

# *In Vitro* Evaluation of a Novel Hemodynamically Optimized Trileaflet Polymeric Prosthetic Heart Valve

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*Calcific aortic valve disease is the most common and life threatening form of valvular heart disease, characterized by stenosis and regurgitation, which is currently treated at the symptomatic end-stages via open-heart surgical replacement of the diseased valve with, typically, either a xenograft tissue valve or a pyrolytic carbon mechanical heart valve. These options offer the clinician a choice between structural valve deterioration and chronic anticoagulant therapy, respectively, effectively replacing one disease with another. Polymeric prosthetic heart valves (PHV) offer the promise of reducing or eliminating these complications, and they may be better suited for the new transcatheter aortic valve replacement (TAVR) procedure, which currently utilizes tissue valves. New evidence indicates that the latter may incur damage during implantation. Polymer PHVs may also be incorporated into pulsatile circulatory support devices such as total artificial heart and ventricular assist devices that currently employ mechanical PHVs. Development of polymer PHVs, however, has been slow due to the lack of sufficiently durable and biocompatible polymers. We have designed a new trileaflet polymer PHV for surgical implantation employing a novel polymer—xSIBS—that offers superior bio-stability and durability. The design of this polymer PHV was optimized for reduced stresses, improved hemodynamic performance, and reduced thrombogenicity using our device thrombogenicity emulation (DTE) methodology, the results of which have been published separately. Here we present our new design, prototype fabrication methods, hydrodynamics performance testing, and platelet activation measurements performed in the optimized valve prototype and compare it to the performance of a gold standard tissue valve. The hydrodynamic performance of the two valves was comparable in all measures, with a certain advantage to our valve during regurgitation. There was no significant difference between the platelet activation rates of our polymer valve and the tissue valve, indicating that similar to the latter, its recipients may not require anticoagulation. This work proves the feasibility of our optimized polymer PHV design and brings polymeric valves closer to clinical viability. [DOI: 10.1115/1.4023235]*

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## Introduction

Prosthetic heart valves (PHVs) have been in clinical use with an overall operative mortality rate of less than 5% for decades [1]. However this success has not been without risks. Traditionally, PHVs are surgically implanted at the symptomatic end stages of valvular heart disease, with the most common and life threatening form being aortic stenosis (AS) [1]. Approximately 4% of individuals over the age of 65 suffer from AS resulting from calcific aortic valve disease, with an associated mortality of up to 54% [1]. Today's PHVs are comprised of either chemically fixed xenografts (tissue) or pyrolytic carbon mechanical valves, each carrying significant risks of structural valve deterioration or thrombosis, respectively, effectively offering clinicians the choice between one of two major complications: early device failure or chronic anticoagulation [2]. Up to 33% of patients who need valve replacement are considered inoperable due to significant comorbidities [3]. This subset of patients is now benefiting from the newly approved transcatheter aortic valve replacement (TAVR) procedure, reserved for inoperable patients with severe AS [4],

however, there is evidence that the tissue valves currently utilized in TAVR procedures are damaged during the deployment process [5,6]. It is evident that the current prosthetic valves are not ideal. Polymeric PHVs, whose goals are to eliminate the deleterious side effects of tissue and mechanical valves while combining their respective strengths, namely, the minor thrombotic complication rates in tissue valves and the lifetime durability of mechanical heart valves, into one device, may also offer a better solution for TAVR procedures. Polymeric PHVs may also be incorporated into pulsatile mechanical circulatory support devices such as the total artificial heart [7] or the Penn State pediatric ventricular assist device [8]. However, developing a clinically viable PHV has proven to be extremely challenging. Recently, the development of new promising super-biostable polymers [9] may pave the way to fulfill the clinical potential of polymer PHVs.

Polymeric PHVs have been researched since 1958 [10], but, to date, no one has been able to produce a clinically viable device. However, the advent of biostable polymers in this century has produced promising PHV prototypes [11–14]. Several new and improved polymeric materials are being investigated for use in PHVs including: the first biostable polyurethane: polycarbonate-urethane (PCU) such as Bionate [15], a nano-composite polymer comprised of polyhedral oligomeric silsesquioxane nano-particles and PCU [13], polyurethane with a poly(dimethylsiloxane) soft segment known as Elast-Eon<sup>TM</sup> by AorTech Biomaterials [16],

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Pellethane<sup>®</sup> 2363-80AE elastomer is a polytetramethylene glycol based polyurethane elastomer, by Lubrizol [17], the thermoplastic polyolefin poly(styrene-block-isobutylene-block-styrene), or SIBS [18], and the new polyolefin thermoset elastomer, xSIBS, by Innovia LLC [19]. Other materials that may potentially be applicable in polymer PHVs include: fluoropolymers such as polyvinylidene difluoride (PVDF) and poly(vinylidene fluoride-co-hexafluoropropene) (PVDF-HFP) [20] and hyperbranched polyurethanes demonstrating shape memory [21]. These polymers offer improved biostability over previous generations.

