The Pursuit of Engineering the Ideal Heart Valve Replacement or Repair

On the Mechanics of Transcatheter Aortic Valve Replacement

Lakshmi P. Dasi,[1] Hoda Hatoum,[1] Arash Kheradvar,[2] Ramin Zareian,[2] S. Hamed Alavi,[2] Wei Sun,[3] Caitlin Martin,[3] Thuy Pham,[3] Qian Wang,[3] Prem A. Midha,[3] Vrishank Raghav,[3] and Ajit P. Yoganathan[3]

[1]Department of Biomedical Engineering, Dorothy Davis Heart and Lung Research Institute, The Ohio State University, 473 W 12th Avenue, Columbus, OH 43210, USA; [2]The Edwards Lifesciences Center for Advanced Cardiovascular Technology, Department of Biomedical Engineering, University of California, Irvine, CA 92697, USA; and [3]Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology, Atlanta, GA 30332, USA

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Abstract—Transcatheter aortic valves (TAVs) represent the latest advances in prosthetic heart valve technology. TAVs are truly transformational as they bring the benefit of heart valve replacement to patients that would otherwise not be operated on. Nevertheless, like any new device technology, the high expectations are dampened with growing concerns arising from frequent complications that develop in patients, indicating that the technology is far from being mature. Some of the most common complications that plague current TAV devices include malpositioning, crimp-induced leaflet damage, paravalvular leak, thrombosis, conduction abnormalities and prosthesis-patient mismatch. In this article, we provide an in-depth review of the current state-of-the-art pertaining the mechanics of TAVs while highlighting various studies guiding clinicians, regulatory agencies, and next-generation device designers.

Keywords—TAVR, Transcatheter aortic valve, Stent, Minimally invasive, Thrombosis, Paravalvular leak, Valve-in-valve.

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is an exciting new approach to treat aortic valve stenosis in patients who are classified as high-risk for open heart surgical aortic valve replacement (SAVR). A transcatheter aortic valve (TAV) is designed to be compressed into a small diameter catheter, remotely placed within a patient's diseased aortic valve under fluoroscopic guidance to take over the function of the native valve. Some TAVs (e.g., Edwards SAPIEN family) are balloon-expandable, while others (e.g., Medtronic's CoreValve) are self-expandable owing to their shape-memory nitinol stents. In both cases, the TAVs are deployed within a calcified native valve that is forced permanently open and becomes the surface against which the stent is held in place by friction. More recently, TAVs have been used to replace failing bioprosthetic or transcatheter valves that were previously implanted in a procedure known as valve-in-valve (ViV). Figure 1 shows the TAVs that are currently approved by the Food and Drug Administration (FDA) for clinical use in the United States.[58] The design features, which most distinguish TAVs from their surgical counterparts—except for suture-less SAVRs—are the lack of a sewing cuff and the presence of a collapsible stent frame that houses the valve leaflets.

Due to its minimally invasive approach, TAVR has a strong appeal to becoming the standard of care for low-risk patients. However, like any new device technology, the high expectations are dampened with growing concerns arising from frequent complications that develop in patients, indicating that the technology is far from being mature. Some of the most common complications that plague current TAVR devices include malpositioning, crimp-induced leaflet damage, paravalvular leak, thrombosis, conduction abnormalities and prosthesis-patient mismatch (PPM). These complications are currently difficult to predict prior to the procedure.; however, patient-specific risk factors are thought to include the calcification landscape of the native valve, geometric and mechanical properties of

Address correspondence to Lakshmi P. Dasi, Department of Biomedical Engineering, Dorothy Davis Heart and Lung Research Institute, The Ohio State University, 473 W 12th Avenue, Columbus, OH 43210, USA. Electronic mail: dasi.1@osu.edu
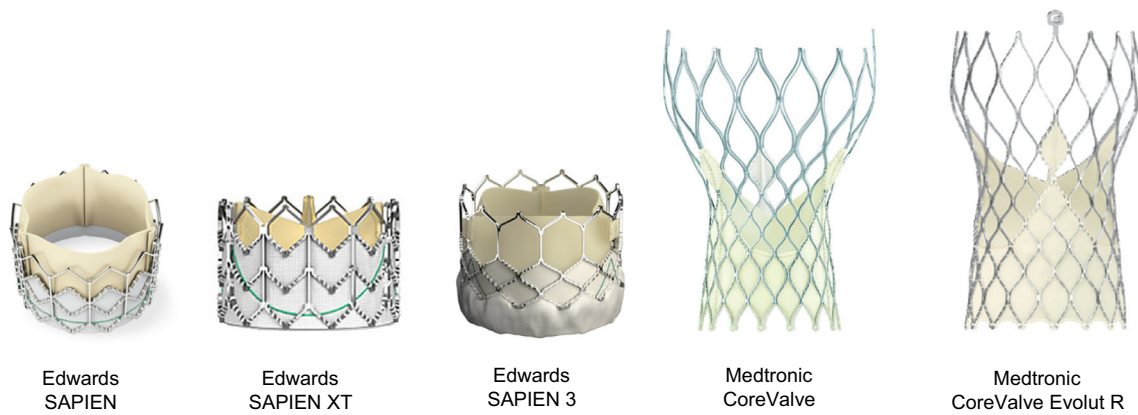
FIGURE 1. Transcatheter aortic valves FDA-approved for clinical use in the US. The figure is from Kheradvar *et al.*,[58] with permission.

the aortic root, blood biochemistry and coagulability, and concomitant conditions such as hypertension, coronary artery disease, heart failure, *etc*. To ensure the robustness and safety of current and future TAVR devices, it is crucial to understand the relationship between potential complications, and their underlying mechanics. This work provides an in-depth review of the current state-of-the-art pertaining to TAVR mechanics and highlights various engineering studies guiding clinicians, regulatory agencies, and next-generation device designers. In what follows, we have divided the article into three main parts focusing on the fluid mechanics, solid mechanics, and future design concepts, respectively.

FLUID MECHANICS OF TAVR

Due to their particular design features, TAVs can undergo fluid and structural failure modes. The following sections provide a review of the major fluid mechanics-related failure modes, including paravalvular leak, PPM (particularly in ViV applications), thrombosis, and non-circular deployment.

Paravalvular Leak (PVL)

Valvular regurgitation is more prevalent after TAVR than SAVR.[72,86,95,105] In general, valvular leakage can be central or commissural (between the leaflets), paravalvular (between the prosthesis and deployment zone), or supra-skirtal (a form of PVL). Clinical studies have shown that even mild regurgitation can be associated with increased post-TAVR mortality.[64,128,146] Figure 2 illustrates each mode of valvular leakage in the Edwards's SAPIEN and the Medtronic's CoreValve. Central or commissural regurgitation occurs in diseased, damaged, or improperly-deployed TAV when the leaflets do not fully coapt, while some prostheses have minor central leakage by design.[72] If a TAV is implanted too low within the annulus, supra-skirtal leakage can occur through the uncovered region of the stent. This has been observed in both SAPIEN and CoreValve, as only the lower part of their stents are shielded by a skirt.[121] However, PVL is more frequent, affecting as many as 50% of patients with at least mild regurgitation.[64,72] PVL can lead to congestive heart failure, hemolysis,[103,118] forceful contractions of the heart, and arrhythmias.[50] Risk factors for PVL include heterogeneous calcification of the native annulus,[24,37,72,115,139] malposition of the prosthesis [24,93] and TAV undersizing.[22,24,37,39,72] Figure 3 shows PVL at both coronary and non-coronary cusps in presence of different calcific lesions. Di Martino *et al.* suggested that self-expandable prosthesis may undergo resistance from the calcified native valve during deployment that may lead to a higher incidence of paravalvular leak.[24] Accordingly, Abdel-Wahab *et al.* found that the occurrence of PVL was higher with CoreValve than SAPIEN.[3,51]

Anatomical and procedural factors have also been correlated with occurrence of PVL. A large aortic annulus as measured by CT may increase the chance of PVL.[52,98] Detaint *et al.*[22] defined a cover index representing the ratio of the difference between the TAV and annulus diameters. This index is a measure of TAV oversizing.[47] A low cover index is associated with greater PVL.

