
**Methods**

- Computer-aided design: development of a bioinspired valve design digitally
- Polymeric heart valve: *in vitro* testing. Tested for EOA and RF.

**Results**

- A bioinspired valve design with minimized commissural gaps was created digitally.
  - EOA = 1.05-1.35 cm².
  - RF < 7%.
- Opening performance of polymeric valves was comparable to simulated valves.
- Increase in leaflet thickness lead to decrease in EOA and RF, but all valves tested were still hydrodynamically within acceptable ranges.

**Implications**

Computational and experimental outcomes in this study demonstrate good hydrodynamic function of a novel bioinspired valve design derived from micro-CT scans of a real heart valve. Valve thickness was inversely correlated to both EOA and RF. All valves tested were able to meet the ISO 5840 standard. With this knowledge and further optimization of design and fabrication processes, a polymeric valve with better functionality and durability than current treatments may be producible.
Bioinspired Polymeric Heart Valves: A Combined *In Vitro* and *In Silico* Approach

Aeryne Lee, PhD, a,b,§ Xinying Liu, PhD, a,§ Jacopo Emilio Giaretta, PhD, a,§ Thanh Phuong Hoang, a,§ Matthew Crago, BE, a Syamak Farajikhah, PhD, a,c Luke Mosse, PhD, d David Frederick Fletcher, PhD, a Fariba Dehghani, PhD, a,c David Scott Winlaw, MD, b,e Sina Naficy, PhD, a,b,c,*

a School of Chemical and Biomolecular Engineering, The University of Sydney, Darlington, NSW 2008, Australia

b School of Medicine, The University of Sydney, Camperdown, NSW 2050, Australia
c Sydney Nano Institute, The University of Sydney, Camperdown, NSW 2050, Australia
d Leap Australia, Suite 6, 750 Blackburn Road, Clayton North, Victoria 3168, Australia
e Department of Cardiothoracic Surgery, Heart Institute, Cincinnati Children’s Hospital, Cincinnati, OH 45229, United States

* Corresponding Authors: Dr. Sina Naficy (sina.naficy@sydney.edu.au), School of Chemical and Biomolecular Engineering, The University of Sydney, Darlington, NSW 2008, Australia, +61 2 9351 4147

§ These authors have contributed equally.

Disclosure Statement: The authors report no conflicts of interest.

Funding Statement: This work was funded by the Medical Research Future Fund (Grant No. MRFF-ARGCHD000015) and the Australian Research Council (Grant No. ARC DP200102164; Funder ID: 10.13039/501100000923).

Article Word Count: 3,450 words
<table>
<thead>
<tr>
<th>No.</th>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td><strong>Glossary Of Abbreviations</strong></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>ALE</td>
<td>Arbitrary Lagrangian-Eulerian</td>
</tr>
<tr>
<td>26</td>
<td>CAD</td>
<td>Computer-aided design</td>
</tr>
<tr>
<td>27</td>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>28</td>
<td>EOA</td>
<td>Effective orifice area</td>
</tr>
<tr>
<td>29</td>
<td>FSI</td>
<td>Fluid structure interaction</td>
</tr>
<tr>
<td>30</td>
<td>GOA</td>
<td>Geometric orifice area</td>
</tr>
<tr>
<td>31</td>
<td>PHV</td>
<td>Polymeric heart valve</td>
</tr>
<tr>
<td>32</td>
<td>PPD</td>
<td>Positive pressure difference</td>
</tr>
<tr>
<td>33</td>
<td>PSU</td>
<td>Polysiloxane urethane</td>
</tr>
<tr>
<td>34</td>
<td>RF</td>
<td>Regurgitant fraction</td>
</tr>
<tr>
<td>35</td>
<td>RMS</td>
<td>Root mean square</td>
</tr>
<tr>
<td>36</td>
<td>ΔP</td>
<td>Pressure difference</td>
</tr>
<tr>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>38</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Central Picture Legend: Bioinspired heart valve systolic performance: polymeric construct vs. computational model

Message: A bioinspired valve geometry is created using computer-aided design software and tested for its valvular performance both computationally and experimentally via pulse duplicator technology.

Perspective statement: A novel valve design incorporating bioinspired leaflet curvatures demonstrated hydrodynamic performance that met the conditions set by the ISO 5840 standards. Computational simulation was also able to successfully capture the valves’ behavior under systole. In the future, full FSI analysis, in addition to optimization of fabrication processes could lead to a PHV with enhanced performance and durability.
Structured Abstract

Objective Polymeric heart valves (PHVs) may address the limitations of mechanical and tissue valves in the treatment of valvular heart disease. In this study, a bioinspired valve was designed, assessed in silico, and validated by an in vitro model to develop a valve with optimum function for pediatric applications.