We and others have previously utilized such a polymer, the thermoplastic polyolefin poly(styrene-*b*-isobutylene-*b*-styrene) or SIBS (Innovia LLC, Miami, FL) [18], to design and test a polymer PHV fabricated from SIBS with embedded Dacron reinforcement mesh, with mixed outcomes [12,14,22–26]. We continue to collaborate with Innovia, who have since developed an improved version of this polymer, xSIBS [19], which is designed to eliminate the significant dynamic creep of thermoplastic SIBS that has limited its utility in PHVs [27]. We have designed a new trileaflet polymeric valve using our device thrombogenicity emulation (DTE) methodology [28,29], which employs state-of-the-art numerical and experimental methods to virtually test and hemodynamically optimize, via an iterative process, blood recirculation medical devices with the goal of eliminating the need for anticoagulants and making the research and design process more efficient. The results of the DTE evaluation, including detailed computational fluid dynamics and platelet activation experiments, have been published separately. Here, we present our new DTE optimized surgical implantable PHV design, prototype fabrication methods, *in vitro* hydrodynamics, and bulk human platelet activation studies conducted in this optimized design prototype.

## Methods

**Valve Design.** We have closely examined the original surgically implantable SIBS-Dacron composite polymeric valve design (Innovia; see Fig. 1(a)) and analyzed the failure modes that were observed in preclinical animal trials [25], additionally drawing upon the native human aortic valve characteristics and functional mechanisms [30]. The original Innovia composite valve leaflet design, with the reinforcing Dacron mesh embedded in cast SIBS dissolved in toluene, had a uniform thickness leaflet material fabricated from a flat sheet (see Fig. 1(b)). The leaflet was cut and sewn onto a high styrene content molded SIBS valve stent using polyester sutures. The valves explanted from the animal trials exhibited cracking in the SIBS leaflet coating with subsequent

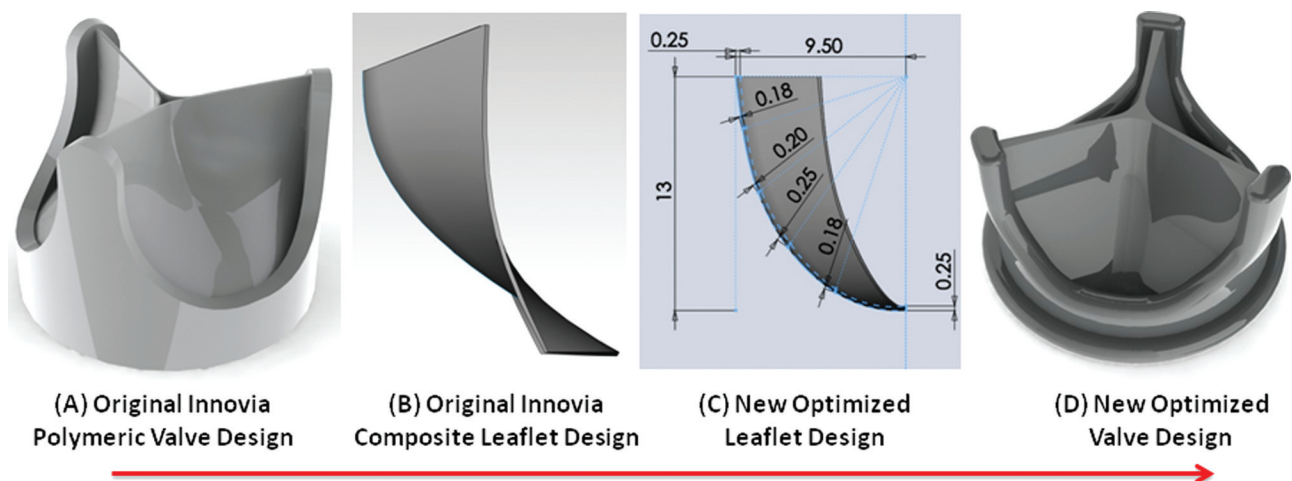
Dacron calcification and fatigue failure. Finite element modeling predicted high stress concentrations in the free edges of the leaflets and its belly, corresponding to the locations of leaflet fracture [31]. The native human aortic valve has hemispherical leaflets with variable thickness across the radial cross-section, in addition to a complex tissue structure [30]. In an iterative design process, we have modified the original Innovia composite leaflet design from cylindrical to hemispherical, created a variable thickness leaflet for optimized stress distribution and functionality (see Fig. 1(c)), smoothed and rounded the edges of the stent, widened the outflow orifice of the valve by 2 mm, and maximized the coaptation area for optimal closing load distribution (see Fig. 1(d)). The valve was designed for a 21 mm tissue annulus diameter so that it would fit into both the smallest adult human and the animal model (young sheep). The designs were created with the computer aided design software SolidWorks (Dassault Systèmes SolidWorks Corp., Waltham, MA).

**Finite Element Analysis (FEA).** We have utilized structural FEA using the ADINA package (ADINA R&D, Inc., Watertown, MA) as part of the design verification process in which we examined the original Innovia composite SIBS-Dacron valve, a benchmark tissue valve, and our optimized valve design. We utilized the two-parameter isotropic hyperelastic Mooney-Rivlin material model in each simulation of normal diastolic pressure loading (80 mm Hg), given by the strain energy function in Eq. (1) [32]