The impact of PVL on patient mortality has motivated design changes to improve sealing.[116] Design features, such as inflow skirts or cuffs as in Edwards' SAPIEN 3, Boston Scientific's Lotus, FoldaValve's[59] and St. Jude Medical's Portico or alternative frame materials as used by Direct Flow are some examples that are being explored and utilized with some success.[141]
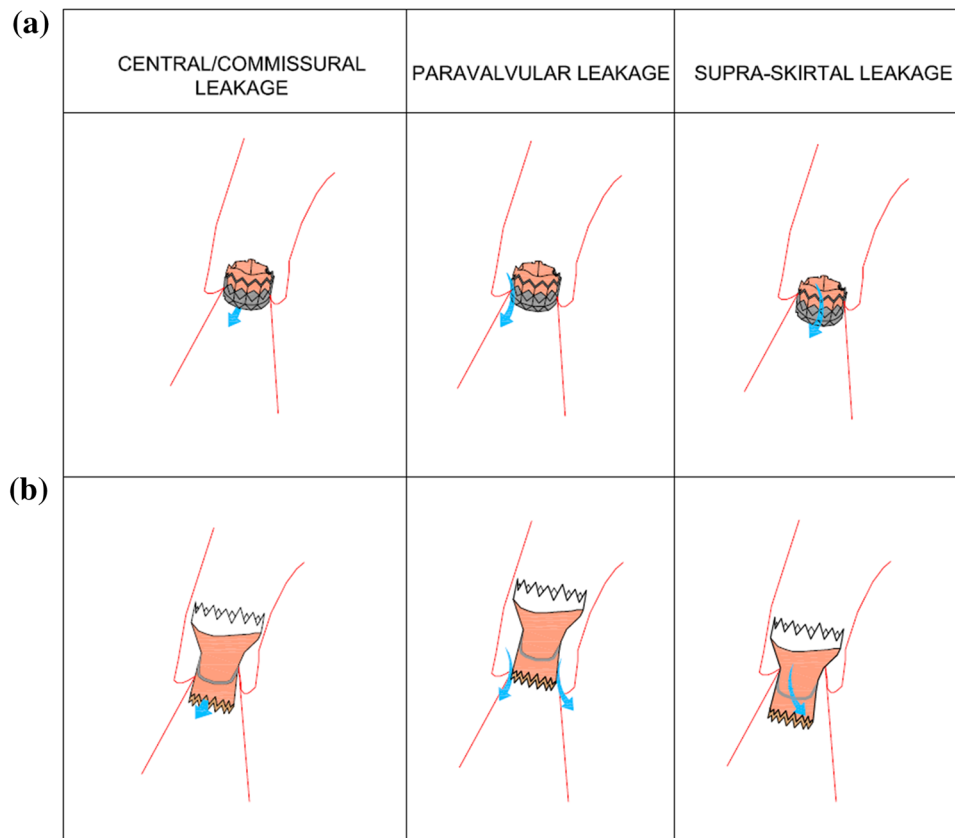
FIGURE 2. Types of valvular leakages in (a) Edwards SAPIEN valve and (b) CoreValve.

TAVR Thrombosis

Thrombosis is the formation of blood clots or thrombi that can lead to partial or complete restriction of heart valve leaflet motion and/or embolization. Thrombosis in the cardiovascular system is traditionally discussed in terms of Virchow's triad (fluid flow, foreign materials, and blood biochemistry). Presence of non-hemocompatible material in a blood circulation may lead to platelet activation.[8] Sensitized platelets exposed to extended periods of flow stagnation and/or recirculation can result in thrombus formation.[27,60,148] For example, stagnant flow in the sinus may expose these sensitized platelets to extended exposure time, making this site prone to thrombus formation.[43,111] Furthermore, it was shown that flow stagnation in the sinus was exacerbated with supra-annular implantation of the TAV.[42,66,83] Particle tracking results illustrated in Fig. 4, show that there is a significant increase in the time taken for a given number of particles to exit the sinus at the highest supra-annular deployment.[83,85] These studies also demonstrate that the flow stagnation primarily occurs at the base of the sinus.[42,66,83] After TAVR, the risk of thrombus formation rises in some patients.[67] Factors that are thought to trigger post-TAVR thrombus formation are summarized as follows: small or under-expanded valves, premature stopping of antithrombotic or antiplatelet therapy, aggressive post-dilation, crimp-induced leaflet damage and geometric deformation of the valve stent.[67,90] Recently Makkar *et al.*[76] revealed evidence of reduced leaflet mobility to happen more frequently in transcatheter aortic valves compared to surgically-implanted bioprosthetic valve, which may explain consequent embolic stroke in patients undergoing TAVR. They also observed that warfarin improves leaflet mobility that supports their hypothesis indicating the reduced leaflet mobility is due to subclinical leaflet thrombosis. While the authors acknowledge the small sample size, p values of 0.08 and 0.18 for Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Graft (CABG), respectively, may indicate that diminished coronary perfusion could be a factor in thrombus formation. In a correspondence to Makkar's publication, Hatoum *et al.* proposed a potential relationship between reduction in flow and formation of thrombus.[48] Figure 5 shows some clinical images taken from Makkar *et al.* illustrating the reduced leaflet motion relative to the coronary ostia.[48,76] As can be seen in the figure, non-coronary sinuses as well as non-anatomical positioning of the TAV may explain possible flow stasis that correlates with the thrombus locations.
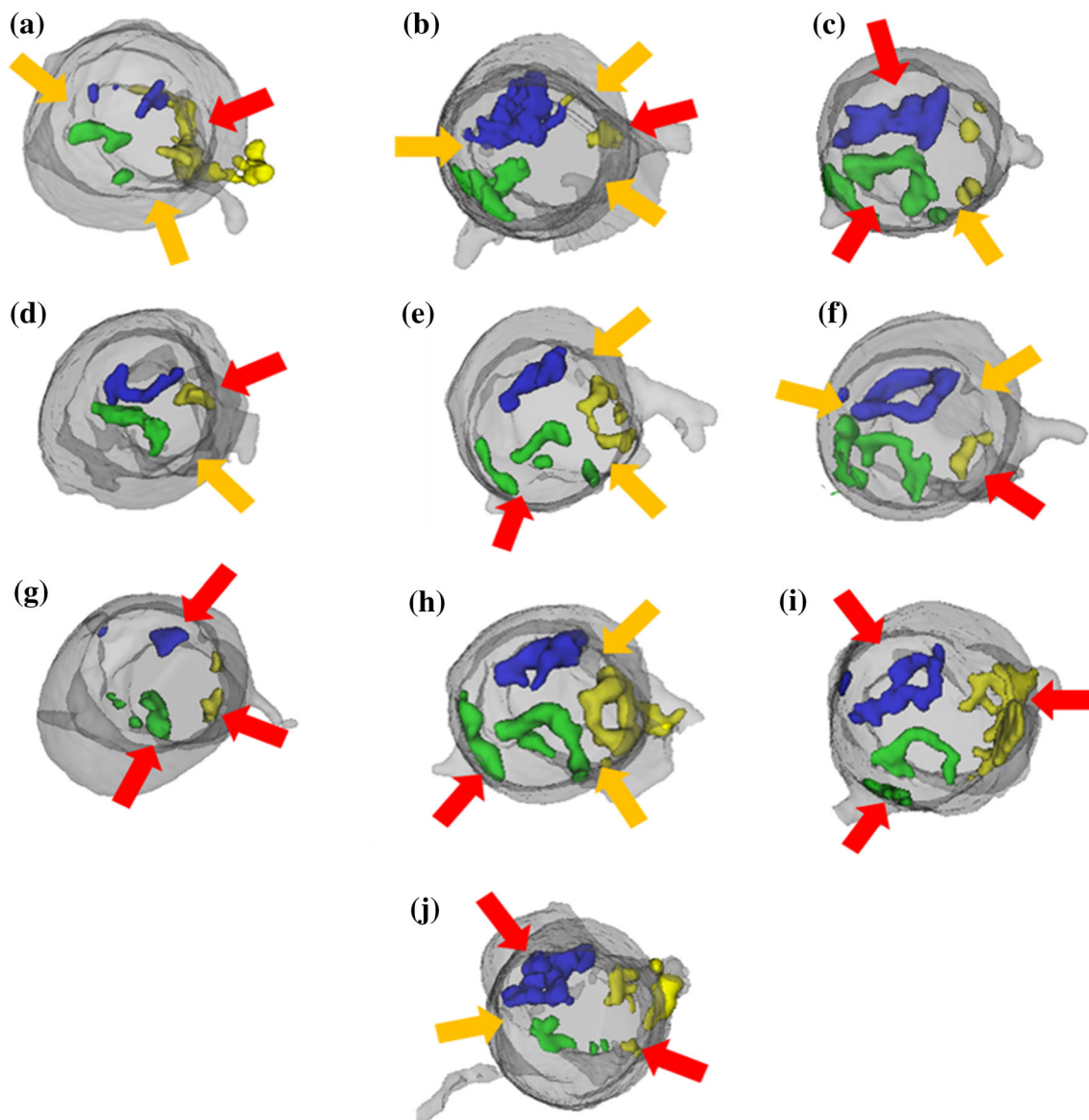
FIGURE 3. Segmented Computed Tomography (CT) scans presenting reconstructed 3D models of the aortic root and calcific lesions overlaid with positions of paravalvular leak after TAVR based on respective transesophageal echocardiography scans. The figure is from Zebhi *et al.* with permission.[150] Red arrows correspond to PVL at cusp side and orange arrows correspond to PVL at commissure between two cusps. Green, blue and yellow denote the calcification in the right coronary, non-coronary and left coronary cusps respectively.

Non-circular TAV Deployment

As mentioned earlier, the interaction between the TAV and native aortic valve is not predictable. Sometimes, the stented-valve assumes an eccentric shape due to deployment in irregularly calcified native leaflets. For example, circular deployment is achieved only in 86% of the patients undergoing TAVR with a balloon-expandable prosthesis e.g., Edwards SAPIEN.[21,47] Likewise, a non-circular deployment in such cases is associated with further calcification and paravalvular regurgitation.[21,38,149] Schultz *et al.*[108] reported that this problem is also prevalent in self-expandable valves such as the Medtronic's CoreValve,

where a majority of valves implanted in patients achieved a non-circular conformation. Abbasi *et al.*[2] investigated the synergistic impact of eccentric and incomplete stent deployment and showed that it may lead to higher localized stress regions over TAV leaflets *in vitro*. In addition, high mechanical stresses over TAV leaflets may induce enhanced tissue degeneration and reduce long-term valve durability.[2,4,28,126] On the contrary, some studies show that the relationship between non-circular deployment and paravalvular leak is not conclusive.[70,147] In a case-report, Jilaihawi *et al.*[53] noted that TAV under-expansion can lead to good hemodynamic function and excellent symp-
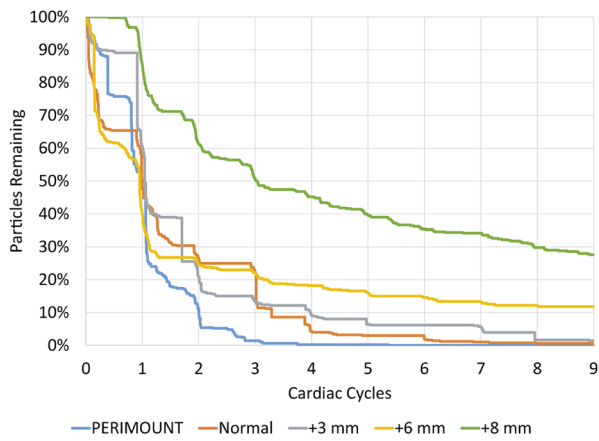
FIGURE 4. Sinus washout curves for various supra-annular ViV (SAPIEN in PERIMOUNT) deployments. The figure is from Midha *et al.* [85] with permission.