Methods A bioinspired heart valve was created computationally with leaflet curvature derived from native valve anatomies. A valve diameter of 18 mm was chosen to approach sizes suitable for younger patients. Valves of different thickness were fabricated via dip-coating with siloxane-based polyurethane and tested in a pulse duplicator for their hydrodynamic function. The same valves were tested computationally using an Arbitrary Lagrangian-Eulerian (ALE) plus immersed solid approach, where the fluid structure interaction between the valves and fluid passing through them was studied and compared with experimental data.

Results Computational analysis showed valves of 110-200 μm thickness had effective orifice areas (EOAs) of 1.20-1.30 cm² with thinner valves exhibiting larger openings. In vitro tests demonstrated PHVs of similar thickness had EOAs of 1.05-1.35 cm² and regurgitant fractions (RFs) less than 7%. Valves with thinner leaflets exhibited optimal systolic performance while thicker valves showed lower RFs.

Conclusions Bioinspired PHVs demonstrated good hydrodynamic performance that exceeded ISO 5840-2 standards. Both methods of analysis showed similar correlations between leaflet thickness and valve systolic function. Further development of this PHV may lead to enhanced durability and therefore become a more reliable heart valve replacement than contemporary options.
Structured Abstract Word Count: 235 words

KEYWORDS: polymeric heart valve, heart valve engineering, bioinspired valve design, computational modeling, hydrodynamic testing
Introduction

Heart valve diseases and defects affect both children and adults, leading to approximately 300,000 valve replacements being performed annually worldwide.\textsuperscript{1} Many congenital heart diseases often necessitate intervention in the right ventricular outflow tract.\textsuperscript{2} The current modes of treatment include mechanical, bioprosthetic, and homograft valves. Despite restoring valve function, the replacement valves become dysfunctional over time and typically fail within 15-20 years of implantation.\textsuperscript{3-10} The main concern with mechanical valves is the high risk of thrombosis, which necessitates the lifelong use of anticoagulants. While bioprosthetic valves have demonstrated hemodynamic flows comparable with the native valves and fewer thrombogenic events than mechanical valves, they may suffer from immune responses that accelerate structural valve deterioration. The main drawback of homografts is donor supply and availability of smaller sizes. For all valve types, structural valve deterioration and somatic outgrowth lead to the need for repeated valve procedures in pediatric patients.\textsuperscript{11} Whilst they have been the subject of research since the 1950s, polymeric heart valves (PHVs) have recently demonstrated clinical potential. Early outcomes in adult aortic valve replacements exhibited satisfactory hemodynamic performance, although further clinical studies are needed to assess long-term biostability and biocompatibility.\textsuperscript{12} The aim of this paper was to develop a PHV with optimized geometry to improve its hydrodynamic function by increasing EOA and comparing the performance of valves with different leaflet thickness. This study is a continuation of our previously developed bioinspired valve design, where we used CT scanned images of native pulmonary valves to derive geometries based on the native valve.\textsuperscript{13} In the current study, the valves were downsized from
30 mm (adult) to 18 mm (pediatric) in diameter in order to test their performance in the pulmonary position and the suitability for pediatric patients. The geometry of leaflets free edge was improved to minimize commissural gaps. Additionally, a fluid structure interaction (FSI) simulation was performed using an Arbitrary Lagrangian-Eulerian (ALE) coupled to an immersed solid approach instead of conducting a structural analysis alone which was shown in our previous work. This allowed us to account for the impact of the fluid motion and calculate the EOA *in silico*. In the FSI simulation, the performance of bioinspired valves was assessed for systolic function and stress distribution. PHV prototypes were fabricated with the same design using polyurethane and tested in a pulse duplicator system to evaluate their hydrodynamic performance and compare their opening behavior with results predicted *in silico*.
Methods

Bioinspired Valve Design

A bioinspired valve geometry was developed as described previously based on a micro-computed tomography (micro-CT) scanned sheep valve.\textsuperscript{13} Sheep valves were selected for use in this study as their anatomy is relatively similar to the human valve. Additionally, they can be easily sourced from a local butcher. Briefly, to create a leaflet geometry emulating the natural curvature of native valves, one curve lying longitudinally through the middle of the leaflet surface was extracted. This curve was defined using a third-order polynomial function. Three copies of this curve were produced and lofted together (where surfaces are built between chosen edges) to produce a single leaflet geometry.