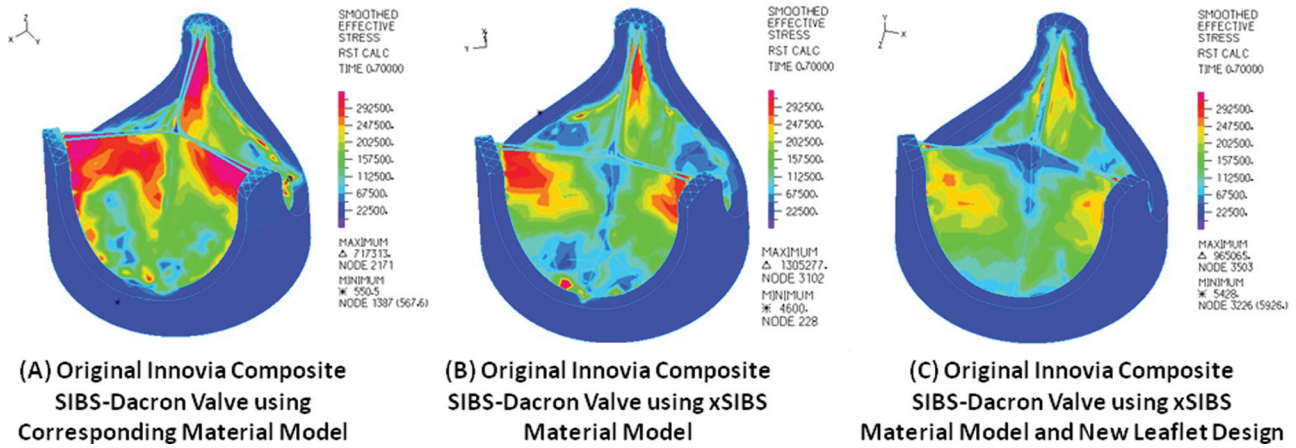
$$W_D = C_1(I_1 - 3) + C_2(I_2 - 3) + D_1(\exp(D_2(I_1 - 3)) - 1) \quad (1)$$

Contact conditions were applied to the ventricular surface of the leaflets to model valve closure [33]. The geometries were discretized with unstructured 4-node tetrahedral elements with each valve having the same mesh density. Mesh independence studies were conducted at three different mesh densities (0.0008, 0.0004, and 0.00025 times length scale, corresponding to approximately 12,500, 55,000, and 170,000 elements). Simulations that produced a less than 5% difference in stress and hemodynamic parameters established the mesh density at 0.0005 for all three valves, corresponding to approximately 25,000-30,000 elements, according to the specific valve geometry.

In each study, respectively, the xSIBS tensile test data was used for the optimized valve, tensile test data from Gallocher [34] for the original composite SIBS-Dacron PHV, and the fixed pericardial patch Mooney-Rivlin constants  $C_1$ ,  $C_2$ ,  $D_1$ , and  $D_2$  from Tang et al. [35] were used for the tissue valve. The 3-D geometry



**Fig. 1** (a) The original Innovia composite polymer valve geometry, (b) the original Innovia composite polymer valve leaflet geometry featuring a curved profile and uniform thickness, (c) the new optimized polymer valve leaflet geometry featuring a flat profile and variable thickness along the radial cross-section, and (d) the optimized polymer valve geometry



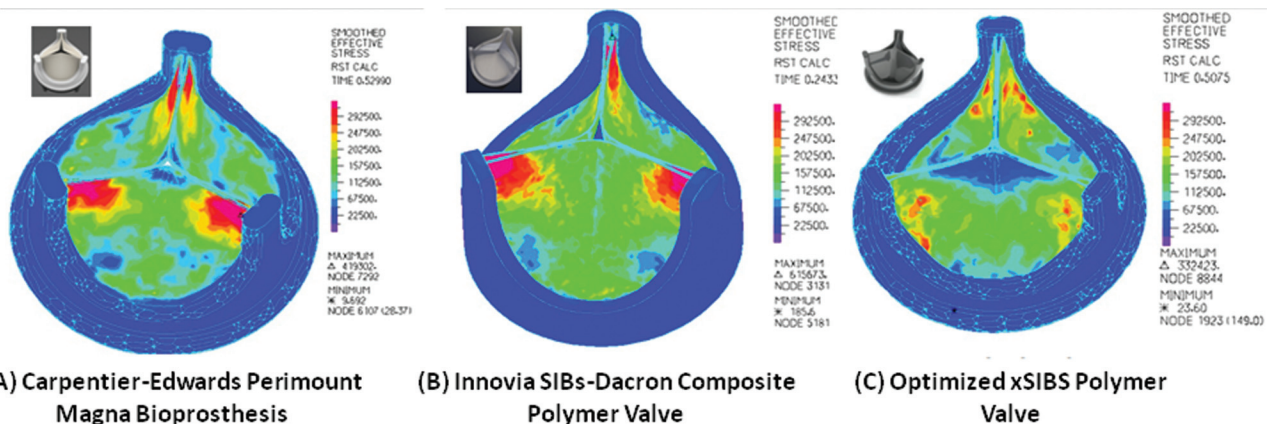
**Fig. 2** Structural FEA comparing the (a) original Innovia SIBS-Dacron composite valve with corresponding material constants to (b) the same valve with the xSIBS material constants and to (c) a simulation in which the Innovia valve stent was fitted with our new tapered thickness leaflets modeled with the xSIBS material constants. The stress scales are identical in each frame. Reduced stress concentrations are clearly evident as we altered the valve design, first changing the material to xSIBS, then changing the valve leaflets to a tapered thickness profile.

of the Carpentier-Edwards Perimount Magna bovine pericardial tissue PHV (Edwards Lifesciences) was acquired using micro-CT ( $\mu$ CT40, Scanco Medical, Switzerland). The scans were conducted at  $36\ \mu\text{m}$  isotropic resolution with an energy level of 70 kV and  $114\ \mu\text{A}$ . A 3-D geometry was reconstructed from the micro-CT scans using Mimics (Materialise, Leuven, Belgium) and imported into Gambit (ANSYS, Inc. Canonsburg, PA), where it was reconstructed in preparation for the FEA.