tomatic recovery. Bench-top experiments conducted by Gunning *et al.*[43] using particle image velocimetry downstream of an eccentrically-deployed TAV suggested that the hemodynamic performance is invariable to the TAV configuration. They also noted that the eccentric TAV deployment may result in an asymmetric systolic jet with elevated turbulence and shear stress downstream of the valve; however, this phenomenon may not be significant enough to induce blood damage.[43] While TAV oversizing can be used as a solution to compensate for eccentric TAV deployment, many studies have shown that oversizing contributes to annular injury or even rupture.[70,77] Oversizing by specific percentages optimizes risk/benefit ratio in terms of paravalvular leakage and conduction disorders.[47,68,75] Sun *et al.*[126] demon-
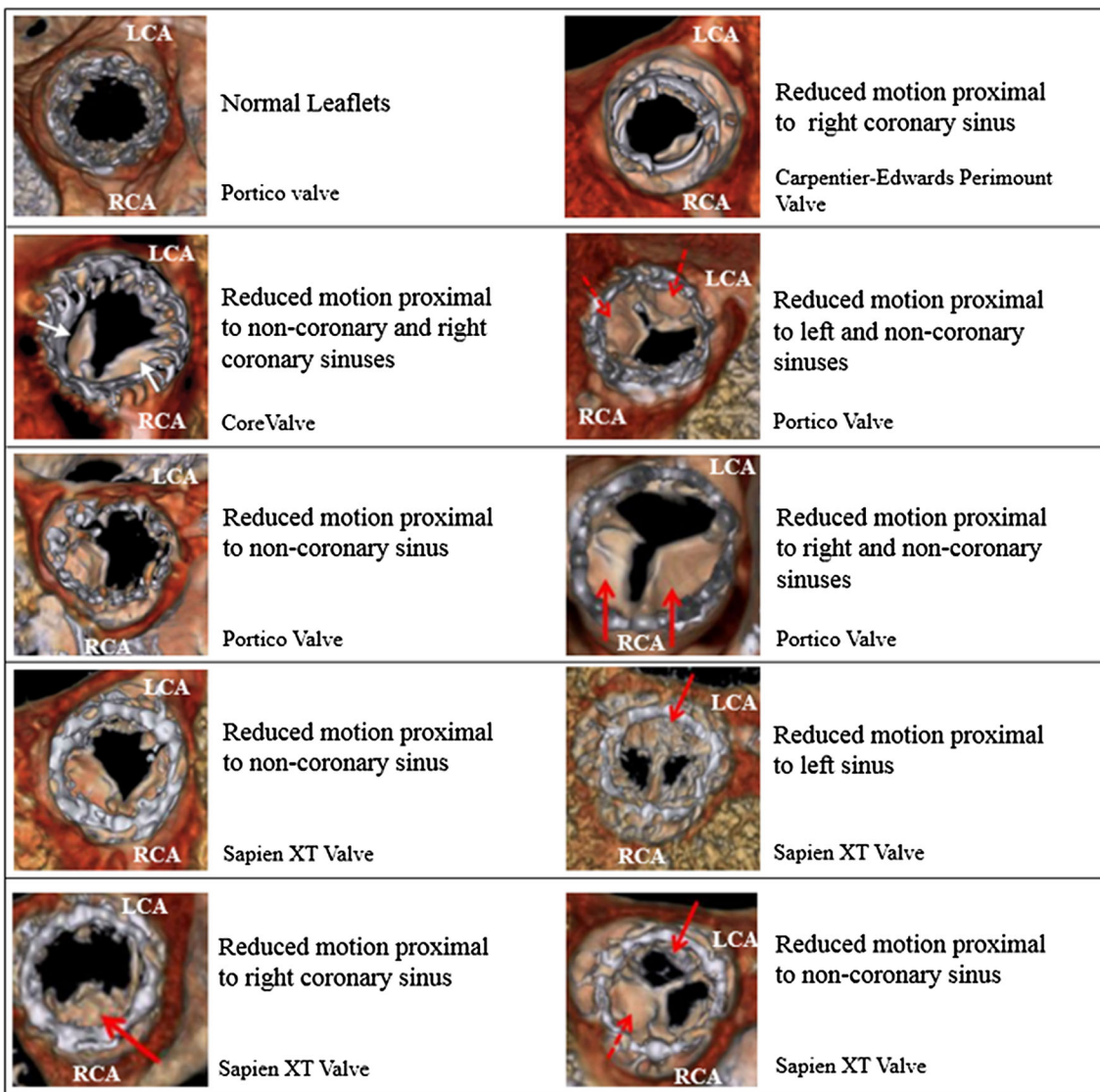

FIGURE 5. Reduced motion leaflet identification images of different prosthetic and surgical valves presented in Makkar *et al.*[76] with respect to their corresponding sinuses. The figure is from Makkar *et al.*[76] with permission. LCA, left coronary artery and RCA, right coronary artery.

strated that when the eccentricity value is above 0.5, the TAV may not properly close and is likely to result in increased commissural backflow leakage.[108,126]

Fluid Mechanics of Prosthesis-Patient Mismatch (PPM)

Rahimtoola et al.[19,97] defined prosthesis-patient mismatch as an effective orifice area (EOA) smaller than that of a normal human valve. Successively Dumesnil and Pibarot explained that this definition can be applied to almost all valve replacements.[28] Therefore, the heart must overcome the additional flow resistance via elevated pressures.[10] Gorlin and Hakki[46] describe that transvalvular gradients depend on both EOA and transvalvular flow rate. While the cutoffs for PPM have been debated, PPM occurs when the prosthesis' EOA normalized by body surface area is less than $0.85 \text{ cm}^2/\text{m}^2$.[28]

Valve-in-Valve (ViV) implantation is a procedure in which a TAV is deployed within a failing bioprosthetic or transcatheter valve.[80] Due to the typically high-risk or inoperable classification of these patients, ViV provides a viable valve replacement option when a second surgical procedure is not an option.[33,142,144] With this procedure being the patient's second valve replacement, there is always a high probability of coronary obstruction, PPM and residual stenosis.[34,140] Other in vitro studies have also suggested similar consequences such as the study by Azadani et al.[13] conducted to test the hemodynamics of TAVs in degenerated—and particularly small-sized—bioprostheses. Careful selection of the TAV for ViV needs to be considered to mitigate the risk of paravalvular leakage as well as residual stenosis.[12,13] When Edwards' SAPIEN and Medtronic's CoreValve were implanted in surgical valves with internal diameters less than 20 mm, elevated post-procedural gradients (> 20 mmHg) were found in 59 and 20% of patients, respectively.[32,134,140] This is thought to be due to the intra-annular nature of the SAPIEN family of valves, whereas CoreValves are supra-annular by design.[29] A recent in vitro study by Simonato et al.[112] has emphasized the likelihood of having low pressure gradients associated with the supra-annular TAV implantation in particularly-small bioprostheses. The type of the bioprosthesis used also plays a role in the function and hemodynamic assessment of the ViV setup. The differences are elaborated in a study by Sedaghat et al.,[109] as the paravalvular leakage was found higher when an Edwards' SAPIEN was implanted within a 23 mm Edwards' Perimount compared to that seen when a Medtronic's CoreValve was implanted in the same valve. Surprisingly, conflicting results were observed when the same TAVs were implanted within a St. Jude Medical's Trifecta. The design of the Trifecta valve with leaflets sutured on the outside of the stent rather than on the inside may be a reason for this difference.

Other studies have shown that optimal size and placement of TAVs may exist outside the current guidelines.[29,83,84] One possible solution to improve post-procedural gradients and minimize PPM is to implant the TAV in a supra-annular position (Fig. 6a), effectively bypassing the geometric constraints imposed by the semi-rigid bioprostheses.[83,112,153] However, several risks are associated with supra-annular deployment, including device migration or embolization (Fig. 6b), coronary obstruction[31,124] as described by Dvir et al.[31] tested in vitro by Stock et al.,[124] and thrombus formation due to flow stagnation within the sinus region (Fig. 6c). An in vitro risk–benefit analysis of supra-annular deployment of a SAPIEN XT in a small surgical bioprosthetic valve demonstrated that the optimal deployment is in the range of 3 to 6 mm supra-annular. Another in vitro study by Groves et al. has shown that placement of a TAV within the annulus of a bioprosthetic valve with no more than 5 mm distance from its annulus should be ideal.[42] Any further displacement of the valve can be associated with detrimental effects on the observed hemodynamics. Groves et al. suggested that the transcatheter valve placement as close to the bioprosthetic valve annulus as possible provides optimal hemodynamics in the sinuses of Valsalva and ascending aorta.[42]

Considering all the above-mentioned in vitro studies, we emphasize that clinicians must first consider patient-specific anatomic characteristics and carefully weigh the benefit of intra- or supra-annular valve implantation in reducing post-procedural gradients against the potential risk for valve thrombosis, conduction abnormality and device migration.