This single leaflet was rotated about the central axis of the valve to form a tri-leaflet valve. Due to the curved leaflet shape, the outcome was a valve with overlapping cusps as seen in Figure 1b. In the previous method, this was addressed by pulling the leaflets away from each other with respect to the central axis until they were no longer overlapping. This inevitably generated larger gaps at the free edge (Figure 1c). Whilst this geometry performed very well computationally during systole, additional \textit{in silico} and \textit{in vitro} studies assessing closing performance suggested gaps at the commissures could be minimized to reduce regurgitation and therefore optimize function.

In the new and improved design, a line was drawn from the commissure to the center of the valve between each leaflet (indicated in green in Figure 1d). The free edge was redefined based on the three lines. Each leaflet geometry was re-lofted with the newly constructed lines in addition to the three existing third-order polynomial-based curves. The resulting surface however had sharp changes in curvature on the leaflet surface (Figure 1e) and therefore
required filleting to achieve a smoother leaflet curvature (Figure 1f). The resulting valve (shown in Figure 1g) was then tested for its hydrodynamic performance via *in vitro* and *in silico* approaches.

**Figure 1.** Step-by-step top-view diagram showing the design process of the bioinspired valve design with minimized commissural gaps: (a) side view of valve; green arrow indicates top
view of the valve where the following steps are illustrated, (b) tri-leaflet valve developed from rotating the highlighted leaflet around a central axis with overlapping cusps, (c) original design created from pulling leaflets away from a central axis, (d) overlapping leaflet geometry with lines drawn from center of valve to each commissure used to redefine the free edges, (e) improved leaflet design defined by the new free edge and original equation-based curves derived from micro-CT scan, (f) filleted leaflet geometry with smoother belly region, and (g) full bioinspired tri-leaflet valve design with minimized commissural gaps.

Hydrodynamic Testing

PHV prototypes were produced by dip-coating. Briefly, molds based on the design described above were 3D printed (Flashforge Adventurer 4 3D Printer) using a polypropylene filament. The molds were then manually dip-coated in a siloxane-based polyurethane (PSU, Chronosil 85A, AdvanceSource Biomaterials) dissolved in tetrahydrofuran. PSU was selected due to its ease of manufacturing, favorable mechanical properties, and with potential improvements in biological properties compared with other polymers, such as polytetrafluoroethylene. The parameters of the dip-coating process, such as the temperature and the immersion time, were optimized to improve the homogeneity of the leaflet thickness and reduce bubble formation. The coated molds were then inverted (the outflow surface of the leaflets pointing downwards) to dry before the coating was removed and the top orifice opened with a surgical blade, obtaining 18 mm diameter valves (Figure 2a). Different leaflet thicknesses were achieved by changing the PSU concentration, ranging between 11-15 weight per volume percent (w/v%), which were found to be the manufacturing limits of the solution. The thickness of the valves was measured in different locations of the leaflet (Figure 2b). Thickness was recorded for all
leaflets in three different valves for each concentration tested, for a total of 9 data points per concentration.

Seven PHVs were hydrodynamically tested in the pulse duplicator system (HDTi-6000, BDC Labs) following ISO 5840 criteria and conditions of analysis. The formulae used to calculate the performance indicators such as effective orifice area (EOA) and regurgitant fraction (RF), were obtained from this standard. Other valve assessments including corrosion, accelerated wear testing, thrombogenic and hemolytic potential, and fatigue were beyond the scope of this study. The valves were fixed into a 3D printed rigid holder (polylactic acid) before being mounted into the equipment. All tests were conducted under normotensive conditions in the pulmonary valve position with a simulated cardiac output of 5 L min⁻¹, heart rate of 70 bpm, 35% systolic duration, and 15 mmHg mean arterial pressure for a total of 10 cycles per valve. The test fluid was isotonic saline (0.9 w/v% sodium chloride) with the system temperature was set to 37°C. The three hydrodynamic parameters used for evaluation of valves were EOA, RF, and mean positive pressure gradient (PPD) which were calculated via the equipment software.