The effects of the design changes in the polymer valve were iteratively examined, by comparing the smoothened effective stress maps, starting with the original Innovia composite valve using the corresponding material constants (see Fig. 2(a)). Next, we ran the same original valve geometry with the xSIBS material constants (see Fig. 2(b)) and finally, we ran a study in which we placed the new tapered leaflet design into the original Innovia stent using the xSIBS material constants (see Fig. 2(c)). We then ran simulations with the tissue and optimized valve geometries (including the new stent design) for comparison, using their respective material constants (see Fig. 3).

**Valve Prototype Fabrication.** As previously described, the original composite valve was produced using multiple materials and fabrication steps. Following the DTE design optimization (described in a separate paper), a custom compression mold with

precisely nuanced geometries was machined for fabricating prototype valves in their entirety from the homogenous xSIBS in one step. The xSIBS polymer was supplied in raw uncross-linked form and required forming and thermal cross-linking via a Diels-Alder reaction [19]. The mold (see Fig. 4(a)) was designed using both SolidWorks and Gambit. (The Boolean operations in Gambit were essential to creating certain geometries.) It was machined from aluminum alloy blocks at the Helmholtz Institute of Applied Medical Engineering in Aachen, Germany, using 5-axis computer numerical control machining. To create the prototypes, the mold was coated with dry Teflon mold release (Super Lube Dri-Film, Synco Chemical Corp, Bohemia, NY), filled with raw 23% styrene xSIBS, sandwiched between water-cooled Specac 6100 heating platens set to  $260^\circ\text{C}$  (Specac Inc. Cranston, RI), and compressed with approximately 1 ton (2000 lb) of force (Grobet USA, Carlstadt, NJ) for 30 min. Air and excess polymer were extruded through portholes, which sequestered the material from oxygen during cross-linking (as required for the Diels-Alder reaction). Once the mold cooled to ambient temperature, the valve was carefully removed using 200-proof ethanol (Pharmco-Aaper). Cross-linking of the xSIBS was checked by soaking the valve in toluene (Sigma-Aldrich) and observing swelling without dissolution. The valves appeared whitish and rubbery. The xSIBS optimized valve prototype is shown in Fig. 4(b).



**Fig. 3** Structural FEA comparing the (a) Carpentier-Edwards Perimount Magna bioprosthesis, (b) the original Innovia composite polymer valve, and (c) the optimized xSIBS valve. The stress scales in each image are identical. Reduced stress concentrations are clearly evident in the optimized valve as compared to the composite and tissue valves.

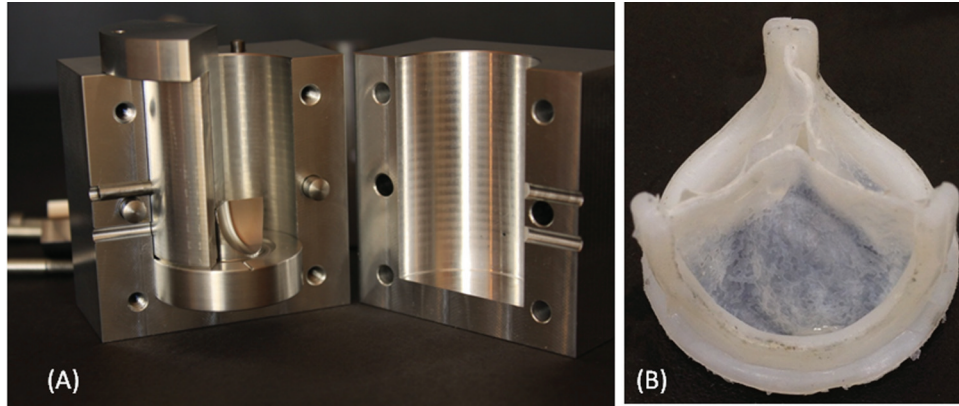


Fig. 4 (a) The optimized valve compression mold, and (b) the molded xSIBS valve prototype

Table 1 The hydrodynamic test regime for the LHS (BPM = beat per minute and CO = cardiac output)

| Heart rate (BPM) | 45  | 70  | 100  | 120  |
|------------------|-----|-----|------|------|
| CO (l/min)       | 2.3 | 3.9 | 6.0  | 7.8  |
|                  | 3.6 | 5.6 | 8.0  | 9.6  |
|                  | 5.0 | 7.4 | 10.0 | 11.4 |