Figure 7 shows a schematic of a typical ViV arrangement in which a transcatheter valve is deployed within a stented surgical bioprosthetic valve. The relative dimensions described in the figure vary among valve types. For instance, a 23 mm Edwards' PERIMOUNT and a 23 mm Medtronic Mosaic are indicated for an annulus approximately 23 mm in diameter, however, the internal diameters are 21 and 18.5 mm, respectively. A 23 mm Edwards' SAPIEN XT could expand 2.5 mm further within the PERIMOUNT rather than the Mosaic, thus leading to less PPM and lower gradients. As shown in the figure, most of the area is occupied by the original surgical valve. Bapat et al.[16] helped creating a standardized ViV sizing and positioning guidelines by deploying various sizes of TAVs in a wide range of surgical bioprostheses. A summary based on that study is shown in Table 1 exhibiting different sizes of a stented surgical aortic
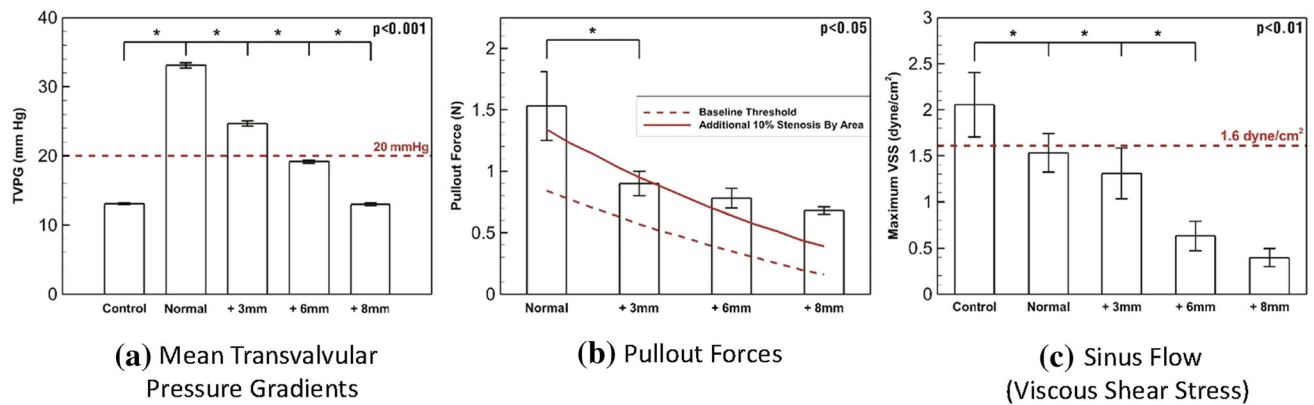
FIGURE 6. Hemodynamic performance and associated risks at various ViV deployment positions (SAPIEN in PERIMOUNT). The figure is from Midha *et al.*[83] with permission.

valve and their corresponding valve-in-valve matches for the Edwards' SAPIEN XT, Medtronic's CoreValve, and St. Jude Medical's Portico. With ViV sizing guidelines in place, knowing a patient's surgical valve type and size allows for appropriate TAVs to be selected for the purpose of ViV.

Figure 8 shows the evolution of the aortic valve area as the condition and configurations of a diseased aortic valve changes. The figure compares the improvement level in aortic valve area after the implantation of a TAV and a surgical bioprosthesis. The Figure considers 3.5 cm^2 as the healthy aortic valve area and the ratio of 1.0 represents a healthy case. Gavina *et al.* show that TAVs may lead to lower gradients than surgical valves in native aortic valve replacement.[36,131] The Figure also shows the level of reduction in valve area after ViV,[74] along with a comparison valve area in ViV configurations when the diseased bioprosthesis is a surgical valve versus a TAV.[100] Due to the lack of published data regarding valve-in-valve-in-valve procedures, the value adopted in this figure is only a projection based on a fractional reduction seen in the ViV configuration results. In this case, a second ViV deployment may drop below the 1 cm^2 cutoff for severe aortic stenosis.[55,94]

STRUCTURAL MECHANICS OF TAVR

Many catastrophic TAV failures observed in clinics can be explained from a biomechanics perspective. For instance, excessive radial expansion force exerted by the TAV stent may lead to aortic annulus injury, while insufficient force may result in PVL and device migration. In addition, improper TAV positioning can cause coronary ostia's occlusion. Thus, a quantitative understanding of the biomechanical interactions between the native aortic tissue and TAV is essential for scientifically-justified design of the next-generation

devices and an enabling step towards patient-specific device selection and procedural planning. More recently, several studies on structural analyses were performed using finite element models to understand the interaction between TAV and aortic root interaction. These studies are mainly classified into two groups: (1) simulation of biomechanical interactions between the TAV devices and the aortic root, and (2) post-TAVR evaluation of the device performance. The accuracy of these models largely depends on three critical factors: geometry, material properties, and boundary conditions. The processes to determine these factors are reviewed in the subsequent section.

Modeling the Interactions Between TAV and Aortic Root

A deployed TAV device comes into contact with the aortic root, leaflets and left ventricle besides any potential calcification spots. Thus modelling these anatomical structures are critical to develop accurate computational models for TAVR. The aortic root, including the aortic sinuses and the ascending aorta, as well as the calcification can be segmented directly using commercial image-processing software such as Avizo (VSG, Burlington, MA) and Mimics (Materialise Inc., Belgium) by selecting an appropriate window width of Hounsfield units (HU).[18,136] For example, Wang *et al.*[136] chose a window width of 950 and -50 HU for the segmentation of the aortic root. However, the valve leaflets typically cannot be directly segmented from the images using the software, and have been ignored in many studies.[11,44] The segmentation of the native leaflets requires manual digitization and reconstruction process,[117,136–138] which can be cumbersome and prone to error.

The aortic root and native leaflets are often modeled using shell elements.[18,44,87,104,117] However, transverse
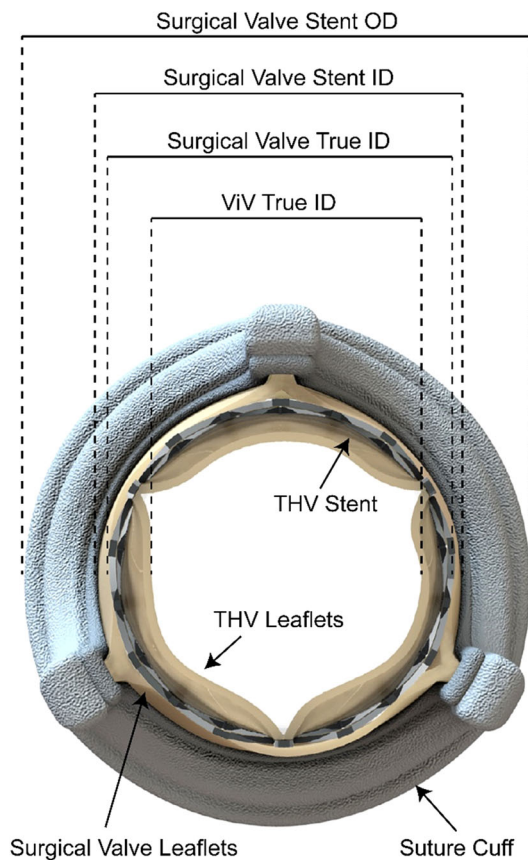
FIGURE 7. *En face* rendering of a SAPIEN valve deployed within a stented surgical bioprosthesis. Note the reduction in geometric orifice area with each additional prosthesis.

capture the tissue response more accurately, providing more accurate simulation results at the expense of computational time.

Patient-specific computational models for TAVR can potentially be utilized as a tool to refine patient selection, evaluate device performance, and eventually improve clinical outcomes for each patient. Many Finite Element (FE) models[11,15,17,18,41,44,87,104,136–138] have been developed over the past several years to analyze the biomechanics involved with TAVR in specific patient groups. These models have been used to evaluate the potential for coronary artery occlusion[18,136–138] and migration,[17] as well as the feasibility of complex clinical cases such as ViV.[18] Notably, Wang *et al.*[136] have described a complex patient-specific TAVR model that includes realistic aged human tissue properties including the aortic root failure criteria defined by experiments,[78] as well as a fluid cavity modeling approach to simulate the balloon expansion of the Edwards' SAPIEN stent (Fig. 9). They simulated TAVR in three patients considered to be at a higher risk of aortic root rupture, and showed that asymmetric calcium deposition within the root may be a cause of TAVR-induced aortic rupture clinically observed. Collectively these studies have shown that the size and location of calcium deposits are critical to the success of TAVR procedure.[104,136–138] Calcification can prevent full or symmetric stent expansion leading to paravalvular leakage[17,87,136–138] and distortion of the TAV leaflet configuration.[11,44,87]

shear stiffness may not be accurate in shell elements, and thus may give inaccurate results when modeling out-of-plane bending responses. Furthermore, the addition of calcification to the aortic root and leaflets requires precise accounting of volume and geometry, for which a 3D element is required. Calcification may result in highly complex geometries and can be embedded into the leaflets and sinuses, which was not included in many of the earlier computational models.[11,15,18,44,87] Recent studies indicate that it is advantageous to model both aortic root and calcification using brick elements.[17,41,136–138] Only a few studies include the left ventricle (LV) in modeling TAVR;[104,136–138] however, Wang *et al.*[138] reported that by including some portion of the LV, the tissue-TAV interaction force increases upon stent deployment; thus inclusion of the LV may improve the accuracy of the analysis.