The pressure difference (\(\Delta P\)) across the valve is defined as the difference between the ventricular and arterial pressure (i.e., inlet pressure – outlet pressure). The mean PPD is calculated from the \(\Delta P\) occurring over the time period when the inlet pressure is greater than the outlet pressure and can be given by:

\[
\text{Mean PPD (mmHg)} = \frac{\int_{t_s}^{t_e} (P_i(t) - P_o(t)) \, dt}{(t_e - t_s)}
\]

where \(P_i\) and \(P_o\) denotes the inlet and outlet pressures, respectively, and \(t_s\) and \(t_e\) are the time at the start and end of when the inlet pressure > outlet pressure, respectively.
The $Q_{RMS}$ is the root mean square (RMS) flow calculated over the same time period, when the inflow pressure is greater than the outlet pressure:

$$Q_{RMS} (\text{mL s}^{-1}) = \sqrt{\frac{\int_{t_s}^{t_e} [Q(t)]^2 \, dt}{t_e - t_s}}$$

The EOA, as defined by the ISO 5840 standard, is calculated by the equation:

$$EOA \ (\text{cm}^2) = \frac{Q_{RMS}}{51.6 \times \left(\frac{\text{Mean PPD}}{\rho}\right)}$$

where $\rho$ is the density of the testing fluid in g cm$^{-3}$.

Finally, RF is calculated as:

$$RF \ (%) = \frac{\text{Total Regurgitant Volume}}{\text{Forward Flow Volume}} \times 100$$

where total regurgitant volume is the sum of the closing volume and leakage volume, and the forward flow volume is the fluid volume moving through the valve between the start and end of forward flow.
Figure 2. (a) Schematic of the manufacturing process. The HV mold is 3D-printed using polypropylene and then dipped in a PSU solution. After the evaporation of the solvent, the PHV can be lifted off the mold. (b) Picture of a PHV with red circles indicating the location where the thickness was measured.

Numerical Simulation

The commercial software Ansys LS-DYNA 2023R1 (Ansys Inc, Canonsburg, Pa) was used in the simulation. The ALE approach\footnote{16} coupled with an immersed solid approach as embedded in the software was employed to study the FSI between the fluid flow passing through the heart valve and the deformation of the valve. The structural deformation of the valve was simulated under dynamic pressure loading from the fluid motion, initiated by the pressure gradient obtained from the hydrodynamic test results. In this model, the fluid was assumed to be incompressible with a density of 1000 kg m$^{-3}$ and to be inviscid. The conduit and leaflets were
assumed to have the same density as the fluid. The material of the leaflets and the conduit were
assumed to be hyperelastic and the model parameters were adapted from Said et al.,\textsuperscript{17} which
were applicable to the design of vascular grafts. The Mooney-Rivlin parameters $C_{10} = -0.854$
MPa, $C_{01} = 1.82$ MPa, and $C_{11} = 0.132$ MPa were used to define the material properties.
In the simulation, the leaflets were connected to the conduit via the interleaflet regions. The
conduit was assumed to have a thickness of 400 μm and four leaflet thicknesses of 110, 150,
180, and 200 μm were studied, which covers the range tested \textit{in vitro}. These thicknesses were
chosen to represent the thickness at the center of the free edge ($w_1$) of PHV prototypes
synthesized for the \textit{in vitro} aspect of this study. Shell elements were used to construct the
structural mesh and an element size of 0.75 mm was applied on all the surfaces, resulting in
70,000 elements in total (mostly hexahedral) as shown in Figure 3. The base case simulation
was performed using refined element sizes of 0.65 and 0.5 mm to ensure the accuracy of the
results. The difference between the resulting EOA values was less than 1% and therefore
0.75 mm was deemed sufficient and was chosen for all future simulations to reduce computing
time.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{meshed_geometry.png}
\caption{Meshed geometry of the valve (leaflets connected with the conduit) with an element
size of 0.75 mm: (a) top view and (b) side view at a cross-section.}
\end{figure}
The pressure profile of the first cycle during opening from the hydrodynamic testing results was adapted and used as the boundary condition in the simulation. This profile was employed as the inlet pressure and the outlet pressure was set to zero to maintain the same pressure difference as the experiment. The model was constrained using a fixed support applied to both ends of the conduit. The flow rate at the outlet was recorded at each timestep. The RMS flow over the time period was used to calculate the EOA with the same equation that is used by the pulse duplicator system for the experimental results. The transient explicit solver was used for the structural model and the ALE solver was used to solve the fluid flow equations. The timestep is determined automatically to maintain stability with the explicit solver, and the average time-step (Δt) used was 5.1 × 10⁻⁸ s.

