Towards the Creation of a Bioprinted Aortic Valve Prosthesis

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Abstract

Aortic valve prosthesis recipients face a choice between mechanical and tissue options, both with significant drawbacks. Thus, developing a durable and biocompatible aortic valve prosthesis is essential, and DLP bioprinting is well-suited for this task. A commercial-grade DLP printer was modified for bioprinting a prosthesis with three leaflets, mimicking the natural human aortic valve. Key evaluations focused on durability, hemodynamics, and mechanical characteristics. A mock circulatory loop (MCL) was created to assess durability over 12 hours. An in-silico patient model, reflecting cardiovascular health indicators, showed the prosthesis had minimal stenosis and slightly increased backflow, leading to stable systolic pressure and acceptable diastolic fluctuations. Cardiac output remained around 4.3 l/min, with favorable hemodynamics and a low hemolysis rate. This study highlights the potential of DLP bioprinted aortic valve prostheses as viable alternatives to existing options, although further improvements in testing protocols and mechanical properties are necessary.

1. Introduction

Aortic valve disease (AVD) is one of the leading causes of heart disease globally, claiming hundreds of thousands of lives annually [1]. Most AVD can be characterized as aortic stenosis or regurgitation. Aortic stenosis is defined as a reduced valvular orifice, whereas aortic regurgitation occurs when the aortic valve does not close properly, allowing retrograde blood flow from the aorta into the left ventricle. In the long-term, regurgitation and stenosis lead to similar symptoms [2].

Aortic valve replacement (AVR) is known to be the most effective treatment for AVD [3]. Currently, two types of valve prostheses exist: mechanical and tissue valves. Mechanical valves offer excellent durability but poor biocompatibility, whereas tissue valves display superior biocompatibility but inferior durability. Due to their drawbacks, neither mechanical nor tissue valves are an ideal treatment.

Aortic valve replacement still is not ideal for pediatric patients, especially for small children. Mechanical prostheses are available at sizes down to 16 mm, and tissue prostheses are unavailable at sizes smaller than 19 mm [4]. However, the pediatric aortic diameter can be as small as 7.6 mm [5].

There have been some attempts to develop artificial valves through the process of 3D printing and bioprinting [6, 7], which offers many advantages such as biocompatibility, scalability, reproducibility [8], and rapid prototyping. The vast majority of bioprinted aortic valve prostheses are created using extrusion-based bioprinting. However, extrusion-based bioprinting has a significantly lower resolution and accuracy compared to its light-based counterpart [9], which leads to poor mechanical performance [10].

To date, there have been only three studies that investigate the use of light-based bioprinting; two do not test for hemodynamics or durability [11,12], which are critical for valve evaluation. Our previous work [7], which uses stereolithographic 3D printing, does test for hemodynamics, albeit using a system limited in functionality and accuracy.

The purpose of this study is to develop an aortic valve prosthesis that is biocompatible, customizable, and durable using digital light processing (DLP) bioprinting.

2. Methodology

2.1 Bioprinter Retrofitting

Due to lack of accessibility, a DLP bioprinter was developed by retrofitting a commercially-available DLP 3D printer (Elegoo Mars 4 Max), fitted with an aluminium build plate. In normal operation, a photopolymer resin is stored in the "vat" of the printer, which is positioned over the LCD screen. The LCD screen and the resin in the vat are separated by a layer of fluorinated ethylene propylene (FEP) film. The LCD screen cures patterns, or "slices", of photopolymer resin onto the print bed. As more slices are printed, a 3D object is formed on the print bed.

To convert the 3D printer to a bioprinter, two major

steps had to be taken: modification of the resin vat and the build platform. The resin vat was modified to allow for a smaller volume of bioink to be used in the bioprinter. This was done by designing a custom bioink well that contained two chambers. The well was adhered to the FEP film using a silicone sealant. After the build vat was retrofitted, the apparatus was calibrated to ensure all prints would occur within the bioink well.

The build plate had to be modified with two criteria in mind; firstly, it had to be able to enter the bioink wells, and secondly, it had to be biocompatible. Eventually, it was decided that two titanium blocks measuring 10 mm on each side would be adhered to the print bed in corresponding location with the wells.

2.2 Valve Design and Manufacturing Process

The valve prosthesis was designed in the OnShape CAD software. Each of these designs were sliced with the Voxeldance Tango software and transferred to the bioprinter with a standard USB drive.

The bioink used was 3DResyns BioFlex A10 Low-Absorption resin. After printing, the valve prosthesis was removed from the print bed with a standard 3D printer scraper, and was washed in 70% isopropyl alcohol for 10 minutes. It was then cured under a commonly available UV sterilizing light for 30 minutes. The valve was stored in 0.9% NaCl solution until testing.