Various material models have been used to describe aortic tissue behavior, including rigid walls,[104] linear elastic models,[15,41,104] isotropic hyperelastic models,[17,18,44,56,87,104] and anisotropic hyperelastic models.[11,87,136–138] A more advanced material model can

Modeling of Post-operative Device Performance

Li and Sun[73] presented the first FE model for TAV leaflet deformations. The leaflet material behavior was defined by the non-linear, anisotropic, hyper-elastic Fung-type model fitted to planar biaxial testing data of thin glutaraldehyde-treated bovine pericardium and porcine pericardium. Li and Sun[73] showed that leaflet stresses decrease with increasing tissue thickness, and under the same loading and boundary conditions, bovine pericardium leaflets have a lower peak stress compared to porcine pericardium leaflets (59%). All the cases of the TAV leaflet stresses and strains[73] were significantly higher compared to those reported by Sun *et al.*[125] for traditional surgical bioprosthetic valve leaflets. These results suggest that TAVs will have a limited long-term durability compared to surgical bioprosthetic valves, particularly the TAVs utilizing porcine pericardium leaflets.

In a follow-up study using this same FE model,[73] Sun *et al.*[126] showed that the elliptical deployment compromises TAV leaflet coaptation and increases leaflet stresses. A stent elliptical eccentricity of 0.68 resulted in a 143% increase in the leaflet peak stress

TABLE 1. Corresponding valve-in-valve matches for different sizes of stented bioprosthetic surgical aortic valves

| Bioprosthetic stented valve true ID (mm)	Appropriate TAV type for ViV	Corresponding TAV annulus size (mm)
16–17.5	Sapien 20	16–18
18–18.5	Sapien 20	16–18
	CoreValve 23	18–20
	Portico 23	19–21
19	Sapien 23	18–22
	CoreValve 23	18–20
	Portico 23	19–21
20.5–21	Sapien 23	18–22
	CoreValve 23	18–20
	Portico 23	19–21
22	Sapien 26	22–25
	CoreValve 26	20–23
	Portico 25	21–23
23	Sapien 26	22–25
	CoreValve 26	20–23
	Portico 25	21–23
24	Sapien 26	22–25
	CoreValve 26	20–23
	Portico 27	23–25
25–26	Sapien 29	25–27.7
	CoreValve 29	23–27
	Portico 27	23–25
27	Sapien 29	25–27.7
	CoreValve 29	23–27
	Portico 29	25–27
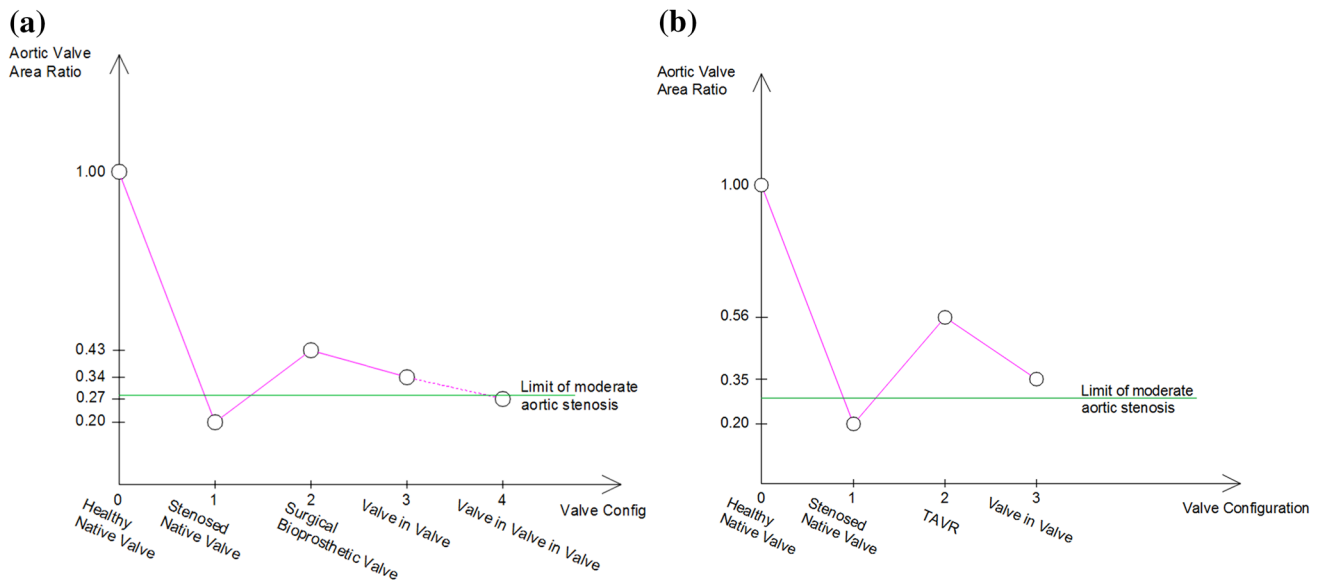
FIGURE 8. Evolution of the aortic valve area as the configuration of the valves change in the case of (a) a surgical heart valve implantation originally and (b) a transcatheter aortic heart valve implantation originally. The value of 1.00 corresponds to a healthy aortic valve area that is taken to be 3.5 cm^2.

compared to the nominal circular configuration. Furthermore, it was shown that an eccentricity exceeding 0.5 can lead to central aortic regurgitation. Incomplete stent expansion has also been shown to distort the configuration of the leaflets.[119,152] Abbasi and Azadani[1] studied the impact of incomplete stent expansion on the TAV leaflet deformation in a 23 mm valve using FE model. They found that reduction of
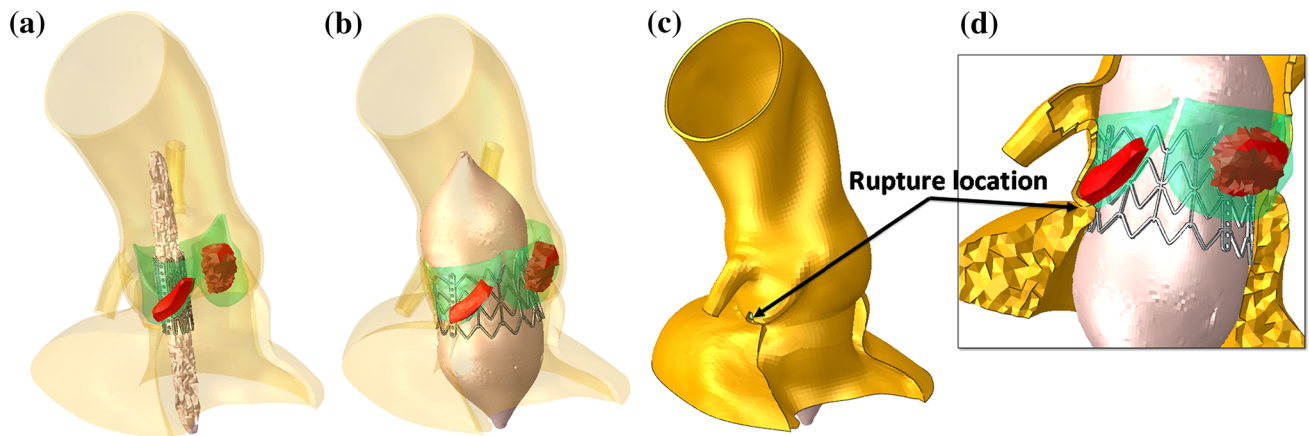
FIGURE 9. (a) Pre- and (b) post-deployment geometries of the aortic root of Case 1. (c) Full and (d) local views of the deformed the aortic root and balloon deployment indicates annulus tearing under the left coronary ostium due to dislodgement of calcification into the vulnerable part of the aortic sinus. The figure is from Wang *et al.*[136] with permission.

the stent diameter by 2–3 mm induces sharp bends in the leaflets during closure, which acted to increase the leaflet peak stress by 40.1–78.2% compared to the nominal valve under identical loading. Further reduction of the stent diameter by 4–5 mm increases the leaflet peak stresses by 124.1–158.6%. In the real scenario, the leaflet peak stresses during systole in the under-expanded configuration would also likely be higher than reported here,[1] because incomplete expansion can lead to increased transvalvular pressure gradients.[14,45,54,63,65,69,88,142] Consequently, both short- and long-term functions may be compromised in an elliptically or under expanded deployed TAV.

Martin and Sun[79] recently investigated TAV leaflet durability through FE analysis by implementing a computational soft tissue fatigue damage model, which includes descriptions of the stress-softening and permanent set effects of glutaraldehyde-treated bovine pericardium subjected to cyclic loading.[110,127] The effects of cyclic loading on TAV and surgical bioprosthetic valve leaflets were compared. In both valves, cyclic loading induced changes in the leaflet tissue properties and geometries, and altered the leaflet stress and strain patterns, which could not be predicted in traditional FE models utilizing instantaneous tissues properties. Under identical loading conditions, the TAV leaflets sustained higher stresses and strains as observed by Li and Sun,[73] which resulted in increased fatigue damage compared to the surgical valve leaflets. The simulation results suggest that the TAV durability may be significantly reduced compared to surgical valves from 20 years to about 7.8 years post-implantation. This model may be useful in optimizing TAV design parameters to improve leaflet durability, and assessing the effects of under expanded, elliptical, or non-uniformly expanded stent deployment on TAV durability.