Results

Hydrodynamic Testing

The thickness of the leaflet was not homogeneous and depended on the location. The center of the leaflets’ free edge (w₁) (equivalent to the position of the nodule of Arantius in a native valve) proved to be the thickest, while the cylindrical area below the leaflet (base of the PHV prototype) was the thinnest (w₄) (Figure 4a). The PSU concentration also influenced the PHV thickness. The value of w₁ increased from 81 μm for a 11 w/v% PSU solution to a maximum of about 250 μm for PSU concentrations of 13 w/v% and 14 w/v%. However, increasing the concentration further drastically decreased the w₁ thickness, reaching a minimum of ~150 μm (Figure 4b and Figure S1). The hydrodynamic performance of the PHVs was also correlated with the average thickness (w̅) of the leaflets. The EOA showed an inverse correlation with the
average thickness of the leaflets, with thinner valves exhibiting the largest EOAs (Figure 4c and 4e). For instance, PHVs with a $\bar{w}$ of around 85 µm reached EOAs of about 1.35 cm$^2$. This value dropped to 1.05 cm$^2$ for leaflet thicknesses of ~150 µm. These data are supported by Figure 4e, where thinner valves demonstrated larger orifices with a more circular shape, and leaflets opening right up against the conduit wall. However, thinner leaflets were also correlated with larger RF values (Figure 4d). RF values ranged from a minimum of about 4% for the thickest PHV, to a maximum of 6.5%.
Figure 4. (a) Thickness in different locations of the valve in PHVs produced using PSU 13 w/v%. Thickness decreases from the center of the leaflet free edge to the sides (towards the commissures) and downward (towards the belly). Box spans from the first to third quartile, whiskers indicate the minimum-maximum range, while the line indicates the median. (b) Values of $w_1$ for PHVs produced using different concentrations of PSU. Box indicates the first
to third quartile range, while the whiskers indicate the minimum-maximum range. (c-d) The
effect of thickness on the EOA and RF; the shaded area in both graphs highlights the trend. (e)
Assessment of opening (top) and closing (bottom) performance of valves under normotensive
conditions with increasing values of \( w_1 \) thickness from left to right (110, 150, 180, and 200 \( \mu m \)).

272

273 Numerical simulation

274 The PPD profile from the \textit{in vitro} testing results was used as the simulation pressure input as
shown in red in \textbf{Figure 5} and the resulting flow rate obtained as the simulation output was
compared against the experimental results, which is presented in the same figure. The
maximum flow rates from the experiment and simulation were well-matched despite the setup
differences, which are explained in detail in the discussion section.
Figure 5. Data comparison between experiment (solid lines) and simulation (dashed lines) with a leaflet thickness of 110 μm for both pressure difference profile (blue – left y-axis) and flow rate (red – right y-axis). Simulation (dashed) lines only cover systole. The blue and red dotted lines represent the zero for the left and right axes, respectively.

The displacement and stress distribution profiles for the valves with leaflet thicknesses of 110, 150, 180, and 200 μm are compared in Figure 6. In general, valves with thinner leaflets performed better in terms of the snap-through behavior. Snap-through was defined previously and is the term which describes a valve whose leaflets can bend against the natural curvature during systole to allow for maximum opening. As leaflet thickness increased, both the maximum displacement of the leaflets and the EOA decreased (Figure 7), demonstrating less
mobility. This pattern was consistent with experimental results. However, the stress distribution profiles between various thicknesses were not significantly different, as seen in Figure 6. The maximum stress varied from 1.3 to 1.7 MPa, which was observed around the commissures and at the edges where the leaflets and the conduits were connected.
Figure 6. Displacement (left) and stress distribution (right) for fully opened valves from side and top views with different leaflet thicknesses (a) 110 μm, (b) 150 μm, (c) 180 μm, and (d) 200 μm.
Figure 7. Comparison of the effect of leaflet thickness ($w_l$) on EOA between simulation and experimental results. Note that the data points for simulation and experiment are overlapping for 180 $\mu m$.

**Discussion**

The ultimate goal of this work was to design PHV replacements with enhanced performance and durability. The performance of our design was tested by both *in vitro* and *in silico* studies. The experimental and simulation results showed similar correlations between leaflet thickness and valve systolic function despite there being some differences in the two approaches. These results show promise for the combined *in vitro-in silico* approach, further highlighting computational modeling as a strong tool for assessing valve function and its role in this workflow for streamlining valve development and testing. See Figure 8 for a graphical abstract of the study.
To test the effect of leaflet thickness, uniform thicknesses were used in the simulation. However, PHV prototypes showed a gradient in thickness due to the drying process, as shown in Figure 4a. Drying the PHVs with the leaflets inverted caused the accumulation of material in the central part of the leaflet free edge, where $w_1$ is measured, while the base of the valve was thinner. The non-uniformity of the thickness across each leaflet attempted to resemble the heterogeneity of native leaflets thickness. Moreover, while in some instances the discrepancy in thickness was minimal, it proved challenging to reduce inter-sample variation in thickness using a manual dip-coating procedure. Thus, there is a need for further optimization of the fabrication process, with automation applied wherever possible for improved reproducibility.

