Design, Fabrication, and Characterization of Microscale Bicuspid Valves 3D Printed in Biocompatible Hydrogels

Samantha J. Paulsen, Bagrat Grigoryan, Jordan S. Miller
Department of Bioengineering, George R. Brown School of Engineering, Rice University, Houston, TX.

Statement of Purpose: Bicuspid valves are essential structures within veins and lymphatic vessels, ensuring unidirectional flow of fluids back towards the heart. The failure of venous valves can result in chronic venous insufficiency **(CVI)**, a disease which affects 2.5 million people within the United States, with symptoms ranging from varicose vein formation and edema, to ulceration, and chronic wound formation. Investigation of valve structure-function relationships is key for improving clinical treatments towards CVI; however, analyzing this structure function relationship of venous and lymphatic valves *in vivo* is hampered by the deep position of veins and lymphatics along with the dynamic nature of valves actuating above 1 Hz[1]. **Here, we sought to develop comprehensive *in silico* and *in vitro* models of microscale bicuspid valves to probe the relationship between valve architecture and fluid dynamics under pulsatile flow.** We implemented computational fluid-structure interactions **(FSI)** models along with a 3D printing approach based on stereolithography to investigate microscale bicuspid valves.

Methods: To generate computational models of fluid flow through PEG-based bicuspid valves, we prepared FSI models using COMSOL Multiphysics 5.2 to simulate flow patterns and linearly elastic leaflet deflection within 2D bicuspid valves under sinusoidal pressure differentials. We fabricated functional bicuspid valves from biocompatible hydrogels using a projection stereolithography **(pSLA)** fabrication technique developed in our lab. Gels consisted of 20% w/w 6 kDa poly(ethylene glycol) diacrylate **(PEGDA)**, fabricated with a cubic voxel resolution of 50 µm. We compared computed flow profiles to those seen in our experimental models by flowing fluorescently labeled beads through the valves and tracking bead flow profiles using Particle Image Velocimetry software PIVlab[2].

Results: We first demonstrated the capability to generate a 2D FSI model of fluid flow through our valve model. These models demonstrate the feasibility of generating FSI models for valve flow in COMSOL Multiphysics and the potential to iteratively alter valve geometry and investigate changes in leaflet movement and valve flow profiles (**Fig 1a-c**).We further demonstrated proof-of-concept for the fabrication of microscale bicuspid valves using the pSLA system developed in our lab (**Fig 1d-f**), and found that the valves function as fluidic diodes which permit forward flow while resisting retrograde flow. Finally, iterative adjustments to valve geometries in FSI models reveals the subtle influence of valve sinus geometry on the formation of vortices and stagnation zones within the sinus region.

Conclusions: This work demonstrates the feasibility of constructing computational FSI models to investigate structure function relationships in microscale bicuspid valves along with the fabrication valve structures from biocompatible hydrogels using our new pSLA system that function as dynamic fluidic diodes. Flow patterns through computational models corresponded with preliminary experimental models, though more advanced particle tracking techniques are needed for future analysis. This work represents a preliminary step towards the investigation of structure-function relationships within venous valves *in vitro*, as a means to guide treatment of CVI in patients along with the development of microscale valves for the incorporation into engineered tissues.

References: 1) Eberhardt RT. Circulation. 2005:111 2398-409.

2) Theilicke W. Journal of Open Source Research Software. 2014:2 e30.

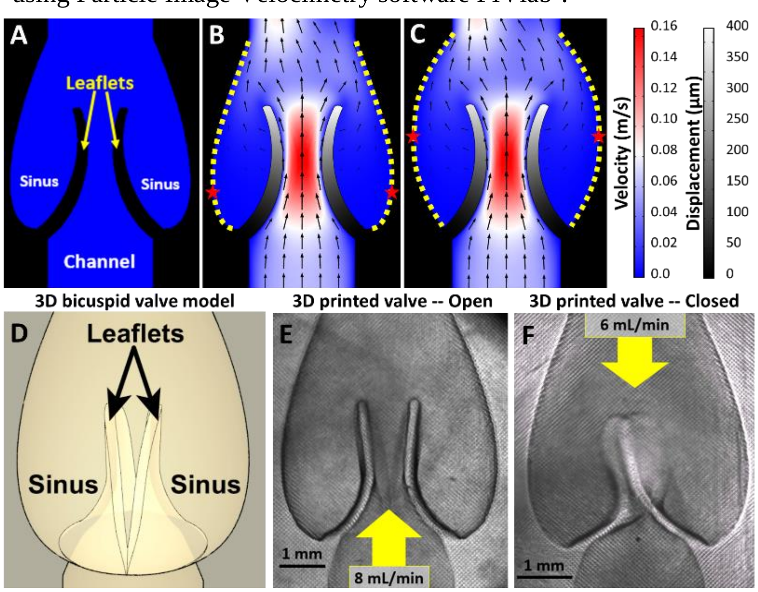

Figure 1: Computational models of fluid flow through microscale bicuspid valves and fabrication of valves using pSLA. (**A**) Initial geometry used for FSI valve model. (**B**) Valve during the opening at 0.4 s (6 Pa forward pressure), plotting fluid flow velocity and valve displacement. (**C**) Model under same conditions, but with an altered sinus geometry. (**D**) 3D model of bicuspid valve containing leaflets, sinus, and cylindrical channel based on FSI valve model. (**E**) Bicuspid valve fabricated using pSLA following equilibrium swelling. Leaflets remain open under forward flow. (**F**) Under reverse flow, valve leaflets close, preventing further flow downstream of valve. These results demonstrate the feasibility of using FSI models to investigate the structure-function relationship of bicuspid valves and the feasibility to fabricate microscale bicuspid valves using pSLA.