FUTURE TAVR DESIGNS

The TAVR introduction has transformed the traditional surgical approach to heart valve disease by offering significantly minimal procedures particularly for high-risk patients who have been considered unsuitable for open-heart surgeries either in its traditional form or minimally-invasive.[58,64] Major TAVR advantages to the traditional surgical approaches can be summarized as refraining cardiopulmonary bypass, aortic cross-clamping and sternotomy that significantly reduces patients' morbidity.[49] However, current guidelines do not yet recommend TAVR for patients with intermediate or lower risk for open heart surgery. These risks are usually quantified based on the Society of Thoracic Surgeons (STS) score[23] or the Euro-SCORE (European System for Cardiac Operative Risk Evaluation).[91,101]

Society of Thoracic Surgeons established a measure—STS AVR composite score—that includes two outcomes domains, risk-adjusted mortality and risk-adjusted morbidity related to aortic valve replacement complications (i.e., reoperation, stroke, kidney failure, infection of the chest wound, or prolonged need to be supported by a breathing machine, or ventilator).[23] In a similar fashion, EuroSCORE is a risk model that calculates the risk of death after a cardiac procedure. The model works based on 17 items of information about the patient, the cardiac condition and the proposed procedure to be performed,[91] and uses logistic regression to calculate the mortality risk.[101] High, intermediate and lower risks are usually quantified based on these scores.

Current guidelines do not recommend TAVR in patients at intermediate or low surgical risk since several issues affecting outcomes remain unresolved, including durability, subclinical thrombosis,[76] vascular

complications, neurological events, rhythm distur-
bances, and paravalvular leakage. Reducing the inci-
dence of major adverse events associated with TAVR is
crucial, as these risks are not acceptable to a standard-
risk surgical population. However, innovations in de-
vices and technologies for delivery system are rapid
and unceasing, leading to the treatment of younger
population in a near future. Additionally, PARTNER
II trial showed that in intermediate-risk patients, sec-
ond generation Edwards' SAPIEN system is compa-
rable to SAVR with respect to the primary end point of
death or disabling stroke.[71] In parallel, there are sev-
eral ongoing trials of novel transcatheter aortic valves,
which aim to solve many of the issues that currently
are major challenges to heart valve developers.[81,132,145]

The current limitations of TAVR that prevents its
use in lower risks patients are summarized below:

Vascular complications from large delivery systems,
which necessitates smaller profiles.
PVL which necessitates better sealing strate-
gies.[59,72,129]
Device malpositioning, which necessitates reposi-
tionable and/or retrievable devices.[133] This is par-
ticularly important when TAVR procedures are
performed by interventional cardiologists with less
TAVR experience.
Permanent pacemaker, which necessitates a better
understanding of the mechanical loads imposed by
TAVR devices on the cardiac conduction system.
Most investigators agree that conduction abnormal-
ities are primarily due to mechanical compression of
the cardiac conduction system by the device,
although other factors may be involved.[92,122,135]
Device failure, which necessitates a better under-
standing of the mechanical and biological durability
of TAVR devices. Durability concerns may arise
from sub-optimal deployment, leaflet calcification,
and thrombus formation to mention a few. More
recently, quantitative data has become available
assessing transcatheter heart valves' leaflets durabil-
ity.[30] The report estimates that TAV degeneration
was about 50% within 8 years post-TAVR with
early-generation balloon-expandable TAV devices.

TAVR involves delivery, deployment, and implan-
tation of a crimped, stented valve within a diseased
aortic valve or degenerated bioprosthesis. A major
limitation of these procedures is the diameter to which
the stent can be crimped without damaging the leaflet
tissues within. Currently, only a handful of FDA-ap-
proved transcatheter valves (Fig. 1) are being used in
elderly aortic stenosis patients.[58] TAV durability has
not yet tested in any of the trials. However, a recent
report from St. Paul's Hospital in Vancouver, Canada

suggests post-TAVR' long-term durability with early-
generation balloon-expandable valves is a concern with
significant increase in degeneration rate 5–7 years post-
TAVR. The report estimates TAV degeneration to be
about 50% within 8 years.[30]

Avoid Stent-Crimp-Induced Leaflet Injury

More recently, quantitative data has become avail-
able assessing the crimping-related damage to tran-
scatheter heart valves' leaflets. Most of these studies
that rely on the histology of pericardial leaflets[20,62,151]
have credibly documented that mechanical stresses
applied to pericardial leaflets result in disruption of
their collagen fibers' natural patterns, and may lead to
calcification and early valve problem.[61,107,151] The re-
sults of a more recent study published in the *New
England Journal of Medicine* by Makkar *et al.* indicate
that transcatheter aortic valves may lead to subclinical
leaflet thrombosis based on the results from PORTICO
IDE trial in comparison to SAVORY and RESOLVE
registries.[76] A potential mechanism could be the in-
jured rough surface of the leaflet facilitating thrombus
formation. Whether the stent-crimp damage to the
leaflets is transient or permanent is a critical question
that Alavi *et al.* have recently addressed.[4] in their
study. They tested the effect of stent crimping on col-
lagen fibers of the bovine pericardial leaflets at the
surface and in deeper layers under scanning electron
microscopy (SEM) and second harmonic generation
(SHG) microscopy.[4] Uncrimped leaflet tissue samples
were imaged, followed by imaging tissue segments after
crimping in a stented valve, immediately following, at
20, and 60 min after crimping. The crimping experi-
ments were performed for multiple crimped sizes (i.e.,
14, 16, and 18 French) The results are shown in
Fig. 10, indicating significant tissue damage occurring
both at the surface of the pericardial tissue and
through its depth. Moreover, the collagen fiber alter-
ation induced by crimping is irreversible and does not
return to its original arrangement over time.

In another study, Sinha and Kheradvar showed
significant levels of elastin fragmentation in stent-
crimped leaflets when compared to intact pericardial
leaflets as shown in Fig. 11.[113,114] In that study, Glu-
taraldehyde-fixed bovine pericardial leaflets (Neovasc,
Richmond, BC, Canada) were sewn into a self-ex-
pandable Nitinol stent to make transcatheter valve.
The valves were divided into two groups of crimped
and uncrimped, and each group was split into two to
be exposed either to a calcifying solution[40] or to con-
trol solution (normal phosphate buffered saline). For
the crimped group, the valves were carefully crimped
with a standard crimper at 18Fr and 14Fr and held
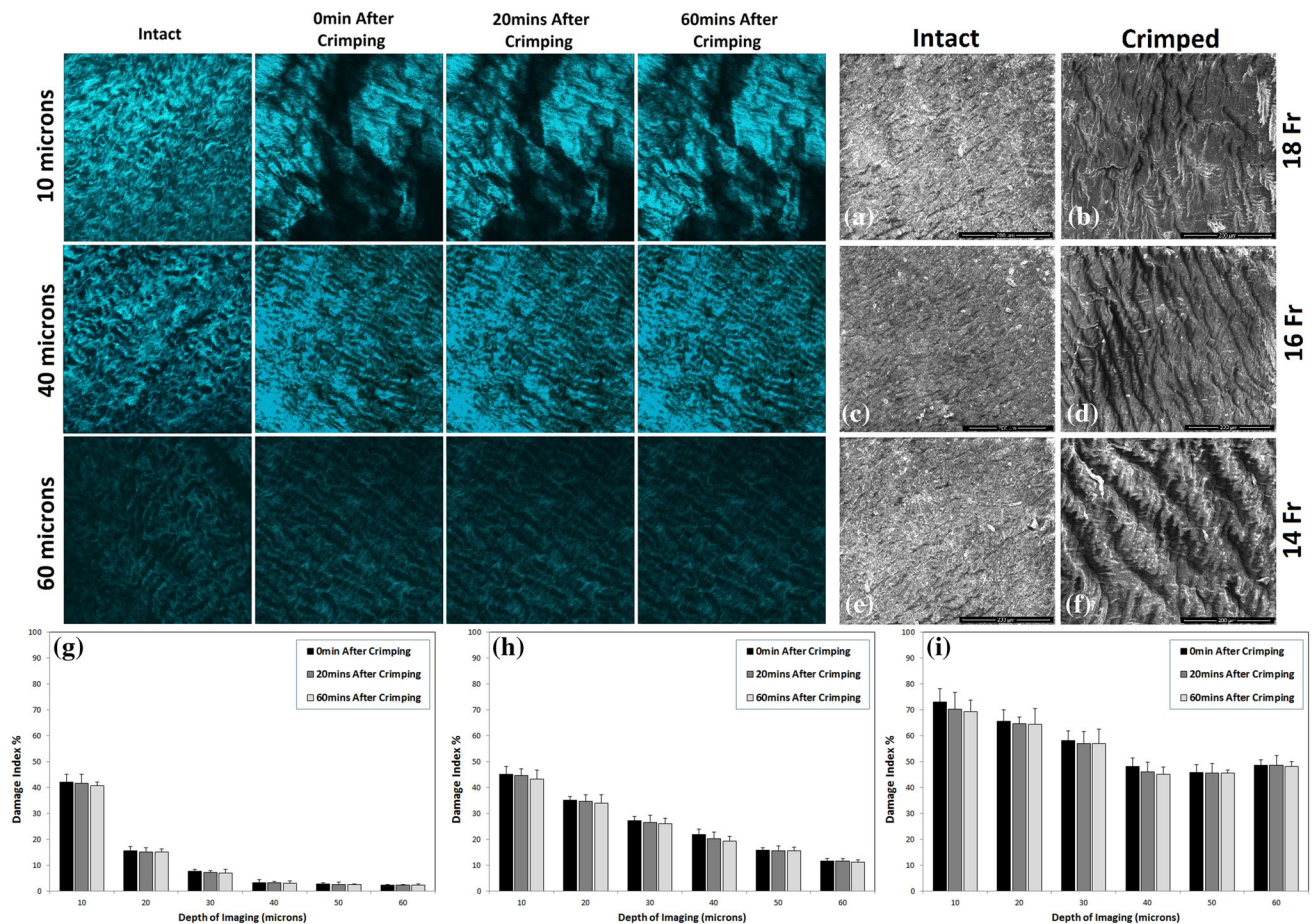crimped for 20 min. All the leaflets were then equally

FIGURE 10. (Left) SHG microscopy images compare the structural changes of intact and crimped pericardial tissues at depths of 10, 40, and 60 microns for crimping sizes of 18Fr over time. (Right) SEM images show intact (a, c, and e) and crimped (b, d, and f) states of three different pericardial leaflets at 18Fr, 16Fr, and 14Fr, respectively. Comparison of SEM images demonstrates substantial changes on the surface microstructure due to crimping, which increased with reduction of the collapsed profile. The images are from Alavi et al.[4] with permission.

cut into 0.5″ × 0.5″ segments and placed in 50 mL of either control, or calcifying solution similar to what described by Grases et al.[40] All groups were maintained at pH 7.5, 37 °C, on an orbital shaker at 400 rpm for 7 weeks. The samples were thoroughly rinsed with saline before embedding for histological analysis. Each tissue sample was individually embedded, sectioned and stained for elastin stain (Verhoff's Van Geison). Figure 11a demonstrates that the elastin fibers remain intact while the elastin fibers in crimped leaflet have been damaged in the depth of leaflet. The images show that elastin fibers in uncrimped leaflets have intact thin fibers morphology as pointed by black arrows in Fig. 11a in comparison to fragmented thin elastin fibers in crimped leaflet in Fig. 11b.