The effect of thickness on the PHVs’ performance was investigated. Both EOA and RF increased with thinner leaflets. Thinner leaflets offer less resistance during systole compared with thicker leaflets, resulting in a larger EOA. This is because thinner leaflets are characterized by a lower flexural rigidity, which is directly proportional to the thickness. Flexural rigidity is a measurement of how much resistance a component would oppose to bending, with lower values indicating more flexible objects. As such, thin valves usually exhibit wider orifices. This explanation is also supported by the simulation results, where thicker valves exhibit smaller displacements and higher stresses during opening. Similarly, valves characterized by thin leaflets show higher RFs. This is most likely due to a combination of causes that arise from reduced thickness, such as the decrease in flexural rigidity and the increased displacement during systole. In fact, with larger displacements the leaflets take longer to return to a closed position during diastole. This leaves the valve open for longer during backflow and slightly increases regurgitation. The hydrodynamic results obtained for all thicknesses are compliant with the ISO 5840-2, with all RF values being below 10% and all EOA values being above $0.85 \text{ cm}^2$ (requirements for a 19 mm valve). In the absence of an 18 mm standard, the 19 mm
value was used in order to avoid overestimation of the hydrodynamic performance. These outcomes are also comparable with clinically used bioprosthetic valves tested in the pulmonary position of a pulse duplicator system. The EOA of 21 mm diameter bioprosthetic valves and polyurethane prototypes from this study were both approximately 60% greater than that outlined by the standard, 1.05 cm² (21 mm diameter) and 0.85 cm² (19 mm diameter), respectively. As this comparison is an underestimation of the hydrodynamic performance, it is further hypothesized that polyurethane valves may perform on par or better than current treatments.

Limitations and future studies

It must be noted that the results shown in Figure 4c and 4d depict the correlation of the average thickness to EOA and RF, respectively. Nevertheless, w₁ had a greater impact on hydrodynamic performance compared with other thickness values (Figure S2). This is possibly due to the discrepancy between w₁ and the rest of the values (e.g., from the 275 µm of w₁ to about 100 µm for w₂ in 13 w/w% valves). The presence of outliers can then be explained by the heterogeneous distribution of thickness along different areas of the leaflet. Although these values (i.e., w₂, w₃, etc.) do not show a direct correlation with either EOA or RF, they may still hold significance in the overall performance of the PHV. The inhomogeneity of the thickness in fabricated samples is possibly the reason why the values of EOA obtained differ slightly from those obtained via simulation. For the in silico studies, the thickness is set to a constant value (i.e., w₁) throughout the leaflets, which is a significant assumption that may lead to differences with the PHV prototypes. Furthermore, PHVs were glued to rigid conduits that drastically narrowed the flow area from the 50 mm valve exchange chamber belonging to the pulse duplicator upstream, to 18 mm (conduit diameter). In simulation, this sudden change in
diameter is not present as the upstream and downstream fluid domain were set to match the
valve diameter, and the valve was placed in a hyperelastic conduit rather than a rigid holder.
Therefore, further studies are required to understand the impact that the leaflet thickness in
different areas has on hydrodynamic performance.
Further, while a bioinspired design was explored, the PHVs produced did not replicate the
mechanical anisotropic behavior of native valves. This may affect hydrodynamic performance
and will be investigated in studies involving leaflet reinforcements. Future studies will also
include optimizing the thickness distribution to better mimic that of native valves,
incorporating valved conduits with sinuses, comparing hydrodynamic performance with PHVs
constructed from different polymers, and *in vivo* analysis in sheep including the evaluation of
thrombogenicity and calcification. Further assessment of material fracture, fatigue, and
durability will be conducted both *in silico* and *in vitro* to evaluate the clinical potential of the
valve.
In the simulation, an ALE plus immersed solid approach was applied to study the interaction
between the valve and the fluid passing through the system. This approach utilized an inviscid
fluid and the fluid boundary layer effects, such as drag and recirculation, were not considered,
which is a limitation of this work. Further investigation will be needed to test these effects and
whether they have significant impact on this dynamic system by involving a viscous fluid. Only
the systolic behavior of the valve was simulated in this study due to limitations in the current
workflow. Due to the computationally expensive nature of the explicit time integration scheme,
only the first cycle instead of the total 10 cycles from the hydrodynamic testing results was
used. In future studies, a full FSI simulation, which includes the fluid boundary layer effect,
should be investigated and compared with the ALE approach.
Conclusions