2.3 Testing Protocols

In order to comprehensively test the valves, a multi-stage testing approach was adopted (put figure for this). This testing process began with a phantom, in this case a mock circulatory loop (MCL). The MCL consists of an elastic chamber compressed by two linear actuators; it is connected to a transparent vinyl tube, analogous to the aorta. The tube is connected to a veinous reservoir, which drains back into the chamber. The valve is located at the base of the vinyl tube.

From the mock circulatory loop, physical data, such as the backflow allowed by the valve and particle image velocimetry (PIV) is collected, as well as endoscopic videos of the valve for visual analysis. Through several stages of analysis, a simple digital twin of the patient is created. This is done by using several models, such as the CircAdapt model **[13]** and the power-law hemolysis model [14]**.** Both simulations gave clinically relevant insights into the physiological effectiveness and biocompatibility of the valve, respectively. The valve was tested every hour for twelve consecutive hours to allow for durability assessment.

3. Results

3.1 Final Valve Design and Principle of Operation

Over the study, over 80 different iterations of the prosthesis were developed. Out of these, only one prosthesis was successful. This final, biomimetic prosthesis was designed to resemble the natural human aortic valve as closely as possible in terms of morphology and function (Figure 1). It consists of three leaflets, each of which has a physiological thickness of 0.75 – 1.00 mm, depending on the required leaflet thickness. Each leaflet has a concave structure, allowing for physiological valve motion.

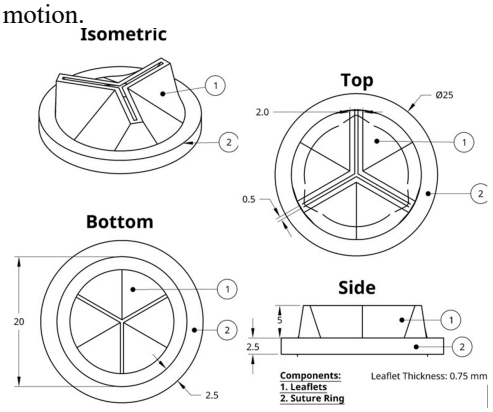


Figure 1. Blueprint of final bioprinted valve prosthesis design.

3.2 The Bioprinted Prosthesis Displays High Biocompatibility

As previously mentioned, the mechanical biocompatibility of the valve was analyzed by collecting PIV data from the mock circulatory loop, extracting it, and analyzing it using the power-law hemolysis model.

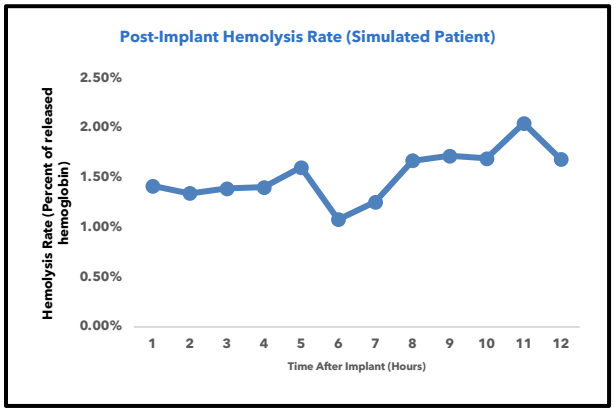


Figure 2. Simulated patient hemolysis over 12-hour testing period.

The post-implant hemolysis rate, displayed in Figure 2, remains generally stable throughout all 12 hours. The average released hemoglobin over the 12 hour testing period is 1.57%, which is significantly lower than that of mechanical and tissue prostheses that Giersiepen et al. tested, which ranged from 4 to 27% hemoglobin release. We can conclude that the bioprinted aortic valve prosthesis displays a higher mechanical biocompatibility than many industry-standard valve options and may not require anticoagulation.

3.3 The Bioprinted Prosthesis Displays Favorable Mechanical Characteristics

For better insight into the functioning of the valve in a patient, the insufficiency and stenosis rates were inputted into the CircAdapt model, which was used to obtain the vitals (blood pressure, cardiac output, etc.) of a simulated patient.