Transcatheter Heart Valve Calcification

Overall, stent-crimping damages in the depth of leaflets may increase calcification. While not yet sys-

tematically studied, microscopic damage to the leaflet collagen fibers is observed to be associated with calcification. In a recent *in vitro* calcification study, Kheradvar group at UC Irvine found that at the locations of significant damage to the collagen fibers within the leaflets, heavy calcification is present. The leaflet samples were studied after 50 million cycle accelerated wear test in presence of calcium–phosphate buffer at 37 °C. Figures 12a1 and 12b1 compare similar cross-section of a stent-crimped pericardial leaflet stained for calcium-phosphate (von Kóssa stain) and collagen fibers (Trichrome stain). Two local zones shown in Figs. 12a2 and 12b2 have been magnified and compared to reveal the association between the calcium deposition and collagen fiber damage in the stent-crimped leaflet. The higher calcium deposition (black color fibrils pointed by white arrows in Fig. 12a2) has been observed wherever collagen fibers are damaged indicated by faded blue fibrils pointed by black arrows in Fig. 12b2. This phenomenon is not noticed in the
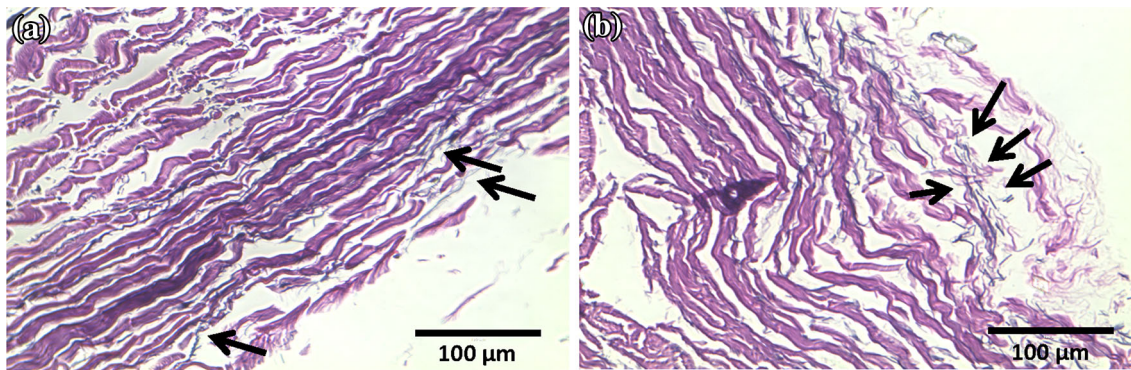
FIGURE 11. Verhoeff Van Gieson (VVG) staining of two cross sections extracted from Uncrimped (a) and crimped (b) bovine pericardial leaflets, respectively. Image A demonstrates intact elastin fibers (long black thin lines) in a cross section of an intact pericardial leaflet and image B shows fragmented elastin (short black thin lines) fibers in a stent-crimped leaflet. Elastin fibers in both cross sections were pointed by black arrows. Bars are 100 μm. The images are from Sinha and Kheradvar.[114]

areas where collagen fibers are still undamaged as shown in Fig. 12. More studies are underway to find out whether stent-crimping damage has causal relationship to leaflet calcification.

Transcatheter heart valves are prone to all the failure modes of surgical bioprosthetic heart valves.[89] In addition to those, specific features to these prostheses may contribute to their failure. Recent studies describe adverse events due to late-stage embolization, subclinical thrombosis and heart valve compression.[76,89] Other investigators reported the failure of Edwards' SAPIEN and Medtronic's CoreValve due to severe leaflet calcification and cusp rupture.[89,96] Structural valve failure is attributed primarily to severe leaflet calcification, causing cusp rupture and obstructive leaflet function.[96] The exact mechanisms that facilitate such rapid matrix degeneration are currently unknown; however, predominant reasons may include repeated chronic mechanical stresses on valvular leaflets causing initiation and accumulation of calcium deposition.[130] In a recent editorial correspondence in the *New England Journal of Medicine* published in March 2015, two patients with severe calcification of 29 mm CoreValve prostheses were presented and discussed only after 5 years post-implantation. Explant of the prosthesis revealed severe leaflet calcification, degeneration, and thrombus formation as shown in Fig. 13.[99]

The recent clinical reports on calcification of transcatheter aortic valves may be only the tip of the iceberg, and now that a few years have passed since the first generation of implants, more clinical cases of crimp-induced problems may be found. Considering the substantial numbers of TAVR in the recent years, the first comprehensive 10-year follow-up data can be expected by 2020.[9] Overall, the field of heart valve engineering currently lacks knowledge about the *in vivo* mechanistic processes involved in transcatheter valvular dysfunction and calcification due to crimping damage.

Transcatheter Tissue Engineered Heart Valves

Transcatheter tissue engineered heart valve (TTEHV) technology is a recent advancement that combines minimally invasive strategies with living tissue engineered heart valves aiming to overcome the limitations of current TAVR technologies by providing growth, remodeling, and regeneration capabilities. There have been promising reports recently demonstrating a potential role for this technology in near future. These reports have taken advantage of the use of either classical *in vitro* tissue engineering approaches[25,82,106] or the newly introduced in situ and "off-the-shelf" procedures.[26,143] In conventional approaches, the tissue engineered valves are developed *in vitro* by seeding cells in a proper scaffold to generate living tissue, whereas the in situ approaches take into account the intrinsic regenerative capacity of the body to repopulate the substrate.[57] The latter provides an off-the-shelf feature that may extremely simplify the commercialization process and greatly enhance the clinical relevance of these valves. To the best of our knowledge, the introduction of TTEHV dates back to 2005 in the work of Ruiz *et al.*[102] where they reported data on percutaneous implantation of decellularized valves made of biodegradable small intestinal submucosa (SIS) in a swine model. Even though the valves had progressive thickening after one-year implantation, the histologic remodeling and formation of new extracellular matrix (ECM) were promising. One year later, Stock *et al.*[123] showed that the use of a thin SIS wall inside a stent would protect the delicate decellularized valves from crimping damages. This suggested the use of tissue engineered valves that included their own vascular wall. Schmidt *et al.*[106] employed this
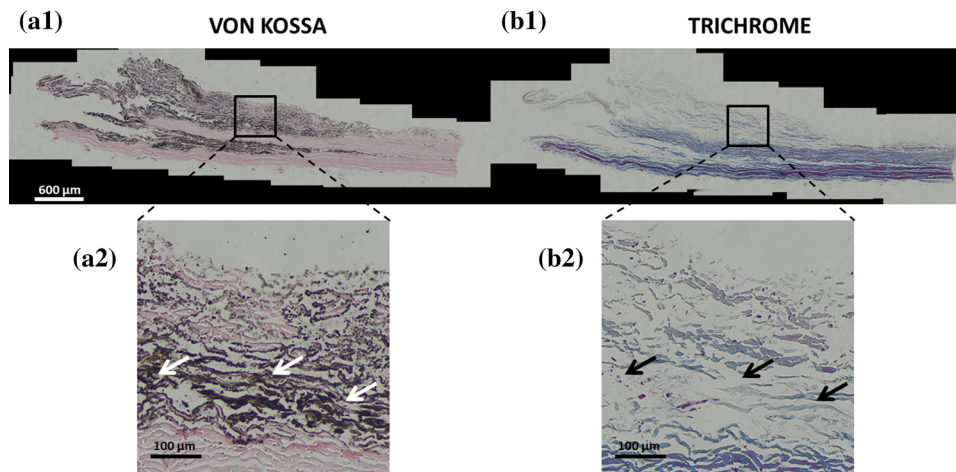
FIGURE 12. Von Kossa and Trichrome staining of a cross section extracted from a crimped bovine pericardial leaflet. Both cross sections were extracted from the same location in the leaflet and then were stained for calcification and ECM investigations. (a1) and (b1) are mosaic images (10 stitched images) of Van Kossa and Trichrome staining of the cross section, respectively. (a2) and (b2) are two magnified local images to compare the calcification versus ECM. Image (a2) and (b2) show hydroxyapatite deposition and collagen fibers in the same location of tissue. Black and white arrows represent the calcified and damaged ECM zones in the leaflet. Bars are 600 and 100 μm in mosaic and magnified images, respectively. The images are from Kheradvar Laboratory.
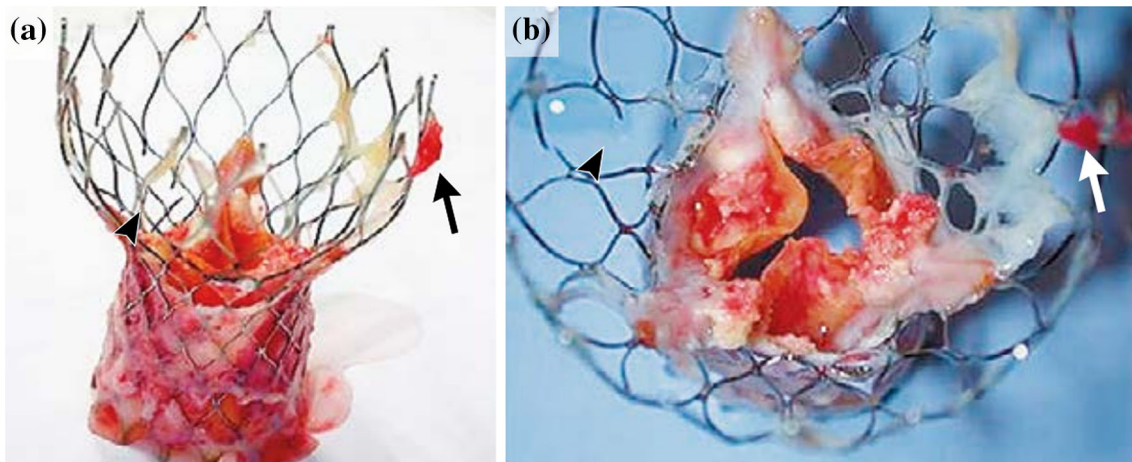