This work presents a coupled workflow for evaluating the performance of a bioinspired valve design with improved free edge geometry. Leaflets demonstrated good mobility, however, limitations in the manual fabrication process prevented fine control over material thickness. Resulting PHV prototypes showed EOAs and RFs ranging from 1.05-1.35 cm$^2$ and 4-6.5%, respectively, and were hydrodynamically acceptable based on ISO 5840-2. In general, valves with thinner leaflets resulted in larger orifice areas but also lead to slightly more regurgitation. Computationally, the same valve counterparts exhibited EOAs of 1.2-1.3 cm$^2$, which are within a comparable range to the in vitro prototypes. *In silico* studies also illustrated snap-through of valves with thinner leaflets and showed the stress distribution profiles were not significantly impacted by leaflet thickness. Further investigation is required to study the effect of thickness on durability, suture retention, and tests with a flexible conduit. Future work will involve optimization of the valve design and fabrication process, and a full FSI analysis with simulation of the diastolic performance of valves.
References


Acknowledgements

The authors acknowledge the use of the National Computational Infrastructure (NCI) which is supported by the Australian Government, and accessed through the Sydney Informatics Hub HPC Allocation Scheme, which is supported by the Deputy Vice-Chancellor (Research), University of Sydney.
Legends

**Figure 1.** Step-by-step top-view diagram showing the design process of the bioinspired valve design with minimized commissural gaps: (a) side view of valve; green arrow indicates top view of the valve where the following steps are illustrated, (b) tri-leaflet valve developed from rotating the highlighted leaflet around a central axis with overlapping cusps, (c) original design created from pulling leaflets away from a central axis, (d) overlapping leaflet geometry with lines drawn from center of valve to each commissure used to redefine the free edges, (e) improved leaflet design defined by the new free edge and original equation-based curves derived from micro-CT scan, (f) filleted leaflet geometry with smoother belly region, and (g) full bioinspired tri-leaflet valve design with minimized commissural gaps.

**Figure 2.** (a) Schematic of the manufacturing process. The HV mold is 3D-printed using polypropylene and then dipped in a PSU solution. After the evaporation of the solvent, the PHV can be lifted off the mold. (b) Picture of a PHV with red circles indicating the location where the thickness was measured.

**Figure 3.** Meshed geometry of the valve (leaflets connected with the conduit) with an element size of 0.75 mm: (a) top view and (b) side view at a cross-section.

**Figure 4.** (a) Thickness in different locations of the valve in PHVs produced using PSU 13 w/v%. Thickness decreases from the center of the leaflet free edge to the sides (towards the commissures) and downward (towards the belly). Box spans from the first to third quartile, whiskers indicate the minimum-maximum range, while the line indicates the median. (b) Values of $w_1$ for PHVs produced using different concentrations of PSU. Box indicates the first to third quartile range, while the whiskers indicate the minimum-maximum range. (c-d) The effect of thickness on the EOA and RF; the shaded area in both graphs highlights the trend. (e)
Assessment of opening (top) and closing (bottom) performance of valves under normotensive conditions with increasing values of \( w_1 \) thickness from left to right (110, 150, 180, and 200 \( \mu \)m).

**Figure 5.** Data comparison between experiment (solid lines) and simulation (dashed lines) with a leaflet thickness of 110 \( \mu \)m for both pressure difference profile (blue – left y-axis) and flow rate (red – right y-axis). Simulation (dashed) lines only cover systole. The blue and red dotted lines represent the zero for the left and right axes, respectively.

**Figure 6.** Displacement (left) and stress distribution (right) for fully opened valves from side and top views with different leaflet thicknesses (a) 110 \( \mu \)m, (b) 150 \( \mu \)m, (c) 180 \( \mu \)m, and (d) 200 \( \mu \)m.

**Figure 7.** Comparison of the effect of leaflet thickness (\( w_1 \)) on EOA between simulation and experimental results. Note that the data points for simulation and experiment are overlapping for 180 \( \mu \)m.

**Figure 8.** Graphical abstract.

**Figure S1.** Dispersion of thickness at different points of the leaflet for all concentration of PSU tested. Note how the thickness follows a somewhat similar trend for all concentrations, being the highest at the center of the leaflet free edge (\( w_1 \)) and being the thinnest at the conduit below the valve (\( w_4 \)). The thickness at \( w_5 \) for the 14% w/v PSU valves does not follow the trend. Hence it will be further investigated in future experiments.

N.B. The process of dip coating produces 100% PSU layers after solvent evaporation (hence material properties do not change). The thickness of this layer depends mainly on viscosity (\( \mu \)) and density (\( \rho \)) of the dipping solution, which depend on the concentration of PSU.

