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Designing an In Vitro Mitral Valve Mounting and Testing System for Micro CT Imaging

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Designing an In Vitro Mitral Valve Mounting and Testing System for Micro CT Imaging

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Honors Thesis

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Abstract

Five million people in the US are diagnosed with valvular disease, of which mitral valve disease is one of the most common. Computational models are informed by high resolution images and have the potential to aid in diagnosing and establishing surgical plans to treat mitral valve diseases. Existing methods using 7T MRI imaging have limitations such as small bore diameter, long imaging times and difficulty in maintaining trans-mitral fluid pressure throughout the scan. Imaging with Micro CT allows for efficient scan times and eliminates bore size constraints which allows for imaging more sizes and types of MVs. There is a need for imaging MV in the systole conformation under dry conditions with Micro CT. Mitral valves were explanted from porcine hearts and 6 anchor measurements were taken. Based on these anchor measurements, mounting hardware was customized and 3D printed. The mitral valve was then sutured onto the customized hardware and mounted in an acrylic case with chambers representative of the left atrium and ventricle. The alternative approach proposed in this study is to close the MV leaflets by applying air pressure from the ventricular side and applying a surgical adhesive to the leaflets. The strengths of multiple surgical grade cyanoacrylates were tested on MV leaflets using a load scale. 3M Vetbond (98% N-butyl cyanoacrylate) was found to be the most effective adhesive with regards to strength and uniformity. The MVs were imaged with a Nikon X TH 225 ST μCT. This alternative approach was found to be effective when imaging the MV in the systole conformation under dry conditions when compared to the previous method for using fluid pressure for MRI imaging. By utilizing high quality imaging data, computational models will be more accurate at capturing MV behavior. These

validated models could then be used to advance our understanding of MV behavior as well as paving the way for new treatments and devices.

Introduction

The mitral valve (MV) is a complex structure in the heart that consists of a mitral annulus, two leaflets, chordae tendineae (CT), and papillary muscles (PM) (1). The mitral valve is responsible for allowing oxygenated blood to flow from the left atrium to the left ventricle during diastole. During systole, the left ventricle contracts and the leaflets of the mitral valve close, forming a tight seal that prevents the backflow of blood to the atrium (1). There are two main types of mitral valve disease. Mitral valve prolapse (MVP) involves regurgitation of the blood into the right atrium due to improper closing of the leaflets (2). Mitral valve stenosis involves the narrowing of the valve and prevents blood from reaching the left ventricle. Currently, treatment options for mitral valve diseases that require surgical intervention involve repairing or replacing the valve (3). Approximately, 5 million people in the United States are diagnosed with valvular disease of which diseases of the mitral valve are the second most common (3).

Computational models of the mitral valve have the potential to aid in diagnosing and establishing surgical plans when treating MV diseases (4). Moreover, computational models are informed with high resolution images. This has been previously demonstrated by the Cardiovascular Biomechanics Laboratory (CBL) in imaging porcine mitral valves, utilizing 7T MRI in the diastole and systole conformation (Figure 1) using customized mounting hardware and fluid pressure to close leaflets (5).

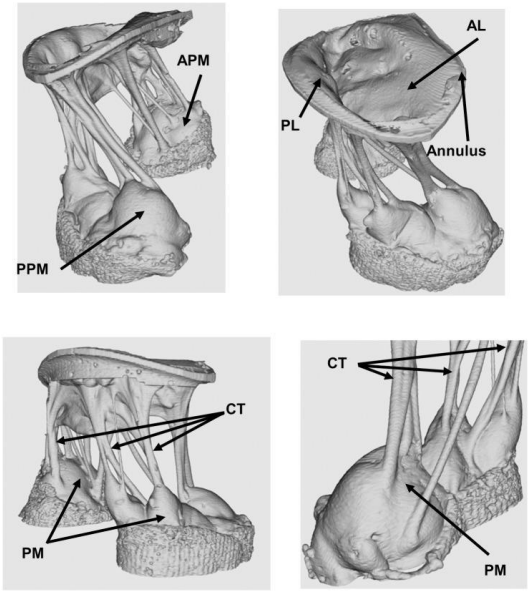


Figure 1. Porcine mitral valve images obtained using 7T MRI imaging (5).

However, imaging with 7T MRI comes with limitations. The small bore diameter of the MRI machine dictates the size of the mounting apparatus for the MVs to not exceed 72 mm (5). This limits the size and types of mitral valves that can be mounted and imaged. Moreover, the small size of the apparatus makes assembly and mounting difficult. Imaging mitral valves with 7T MRI also has long scan times. This makes it challenging to maintain transmitral fluid valve pressure in the systolic conformation throughout a 30 hour scan (5).