FIGURE 13. Panel (a) shows the presence of fresh thrombus (arrow), and panel (b) indicates the severe calcification and rupture of leaflets in a CoreValve. The images are from Richardt et al., NEJM,[99] with permission.

concept and demonstrated the feasibility of TTEHV technology by using stem cells for fabrication of heart valves. Those valves were implanted transapically in sheep at pulmonary valve position and exhibited acceptable in vivo functionality for up to 8 weeks with better extracellular matrix formation but with thickened leaflets. At that time, it was speculated that the thickening effect is due to the crimping procedure, however, later on Dijkman et al.[25] showed that the thickening is due to functional in vivo remodeling procedures rather than crimping effects. Another promising and pioneering study was the work of Emmert et al.[35] where, in contrast to the other works, they tested bone-marrow based TTEHVs at aortic position instead of pulmonary position. The valves successfully withstood the high pressure environment in the systemic circulation for the two-week period of this study. Recently, in two different works Weber et al.[143] and Driessen-Mol et al.[26] studied the use of off-the-shelf TTEHV approach in short term (up to 8 weeks) and long term (6 months), respectively. Both studies showed substantial ECM formation whereas the long-term study revealed significant recellularization and elastin fiber formation. Nevertheless, progressive regurgitation was observed as reported in Fig. 14, which was mentioned to be due to the suboptimal valve design.[26] New studies are currently underway to address these issues.[5–7,120] It is noticeable in all these studies that no matter what approach is used in fabrication of TTEHV, this technology can eliminate the
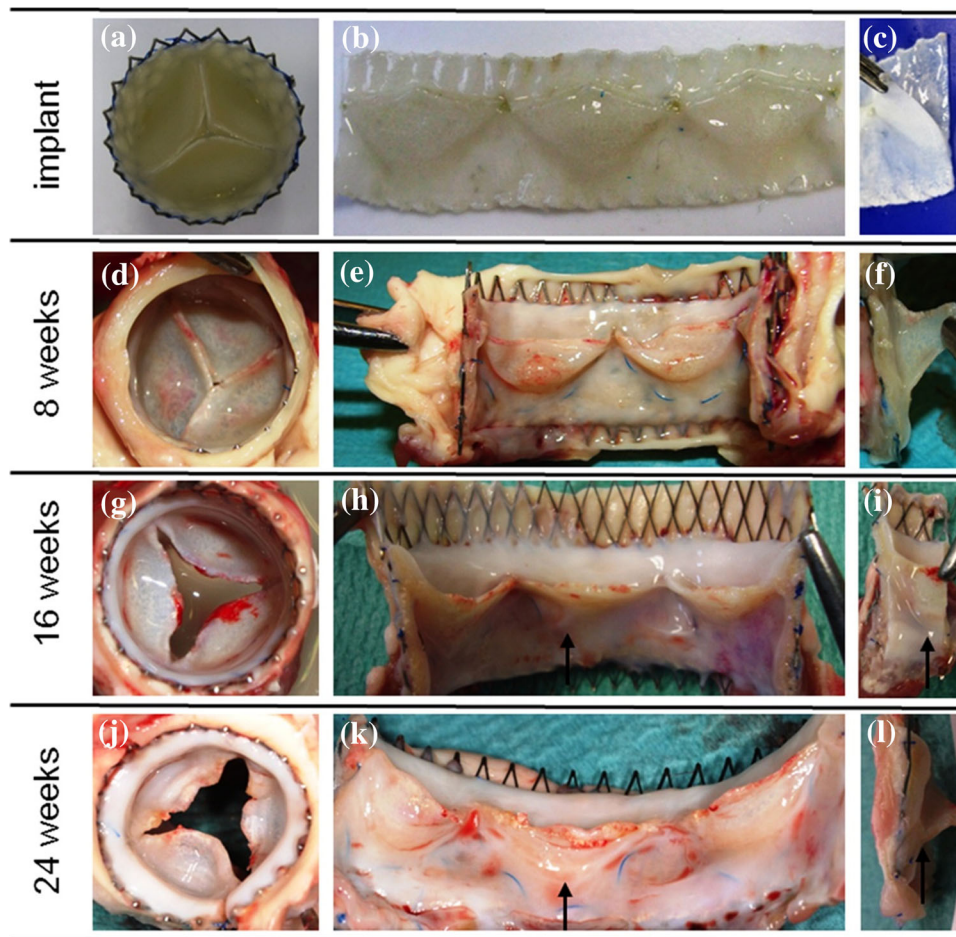
FIGURE 14. Macroscopic images of a TTEHV prior and after implantation in sheep pulmonary position. The valves were fabricated using biodegradable scaffolds and *in vitro* culture of vascular derived cells. The valves were decellularized prior to implantation to provide an off-the-shelf characteristic. The images are from Driessen-Mol *et al.*[26] with permission.

damages caused by TAVR stent-crimping mainly due to the self-repair capacity of the valves, which leads to healing and rapid ECM production post-implantation.[25,106] Although the outcomes of these studies are promising, further studies are required to provide information on long term functionality and clinical safety and durability of these valves.

Summary

Despite the revolutionary aspect of transcatheter aortic heart valves in offering high-risk patients an alternative to open heart surgery, adverse effects are still to a large extent of unresolved causes and consequences. The potential failure modes and durability concerns associated with TAVs fall under fluid mechanics, structural mechanics and microscopic mechanics. More studies *in vivo* and *in vitro* are deemed necessary to better understand and connect the causes to the effects and therefore to better contribute to more efficient and convenient TAV designs. To date, the main problems associated with TAVR revolve around paravalvular leakage, thrombosis, non-circular transcatheter heart valve deployment, conduction abnormalities, crimp-induced leaflet damage and patient-prosthesis mismatch. Paravalvular leakage can lead to congestive heart failure, arrhythmias, forceful contractions of the heart, and high degree of mortality. Valve positioning, types of TAVs (self-expanding versus balloon expanding), locations and size of calcium nodules and the increased stresses on the leaflets due to eccentric deployment have the biggest impact on determining the regurgitation possibility and level. A quantitative understanding of the biomechanical interaction between the native aortic tissue and the TAV is essential for better design and selection of the appropriate valve. Leaflet thrombosis is another major problem associated with TAVR. Stagnation of flow in the sinuses and crimp-induced damage are potential reasons behind leaflet thrombus formation. Position-

ing of the TAV, under-expansion, aggressive post-dilation and the injured rough surface of the leaflets due to possible crimping may be the underlying factors on thrombus formation. Non-circular heart valve deployment is a direct consequence of the complication that arises when the TAV and the native valve interact. The non-circular shape is assumed due to the highly calcified native leaflets. This leads to high stress regions over the TAV leaflets under dynamic loading that may lead to calcification and early valve degeneration. Optimizing the TAV design parameters to improve leaflet durability taking into account the effects of stent-crimping, under-expansion and non-uniform expansion is necessary. Patient-prosthesis mismatch is also one of the most impactful adverse effects of TAVR especially in the valve-in-valve configuration. PPM induces additional flow resistance, which can only be overcome with higher pressures. The types and positioning of TAVs along with the types of the bioprostheses dictate the efficiency and functionality of the ViV configuration. Despite the numerous studies, patient-specific anatomic characteristics are necessary for an optimum ViV setup. Valve-in-Valve-in-Valve procedures constitute another dimension of the ViV setup but more studies are still required for better understanding and assessment of the procedure. Overall, all the previous studies reported her have contributed to a significant understanding regarding TAVR procedures and have a big impact on implementing remedies in future TAV designs. Some of these remedies include implementing an inflow skirt, making a change in the frame material, avoiding stent crimping as it leads to the disruption of the fibers natural pattern and therefore calcification, and developing transcatheter tissue engineered valves that can withstand high pressure environment.

Procedures pertaining transcatheter aortic valve replacement are undergoing fast improvements. Despite the efforts and the diversity of the studies, more investigations are still required to acquire a comprehensive understanding and thus to implement this understanding into future design and developments and clinical applications to improve patients' quality of life and valve durability.

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