**Figure S2.** Effect of thickness of different locations on the leaflet (a) \( w_1 \), b) \( w_2 \), c) \( w_3 \), d) \( w_4 \), e) \( w_5 \), and f) \( w_6 \) on the EOA. Note only \( w_1 \) has a correlation between thickness and EOA.
(with EOA decreasing with increasing thickness). For all other values of thickness, there is no clear trend. This highlights the sensitivity of the hydrodynamic performance on w1.

**Methods**

- Computer-aided design: development of a bioinspired valve design digitally
- Polymeric heart valve: in vitro testing. Tested for EOA and RF.

**Results**

- A bioinspired valve design with minimized commissural gaps was created digitally.
- EOA = 1.05-1.35 cm².
- RF < 7%.
- Opening performance of polymeric valves was comparable to simulated valves.
- Increase in leaflet thickness lead to decrease in EOA and RF, but all valves tested were still hydrodynamically within acceptable ranges.

**Implications**

Computational and experimental outcomes in this study demonstrate good hydrodynamic function of a novel bioinspired valve design derived from micro-CT scans of a real heart valve. Valve thickness was inversely correlated to both EOA and RF. All valves tested were able to meet the ISO 5840 standard. With this knowledge and further optimization of design and fabrication processes, a polymeric valve with better functionality and durability than current treatments may be producible.
Next-generation polymeric heart valve replacement

Presented by
Aeryne Lee, Xinying Liu, Jabopo Giaretta, Tina Hoang, Matthew Crago, Syamak Farajikah, Luke Mosse, David Fletcher, Fariba Dehghani, David Winlaw, and Sina Nasify

The University of Sydney
School of Chemical and Biomolecular Engineering
Supplemental material document for:

Bioinspired Polymeric Heart Valves: A Combined In Vitro and In Silico Approach

Aeryne Lee, PhD, a,b,§ Xinying Liu, PhD, a,§ Jacopo Emilio Giaretta, PhD, a,§ Thanh Phuong Hoang, a Matthew Crago, BE, a Syamak Farajikah, PhD, a,c Luke Mosse, PhD, d David Frederick Fletcher, PhD, a Fariba Dehghani, PhD, a,c David Scott Winlaw, MD, b,e Sina Naficy, PhD, a,b,c,*

a School of Chemical and Biomolecular Engineering, The University of Sydney, Darlington, NSW 2008, Australia
b School of Medicine, The University of Sydney, Camperdown, NSW 2050, Australia
c Sydney Nano Institute, The University of Sydney, Camperdown, NSW 2050, Australia
d Leap Australia, Suite 6, 750 Blackburn Road, Clayton North, Victoria 3168, Australia
e Department of Cardiothoracic Surgery, Heart Institute, Cincinnati Children’s Hospital, Cincinnati, OH 45229, United States

* Corresponding Authors: Dr. Sina Naficy (sina.naficy@sydney.edu.au), School of Chemical and Biomolecular Engineering, The University of Sydney, Darlington, NSW 2008, Australia, +61 2 9351 4147

§ These authors have contributed equally.

Disclosure Statement: The authors report no conflicts of interest.

Funding Statement: This work was funded by the Medical Research Future Fund (Grant No. MRFF-ARGCHD000015) and the Australian Research Council (Grant No. ARC DP200102164; Funder ID: 10.13039/50110000923).
Glossary Of Abbreviations

EOA  
Effective orifice area

PSU  
Polysiloxane urethane

Figure S1. Dispersion of thickness at different points of the leaflet for all concentration of PSU tested.

Note how the thickness follows a somewhat similar trend for all concentrations, being the highest at the center of the leaflet free edge (w₁) and being the thinnest at the conduit below the valve (w₄). The thickness at w₃ for the 14% w/v PSU valves does not follow the trend. Hence it will be further investigated in future experiments.

N.B. The process of dip coating produces 100% PSU layers after solvent evaporation (hence material properties do not change). The thickness of this layer depends mainly on viscosity (μ) and density (ρ) of the dipping solution, which depend on the concentration of PSU.
Figure S21. Effect of thickness of different locations on the leaflet (a) $w_1$, b) $w_2$, c) $w_3$, d) $w_4$, e) $w_5$, and f) $w_6$ on the EOA. Note only $w_1$ has a correlation between thickness and EOA (with EOA decreasing with increasing thickness). For all other values of thickness, there is no clear trend. This highlights the sensitivity of the hydrodynamic performance on $w_1$. 