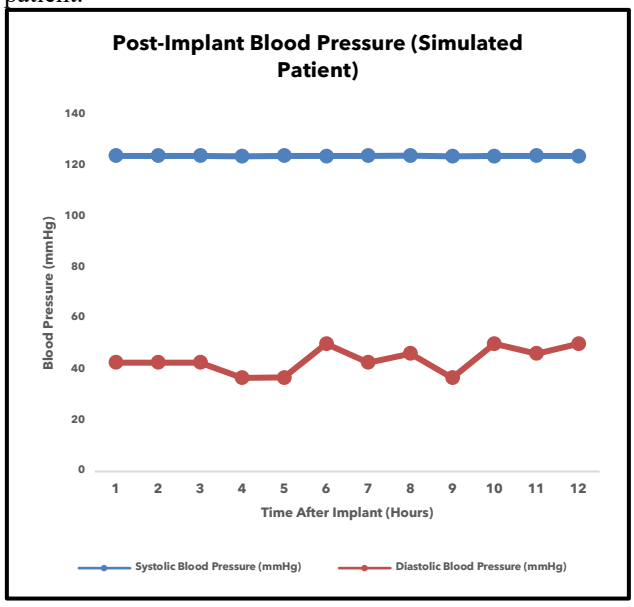
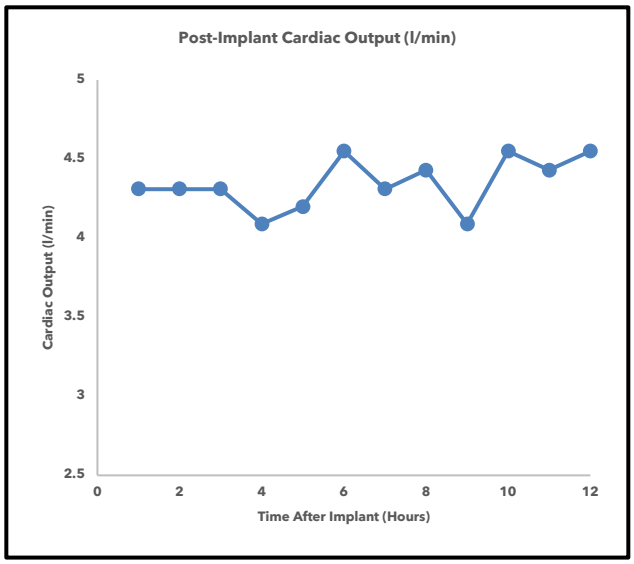


Figure 3. Simulated patient blood pressure over 12-hour testing period.

The simulated systolic blood pressure, shown in figure 3, tended to stay stable at physiological levels throughout the 12-hour testing period. While slightly below physiological levels and more variable than the systolic pressure, the diastolic blood pressure, shown in figure 3, still stays within an acceptable range. This increased variability may be explained by a slight amount of leakage in the prosthesis.

Figure 4. Simulated patient cardiac output over 12-hour testing period.



The cardiac output, shown in Figure 4, displays strongly favorable results; throughout the testing period, it remains at near-physiological levels (12-hour average of 4.34 l/min), and has improving performance during the final 4 hours of the testing period.

3.4 The Bioprinted Prosthesis is Ideal for Clinical Settings

The bioprinted prosthesis displays many characteristics that make it ideal for clinical use. To evaluate its customizability, the model was bioprinted in several sizes from 7.5 cm to 30 cm in diameter. The prostheses were scaled equally in all dimensions. All prostheses printed successfully, suggesting that the bioprinted valve can be scaled to the aortic diameter of any patient, including small children whose aortic diameter is too small for mechanical or tissue valves.

Current valve manufacturing techniques have long turnaround times ranging from weeks to days; however, the bioprinting process allows for much faster and dynamic valve production. The standard (25 mm) valve used in testing took 124 minutes to print, and multiple valves can be printed at the same time, improving scalability. Bioprinting is also significantly more reproducible than other manufacturing techniques; while the creation of tissue, and mechanical valves, involves subjective human technique, additive manufacturing almost completely removes the risk for human error in valve creation.

4. Discussion

This was the first study in which an aortic valve prosthesis was developed through digital light processing (DLP) bioprinting, hemodynamically characterized, and evaluated for durability and biocompatibility. Results suggest that DLP bioprinting is an effective technique in aortic valve prosthetic manufacturing, able to produce valves that are biocompatible, hemodynamically favorable, and durable.

The bioprinted prosthesis is well-suited for clinical use. A common issue facing contemporary mechanical and tissue prostheses is their inability to be produced in sizes small enough for very young pediatric patients. However, our prosthesis can be manufactured to a wide range of sizes, including those of young children and infants. DLP bioprinting also allows for rapid manufacturing of valve prostheses.

DLP bioprinting can potentially transform the artificial heart valve market, addressing many of the concerns that riddle conventional manufacturing techniques for mechanical and tissue prostheses. However, as promising as current results may be, more work is still required. In future studies, we would like to further improve the customizability of the valve by bioprinting reconstructed 3D models of the patient's aortic valve, allowing for significantly more personalized care. In addition, more accurate testing methods may be needed for future studies, such as *in vivo* animal models, which would allow for physiological responses to the bioprinted prosthesis.

Acknowledgements

I would like to sincerely thank Mrs. Rebecca Kehler and Mrs. Hali Flahavan for their assistance in making this work possible.

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