**Hydrodynamics Testing.** The *in vitro* hydrodynamic testing of the valve prototypes was conducted in a Vivitro left heart simulator (LHS) (Vivitro Labs, Inc. Victoria, BC), as previously described [12]. The LHS is capable of simulating precise physiologic pressure and flow waveforms. Custom valve holders were designed and molded for the LHS from silicone rubber. The optimized design xSIBS valve ( $n=3$ ) was mounted in the aortic position of the LHS and a 27 mm St. Jude bileaflet mechanical valve (St. Jude Medical) in the mitral position. The system was filled with 2 liters of a viscous saline solution (35% glycerin and 0.9% NaCl) designed to mimic blood and to facilitate flow recording with an electromagnetic flow meter (Carolina Medical). The test regime in Table 1 was followed for each study with a mean arterial pressure (MAP) (Eq. (2)) of 100 mm Hg maintained throughout the testing

$$\text{MAP} = \frac{p_{\text{systolic}} + 2p_{\text{diastolic}}}{3} \quad (2)$$

The commercially available 21 mm Carpentier-Edwards Perimount Magna Bioprosthesis ( $n=1$ ) was used as a benchmark for comparative testing. Data was recorded, processed, and analyzed with Vivitest software, which also controlled the pump waveform. The transvalvular pressure gradient, regurgitation, energy loss, and effective orifice area (EOA) were plotted for each valve. Vivitest uses Eq. (3) from ISO 5840:2005 to calculate the EOA

$$\text{EOA} \equiv \frac{Q_{\text{RMS}}}{51.6\sqrt{\Delta p/\rho}} \quad (3)$$

where  $\Delta p$  is the mean pressure gradient across the valve,  $\rho$  is the fluid density, and  $Q_{\text{RMS}}$  (root mean square volumetric flow rate) is given by Eq. (4)

$$Q_{\text{RMS}} = \sqrt{\frac{\int_{t_1}^{t_2} Q(t)^2 dt}{t_2 - t_1}} \quad (4)$$

where  $t$  is the time. The regurgitant fraction (RF) is calculated by Eq. (5)

$$\text{RF}\% = \frac{\text{CV} + \text{LV}}{\text{FV}} \times 100 \quad (5)$$

where CV is the closing volume, LV is the leakage volume, and FV is the forward volume. The total energy loss across the valve is calculated by Eq. (6)

$$\text{Energy}_{\text{total}} = \text{FE} + \text{CE} + \text{LE} \quad (6)$$

where FE is the forward energy, CE is the closing energy, and LE is the leakage energy, with energy ( $E$ ) given by Eq. (7)

$$E = 0.1333 \int_{F_n}^{F_{n+1}} \Delta p Q(t) dt \quad (7)$$

where  $F_n$  to  $F_{n+1}$  is the range of a phase of the cardiac cycle corresponding to FE, CE, or LE and 0.1333 is an energy unit conversion from mm Hg\*ml to mJ. For comparison, the maximum velocity can be estimated as shown in Eq. (8)

$$V_{\text{max}} = \frac{Q_{\text{max}}}{\text{EOA}_{\text{max}}} \quad (8)$$

**Bulk Human Platelet Activation Measurements.** The bulk flow platelet activation of the valves was measured as previously described [22]. Briefly, 120 ml of blood was obtained from healthy volunteers of both sexes screened for antiplatelet medication and a history of smoking according to institutional IRB protocols. A Berlin pulsatile left ventricular assist device (LVAD), which is the implantable part of a pneumatic heart-assist system developed by Professor Klaus Affeld (Biofluid Mechanics Laboratory, Clinic of Cardiovascular Surgery, University Hospital Charité, Humboldt University of Berlin), operated with a pulsatile reciprocating pump (Model 1423 blood pump, Harvard Apparatus, Holliston, MA), was used to recirculate 250 ml of solution containing freshly isolated human platelets at a concentration of 20,000/ $\mu\text{l}$  in a HEPES modified Tyrode's platelet buffer. The system held two identical valves mounted inside custom designed valve holders oriented in opposite directions. The inflow and outflow ports were connected with a section of Penrose tubing (CR Bard, Covington, GA), which served as a compliance reservoir. The pump rate was set to 90 beats per minute (BPM) with a stroke volume of 65 ml, corresponding to a cardiac output (CO) of 5.85 l/min. The systole/diastole ratio was set to 0.375. The recirculation test was run for 30 min, with samples taken in duplicate every 10 min. Platelet thrombin generation rates were measured using our platelet activation state (PAS) assay, as previously described [36]. The results were compared to previous measurements ( $n=6$ ) conducted with 21 mm Carpentier-Edwards

**Table 2 Hydrodynamic data comparing the mean functionality of the tissue versus the optimized xSIBS valve prototypes and baseline physiological conditions (HR = 70 BPM and CO = 5.6 l/min)**

|                       | Mean $\Delta P$ (mm Hg) | Mean RF (%) | Maximum velocity at rest (m/s) | EOA at rest (cm <sup>2</sup> ) |
|-----------------------|-------------------------|-------------|--------------------------------|--------------------------------|
| Tissue ( $n = 1$ )    | 16.57                   | 7.08        | 2.96                           | 1.95                           |
| Optimized ( $n = 3$ ) | 20.91                   | 2.43        | 3.42                           | 1.47                           |

Perimount Magna tissue valves mounted in the same LVAD and to a negative control, in which the LVAD was run without valves [22]. One-way ANOVA statistics were performed on the platelet activation rates (PAR) – the slope of the PAS measured over the 30 min. recirculation experiments, calculated from a linear best fit curve for each experiment with significance level  $\alpha = 0.05$ . This new valve design was also optimized for reduced thrombogenicity using our DTE methodology, the results of which will be published separately.

