonic generation imaging has been used to reveal the collagen structures of explanted BHV and glutaraldehyde-fixed BP: the disruption of collagen structure in the explanted BHV leaflet was evident regardless of the extent of calcification (Figure 3).\(^23\) In an in vitro incubation model, it was demonstrated that AGE formation in BP caused the disruption of the collagen structure, indicating that biochemical modification can also affect the structure of BHV tissue.\(^23\)

In summary, structural changes of BHV leaflet via mechanical fatigue and ECM protein remodeling occur after implantation. These structural changes will in turn cause the changes in their biomechanical function and will contribute to the deterioration of overall BHV functionality.

**MANAGEMENT OF BHV SVD**

Currently, clinical management of SVD mainly include repeat surgical aortic valve replacement (redo-SAVR) and transcatheter valve-in-valve (ViV) implantation.

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**Figure 3.** Macro-scoping images and structural analysis of un-implanted and explanted bioprosthetic heart valves. A, Representative unimplanted surgical (Edwards Perimount, top panel) and transcatheter (Edwards SAPIEN XT, bottom panel) bioprosthetic heart valve. B, Second harmonic generation image of unimplanted bioprosthetic heart valve tissue (scale=100 \(\mu \)m). C, Representative failed clinical surgical aortic valve replacement (top two) and transcatheter aortic valve replacement (bottom). D, Micro computed tomography scans and (E) second harmonic generation images of calcified (top row) and noncalcified (bottom 2 rows) failed bioprosthetic heart valve (scale=100 \(\mu \)m). Reproduced from Frasca et al\(^23\) under the terms of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution and reproduction in any medium provided that the original work is properly attributed. SVD indicates structural valve degeneration.
Several retrospective studies have compared the results of ViV versus redo SAVR\(^7\,\text{8}\) which reported similar operative mortality and 1-year survival rates. A recent systematic review and meta-analysis comparing ViV to redo SAVR reported a similar mortality rate at 30 days and 1 year.\(^8\) However, redo SAVR was associated with lower rates of paravalvular leak and patient prosthesis mismatch. This is likely related to redo SAVR allowing for the removal of the failed and calcified valve and the implantation of a larger prosthesis, which results in a larger effective orifice area. Conversely, reports of transcatheter ViV techniques have also demonstrated increased risk of higher residual gradients, coronary obstruction, and increased mortality in patients who received smaller ViV bioprostheses.\(^1\) Although redo SAVR is still considered the treatment of choice for younger patients at good surgical risk with severe SVD, the ViV approach can be considered as an alternative, especially in older patients and those with comorbidities who are at higher risk for redo SAVR.\(^2\) Recent data also suggest that ViV techniques may be used in patients with failed transcatheter aortic valve replacements (TAVRs)\(^3\) as well as in pediatric patients;\(^4\) however, both patient populations are lacking in size and duration of follow-up. Nevertheless, the rapid evolution of techniques and deployment devices continues to push the envelope of valve annulus size that can accommodate a ViV procedure. Importantly, all BHVs (regardless of the method of implantation) are susceptible to SVD over time. The advent and implementation of minimally invasive approaches to both native and bioprosthetic valve replacement will inevitably increase the size of the patient population. Therefore, it is critical to understand the potential differences in the incidence and etiologies of noncalcific SVD in TAVR versus SAVR. Although both technologies use similar or sometimes the same type of tissue and tissue treatment processes, TAVR leaflets are often speculated to be more susceptible to SVD because of (1) thinner leaflets,\(^5\) (2) damages imposed by crimping and balloon expansion,\(^6\) and (3) irregular deployment caused by the geometry of the native aortic annulus or SAVR stent.\(^7\) However, recent results from the Nordic Aortic Valve Intervention trial suggested that at 6 years post-implantation, TAVRs have less SVD when compared with SAVRs.\(^8\) Longer term follow-up of randomized clinical trials are warranted to elucidate the durability of TAVRs.