Imaging the mitral valves with Micro CT will provide the flexibility to expand the size of the mounting apparatus thus permitting more types and sizes of mitral valves to be imaged. A larger apparatus will allow the process of mounting the valves to become a more efficient process while having a substantially shorter scan time.

An obstacle that comes with the use of the Micro CT stems from maintaining transmitral pressure under dry conditions. Previous studies have used air pressure to close the leaflets but with some technical challenges (4). In order to close the leaflets, various adhesives were tested to close the valve and to mimic the natural systole conformation of the mitral valve.

The following is a description of the continuation of previous work to image the mitral valve in transitioning from 7T MRI to Micro CT in the systolic conformation of the mitral valve under dry conditions using air pressure and surgical adhesive.

Materials and Methods

Details of the Case

The imaging apparatus (Figure 2) consists of 3D printed clamps that close around the mitral annulus (6). The papillary muscles are mounted with custom holders. A ⅛ inch thick cylindrical acrylic case holds the mounting hardware. An inner acrylic flange separates the case to represent the atrial and ventricular chambers of the heart with lengths of 1.3 inches and 2.0 inches respectively. The ventricular chamber is sealed with a 3D printed outer flange. There is a ventricular supply line within the outer flange which allows for the connection between a ball valve and the air compressor.

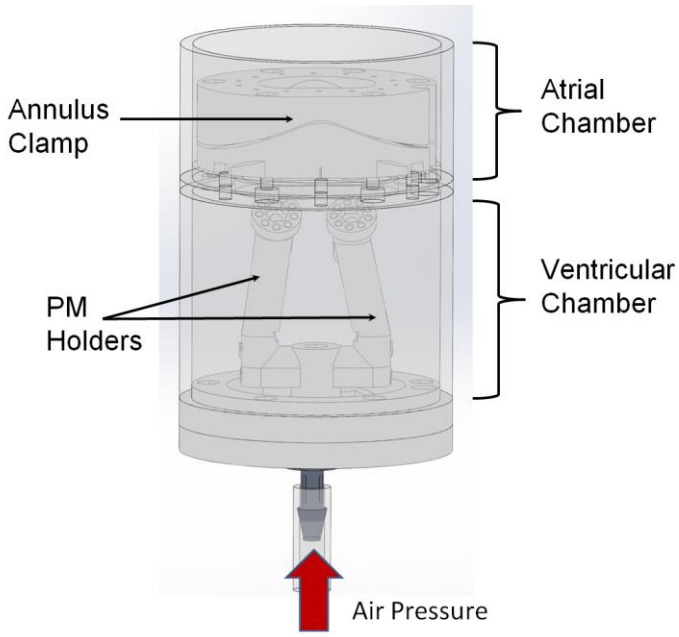


Figure 2. Mitral valve imaging apparatus (6).

From the previous study, the mitral valve case was expanded from 2.75 to 3.5 inches outer diameter to improve the efficiency in mounting the mitral valves (5). The brass screws and hex nuts were replaced by nylon screws and hex nuts to minimize metal interference for Micro CT imaging. Additionally a stepped cap was removed from the atrial chamber and is left open to the atmosphere.

Dissecting the Mitral Valve

The porcine hearts were provided by a commercial abattoir. According to the methodology of the previous work, the mitral valves are explanted from the porcine hearts (5). The heart is positioned anteriorly in the frontal plane. A straight scissor is used to first remove the auricles. The right atrium and ventricle are then carefully cut along the pulmonary trunk. The inferior most portion of the left ventricle is removed until the papillary muscles become visible. The left ventricle was cut upwards before the start of the mitral

annulus. The ventricle walls are then cut carefully from behind the CTs. The papillary muscles are then trimmed leaving approximately 10 mm of muscle. The valves are then also trimmed around the annulus. After explantation, the relative positions of six anchor points (Figure 3) along the mitral annulus are measured along with the locations of each papillary muscle (PM) tip, according to the previous procedure using a Husky Digital Caliper (5).

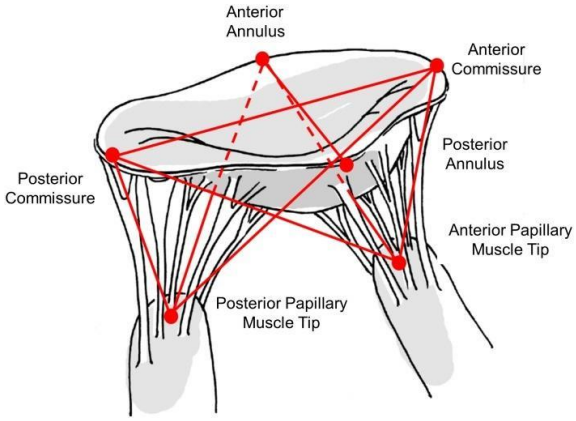


Figure 3. The six anchor points were required to customize mounting hardware (5).