## Results

**Numerical Stress Analysis.** Parametric structural FEA studies in the three valves (under normal diastolic pressure loading of 80 mm Hg) were compared. In the first set of studies designed to test the effects of material properties and geometric optimization of the leaflet, we have compared the original Innovia SIBS-Dacron composite valve (see Fig. 2(a)) with the same original design geometry but with xSIBS material properties and the composite features excluded (see Fig. 2(b)) and, finally, with the optimized leaflet design changes and xSIBS properties (see Fig. 2(c)). In all of the configurations, the original (Innovia) cylindrical stent design was maintained (see Fig. 1(a)). We found decreasing stress concentrations in the leaflets as we progressively changed their design, with the lowest stresses in the new tapered leaflet design coupled with the xSIBS material constants (see Fig. 2(c)). This was followed by the global study in which we have directly compared the benchmark Carpentier-Edwards Perimount Magna tissue valve (see Fig. 3(a)) with the original Innovia composite SIBS-Dacron valve (see Fig. 3(b)) and our optimized design—additionally including the new stent design (see Figs. 1(d) and 3(c)). In this global comparison, each of the valves was simulated with its specific material constants. The results clearly show that the optimized xSIBS valve has the lowest stress concentrations. It also indicates that the new stent design with the smoothed and rounded edges and widened outflow orifice served to further lower the stresses in the leaflets. The maximum P3 strains were less than 1% and the maximum P1 and P2 strains exceeded 20%.

**Hydrodynamic Testing.** The xSIBS valves were tested in the LHS and compared to the Carpentier-Edwards Perimount Magna tissue valve. The mean and baseline physiological conditions (HR = 70 bpm and CO = 5.6 l/min) results are summarized in Table 2. The test regime also included simulating exercise conditions, with a maximum pump rate of 120 BPM and a maximum flow rate of 11.4 l/min. The transvalvular energy loss, a measure of the work that the heart must do to pump blood across the valve, indicated that at baseline conditions at the 4-6 l/min range, the optimized xSIBS valve and the tissue valve curves converge, showing equivalence to the benchmark tissue valve under those conditions (see Fig. 5(a)). However, at higher flow rates the xSIBS valve transvalvular energy loss continues to increase, exceeding that of the tissue valve. The transvalvular pressure gradient during forward flow shows that the two valves follow the same trend, but the gradient was higher in the xSIBS valve as compared to the tissue valve (see Fig. 5(b)). Notably, the xSIBS valves exhibited very low regurgitant flow (RF) as compared to the tissue valves (see Fig. 5(c)). The effective orifice area (EOA) of the tissue valve (see Fig. 5(d)) was larger than that of the xSIBS valve throughout the cardiac output range tested with a mean of

2 cm<sup>2</sup>, corresponding to an approximately 15% higher peak velocity through the polymer valve.

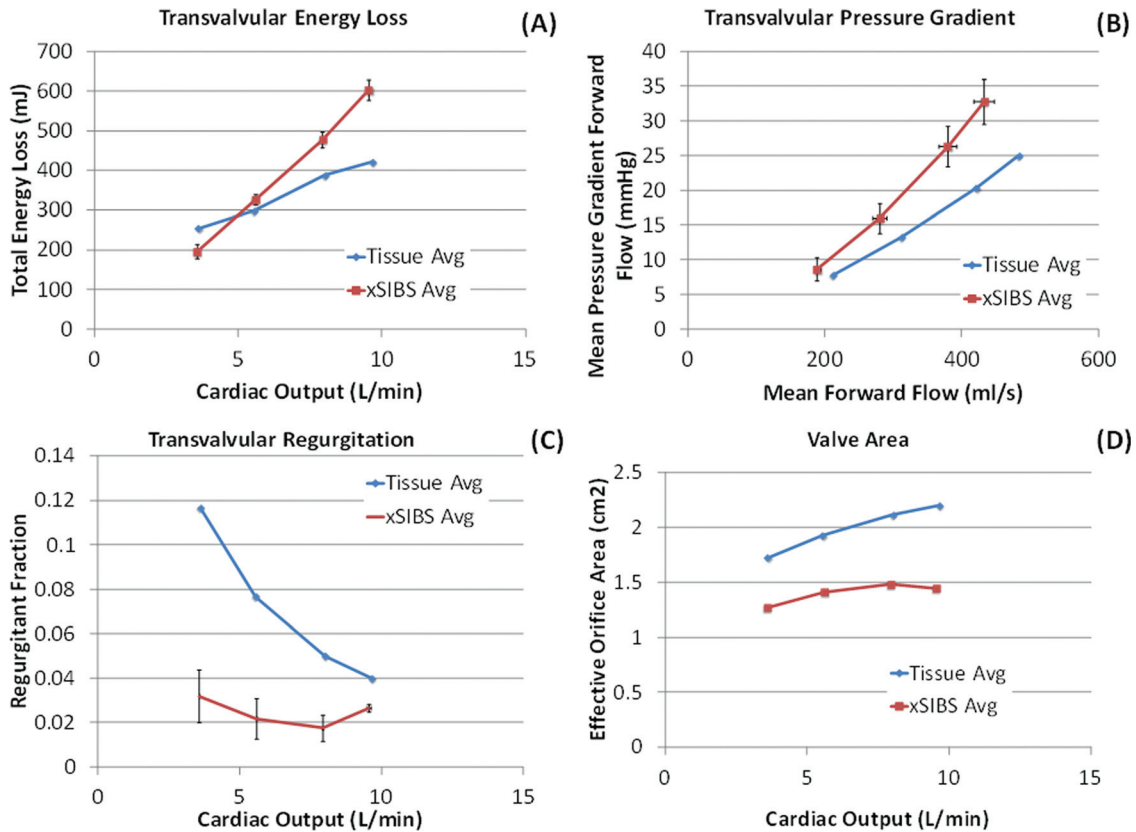
**Bulk Human Platelet Activation Studies.** Freshly isolated human platelet activation measurements were taken in the small volume pulsatile LVAD. The xSIBS valve results ( $n = 6$ ) were compared to prior benchmark tissue valve experiments ( $n = 6$ ) and to control studies in which the pump was run without valves [22], via a one-way ANOVA. There was no significant statistical difference between the platelet activation rates (PAR) of the tissue valve (PAR = 0.0005 min<sup>-1</sup>) and the xSIBS valve (PAR = 0.0008 min<sup>-1</sup>) (see Fig. 6), although the xSIBS valve exhibited a trend of a slightly higher PAR. This result is supported by the hydrodynamic testing results. Both valves PARs were significantly different from the control ( $p < 0.05$ ).