CONCLUSIONS

Elucidation of the pathophysiologic mechanisms underlying SVD is of paramount importance in the evolution of novel predictive, preventive, and therapeutic
| BHV Subgroup | Number Analyzed | Oxidized Amino Acid Levels (μmol/mol Tyr, Mean±SE) |
|--------------|----------------|--------------------------------------------------|
|              |                | di-Tyr     | Cl-Tyr     | m-Tyr     | o-Tyr     | NO₂-Tyr   | Br-Tyr    |
| Unimplanted BP | 10  | 0.00±0.00 | 55.46±11.70* | 170.42±26.15† | 816.69±50.07† | 82.01±10.43† | 1334.41±131.10† |
| Unimplanted PAV | 5   | 0.00±0.00 | 223.49±50.49* | 1764.25±90.26† | 3715.67±188.35† | 66.65±18.02 | 541.58±47.68† |
| All explants   | 47  | 227.55±53.27 | 70.56±10.65 | 254.46±29.04 | 771.33±70.55 | 31.56±5.75 | 800.13±65.41 |
| BP            | 36  | 228.22±36.85 | 70.78±13.25 | 291.38±35.09† | 835.24±84.83 | 29.20±6.44* | 7.81±7±4.74 |
| PAV           | 11  | 225.36±78.78 | 69.84±14.82 | 136.6±23.98† | 562.14±98.41† | 39.29±12.93 | 872.14±139.36 |
| Stenosis      | 20  | 278.16±66.86 | 95.48±22.94 | 307.18±35.09‡ | 872.14±75.41 | 38.67±12.25 | 733.9±108.72 |
| Regurgitation plus stenosis | 20  | 199.60±37.82 | 53.14±7.55 | 248.18±39.16† | 662.7±101.37 | 26.27±5.69 | 880.60±99.46 |
| Regurgitation only | 7   | 162.83±36.30 | 49.12±7.04 | 121.80±16.60‡ | 49.41±7.77§ | 26.36±3.15 | 760.91±135.27 |
| DM            | 11  | 221.48±59.89 | 96.22±26.76 | 325.58±65.71 | 120.78±15.15† | 27.19±7.33 | 938.01±143.41 |
| No DM         | 36  | 229.41±39.83 | 62.72±11.17 | 231.81±31.75 | 638.15±72.23‡ | 32.89±7.16 | 758.00±72.99 |
| CABG          | 16  | 284.12±49.20 | 100.78±25.71 | 259.63±54.90 | 880.76±123.01 | 28.08±6.79 | 1012.51±124.46* |
| With DM       | 7   | 308.30±73.93 | 110.13±35.20 | 355.54±92.50 | 1279.19±153.11 | 24.39±10.66 | 1048.9±217.49 |
| Non-CABG      | 31  | 198.36±43.19 | 54.96±8.33 | 251.79±34.39 | 714.8±85.75 | 33.36±8.04 | 690.5±69.07* |
| With DM       | 4   | 69.55±40.71 | 71.88±43.77 | 281.40±92.01 | 1081.16±176.55 | 69.55±40.71 | 745.36±59.32 |

ANOVA indicates analysis of variance; BHV, bioprosthetic heart valve; BP, bovine pericardium; Br-Tyr, 3-bromotyrosine; CABG, coronary artery bypass grafting; Cl-Tyr, 3-chlorotyrosine; di-Tyr, dityrosine; DM, diabetic mellitus; m-Tyr, metatyrosine; NO₂-Tyr, nitrotyrosine; o-Tyr, orthotyrosine; PAV, porcine aortic valve; and Tyr, tyrosine.

*P=0.028 (Welch t test).
†P=0.001 (Welch t test).
‡P=0.007 (ANOVA with Games-Howell).
§P=0.003 (ANOVA with Games-Howell).
¶P=0.017 (ANOVA with Games-Howell).
‖P=0.17 (Student t test).

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strategies. It could potentially improve the person-alized BHV selection, suggest biomarkers for long-term surveillance of BHV function, inspire potential therapies to reduce SVD rates, and provide insights to the design of the next generation of BHV. The non-calcific mechanisms of BHV SVD may furthermore play an underappreciated role in the development and progression of calcific BHV SVD. Such mechanisms may be mediated by inflammation, oxidative stress, mechanical stress, or some combination thereof (Figure 4). Future studies on the interactions of BHV tissues with circulating proteins and other macromolecule will likely uncover additional mech-anisms of BHV biochemical modification and may generate novel substrates for BHV SVD prevention and mitigation.

ARTICLE INFORMATION

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