## Discussion

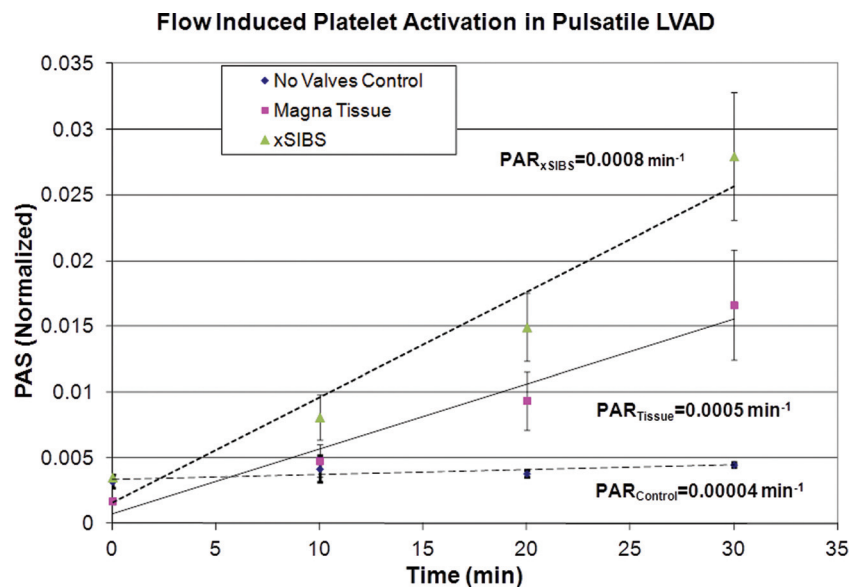
Polymeric PHVs offer a potential solution to the current limitations of mechanical and tissue PHVs, namely, chronic anticoagulation and structural valve deterioration, respectively. They may also be better suited for the new transcatheter valve replacement procedure [4], which currently utilizes tissue valves that have been shown to sustain damage during the delivery process, which involves acute stresses both during the valve crimping into a stent and the deployment over the diseased valve [5,6]. They may also be useful in pulsatile mechanical circulatory support devices such as the total artificial heart [7] or the Penn State pediatric ventricular assist device [8], which currently utilize thrombogenic mechanical valves. We have developed a novel optimized polymeric PHV currently designed for surgical implantation to achieve these goals as an alternative to the current PHV technologies. We are currently working on adapting our novel leaflet design for use in transcatheter valves.

Following an iterative design optimization process, in which we simulated normal diastolic pressure loading on the valves, our studies established a consistent trend of decreasing stress concentrations in the leaflets when the original Innovia composite valve was altered to the xSIBS material properties—with the original stent design and keeping the original uniform thickness leaflets design. This trend continued when the leaflets were changed to our new tapered thickness design and using the xSIBS material constants. Finally, when the new stent design was incorporated, the results clearly show that our design optimization significantly reduced the stresses in the valve leaflets, in comparison to the earlier Innovia composite valve and the benchmark tissue valve, under the highest physiologic load normally encountered by an aortic valve. This is a strong indication that the optimized valve will likely be more durable than prior generations of polymer PHVs.

A comparison to our previously published testing of the SIBS-Dacron composite valve [22] shows a significant improvement in all parameters of the hydrodynamic performance of the optimized valve (increased effective orifice area, much lower transvalvular pressure gradients, and lower velocities across the valve). While showing no evidence of *in vivo* degradation [18], the original thermoplastic SIBS polymer, which was adapted for the PHV application by reinforcing the valve leaflets with Dacron fiber mesh, did exhibit a significant dynamic creep in sheep experiments [25]. The optimized valve was designed around the improved thermoset version of this polymer—xSIBS [19], with



**Fig. 5** The hydrodynamics results from the LHS tests comparing the optimized xSIBS valve to the Carpentier-Edwards Perimount Magna bioprosthesis. (a) The transvalvular energy loss shows favorable results for the xSIBS valve at resting conditions (CO 4–6 l/min), (b) the transvalvular pressure gradient of the xSIBS valve tracks that of the tissue valve, (c) the xSIBS regurgitation is much lower than the tissue valve, and (d) the xSIBS valve Effective Orifice Area (EOA) tracks that of the tissue valve.



**Fig. 6** The bulk flow induced platelet activation measurements with the valves mounted in the pulsatile LVAD. There is no significant difference between the platelet activation rates (PAR) of the xSIBS and tissue valve. Both are significantly different ( $p < 0.05$ ) from the control (LVAD operated with no valves).

the specific goal of reducing its dynamic creep and increasing its tensile strength [27]. This facilitated manufacturing the valve prototypes entirely from xSIBS, using heated compression molding without the reinforcing fiber mesh of the previous design. Further-

more, this allowed for tight control of the nuanced geometry of the optimized design; in particular, the complex geometry of the leaflets, which feature a variable thickness intended to optimize the valve functionality, its hemodynamic performance, and its

durability. This design achieved a significant reduction of the stresses developed in the leaflets during the opening and closing phases. It also further reduced the stresses sustained by the leaflets during the regurgitant flow phase when the valve is fully closed and bearing the full diastolic pressure load (the highest loading phase), leading to superior regurgitant performance in the context of our study that surpasses that of the tissue valve and is a significant improvement when compared with previous polymeric valve designs. Additionally, this may be attributed to the increased coaptation surface area in our optimized design, which facilitated water-tight valve closure and a larger surface area for the distribution of the diastolic pressure load across all three leaflets. A certain disparity in the platelet activation rates between the two generations of this polymer valve may be attributed to the original design's impaired performance in the pulsatile flow loop, which produced a lower platelet activation rate, mostly because of its limited functionality during the regurgitant flow phase. The other hydrodynamic parameters indicate that we have some room to further improve our design, possibly by further modifying the leaflets thickness, modulating the ratio of styrene-to-isobutylene, or by modifying the heating time to alter the degree of cross-linking in the xSIBS polymer.

A direct comparison to similar work in the literature is limited by the variability that the difference between numerical and experimental methodologies can introduce. In terms of the FEA studies described herein, we have used them to provide side-by-side comparisons of different valve designs comprised of different materials, however, in the future, rigorous validation studies for the xSIBS material may be performed, such as those conducted by Sun et al. for tissue valves [37]. Similarly, a direct comparison to hydrodynamic test results from the literature [38] is impeded by the variation in testing methods and the availability of proprietary valves for comparison; however, we have focused on a comparison of the valve performance between designs in our new state-of-the-art Vivitro Left Heart simulator, a gold standard in valve testing. These data are preliminary and will be further verified and validated as we progress in the research and development process toward a viable commercial product.

In summary, our first round optimized valve prototypes produced: (1) platelet activation rates that are similar to that of the tissue valve, (2) transvalvular energy loss similar to that of the tissue valve at baseline operating conditions, albeit higher at exceeding exercise conditions, and (3) lower regurgitant flow than that of the tissue valve across all test regimes. The latter is a significant improvement over the tissue valve in terms of improved valve functionality (less regurgitation through the closed valve). It also further reduces the platelet activation in the optimized polymeric valve, bringing it down to a tissue valve platelet activation level, which mostly does not require anticoagulation. The significantly improved hemodynamic features and functionality that were superior to the original composite polymer valve design, coupled with the reduced thrombogenicity of the optimized valve, may demonstrate competitiveness with benchmark tissue valves.

This work has been limited by the number of available benchmark valves for comparison and the use of freshly isolated human platelets, which have been removed from red blood cells and plasma proteins that may modulate their activation *in vivo*. However, we have demonstrated in many applications of the PAS assay in the past that the one-to-one correlation between fluid shear stress and platelet thrombin generation measured is a very sensitive and effective tool for comparing the thrombogenic performance of various blood recirculating devices. We made simplifying assumptions in our FEA studies, including the use of an isotropic material model for pericardium and normal pressure loading to simulate valve closure and a full diastolic pressure load. However, we believe that the isotropic Mooney-Rivlin model sufficiently models the strain stiffening behavior of tissue when using experimentally derived constants and that, when the valve is closed, normal pressure dominates the stress response of the leaflets over other components of the stress tensor. These

results suggest that as the optimized polymer valve has thrombogenicity comparable with that of a clinically proven tissue valve, which does not require chronic anticoagulation for most patients, it may also not require anticoagulation. Offering functionality similar to that of a benchmark tissue valve, this new valve is approaching clinical viability, yet with better applicability to TAVR procedures.

Results from our DTE evaluation, which will be published separately, have already pointed to improved hemodynamics and improved thromboresistance (reduced platelet activation) for the optimized design (compared to the original SIBS-Dacron composite valve). The optimized design favorably compares with the tissue valve, which is an impressive outcome for a polymeric PHV. We have now completed one optimization cycle—currently followed by durability testing in which valve prototypes will endure 200 million accelerated opening and closing cycles for approximately 4 months (corresponding to 5 years of valve operation) in a commercial PHV durability tester (Vivitro HiCycle). This iterative optimization process may be repeated as needed in the future, until full optimization is achieved.

## Conclusions

We have designed, developed, and evaluated a novel surgically implantable polymeric prosthetic heart valve. The valve has been hemodynamically optimized via our DTE methodology. The structural stress analysis demonstrates a clear reduction in potentially damaging stress concentrations. The *in vitro* hydrodynamics and bulk platelet activation measurements are comparable to a commercially available benchmark tissue valve. These remarkable results encourage the further development of our design, moving the polymeric valve closer to clinical viability.

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