Printing Hardware and Assembling the Case

The two mitral valve clamps and papillary muscle holders are modified according to the six anchor measurements on SolidWorks and 3D printed on the Objet using VeroWhite material. A 3.5 inch acrylic cylinder was cut at lengths 1.3 and 2.0 inches for the atrial and ventricular chambers respectively. Acrylic glue was used to glue the representative chambers and inner flange of the case. The outer flange was also glued to the ventricular chamber.

Mounting the Mitral Valve

Fabric was sutured with Dacron sutures to the papillary muscles. The covered papillary muscles are then additionally sutured onto the stitching rings, which are screwed to the customized papillary muscle holders. The two holders are then screwed onto a base. The annulus of the valve is then secured between the custom clamps and screwed in. The valve is then threaded through from the atrial side of the case.

Testing the Adhesives

Various adhesives including aerosol adhesives, several dental UV resins, as well as surgical grade cyanoacrylates were tested to measure adhesive strength on the mitral valve leaflets. Each porcine heart was cut leaving the papillary muscles attached to the ventricle walls. Several drops of each adhesive were applied along the coaptation zone from both the atrial and ventricular side. Once the valves were shut and the adhesive was added, a small load scale was used to measure the strength of the glues. An initial weight of the heart was taken. The load scale was hooked onto the medial papillary muscle and pulled downward until the leaflets were pulled apart. The difference between the two weights was considered the load that the leaflets could maintain with the adhesives. The adhesive with the highest strength was tested again using adhesive barriers such as Skin Tac liquid adhesive barrier and Sureprep No Sting Protective Barrier wipe. The adhesive barriers were saturated onto the MV leaflets before applying the adhesive.

Closing the Valve

The mitral valve leaflets are closed in the systole conformation. This was achieved by using an air compressor that applies pressure to the leaflets from the ventricular side. A

ball valve connected to the ventricular supply line and a needle valve is slowly opened to gradually apply air pressure onto the leaflets. Once the leaflets are closed, 2-3 drops of the adhesive are applied along the edges of the anterior and posterior leaflets and the uniformly distributed across the leaflets. After testing the various adhesives, the 3M Vetbond surgical adhesive was found to be the most desirable adhesive to maintain closure of the leaflets. The air compressor continues to apply pressure for approximately an additional minute. The needle valve is then gradually closed to relieve the air pressure.

Micro CT Imaging

The mounted valves are imaged with a Nikon X TH 225 ST μCT (Nikon, Tokyo, Japan). The mitral valve case was put on a stand at 45° (Figure 4). A MATLab code was used to compile the images and to extract the mounting hardware and background from the mitral valves.

Figure 4. Mounted mitral valve is imaged using Micro CT at 45°

Results

None of the aerosol adhesives and resins were effective in bonding the leaflets. The surgical grade cyanoacrylates were the only adhesives that were effective in closing the leaflets. Table 1 displays the measured strength and composition of the cyanoacrylates. The adhesive with the highest strength, 3M Vetbond, was then tested with tissue preparatory barrier including Skin Tac by Torbot Group and Sureprep Protective wipe.

Table 1: The strength of various surgical grade cyanoacrylates were tested on MV leaflets with a load scale.

Adhesives	Composition	Initial Wt. (kg)	Final Wt. (kg)	Strength (kg)
Surgi-Lock 2oc	2-octyl-cyanoacrylate	0.16	1.14	0.98
LiquiVet	butyl-cyanoacrylate (histoacryl)	0.18	1.00	0.82
Gel dental	gel cyanoacrylate	0.14	0.16	0.02
GLUture	60% 2-octyl & 40% N-butyl cyanoacrylate	0.12	1.56	1.44
3M Vetbond	98% N-butyl CA Hydroquinone (<1 % by wt.)	0.21	1.75	1.54
3M Vetbond w/ Torbot Group Inc Skin Tac	98% N-butyl CA, Hydroquinone (<1 % by wt.) & Isopropyl Alcohol	0.16	1.46	1.30
3M Vetbond w/ Sureprep wipe	98% N-butyl CA Hydroquinone (<1 % by wt.) & Isopropyl Alcohol (40-60%)	0.32	1.27	0.95

Figures 5A and 5B show a comparison between the two approaches in closing the leaflets in the systole conformation using fluid pressure for 7T MRI and using air pressure and Vetbond adhesive for Micro CT imaging. The air pressure and Vetbond were effective in maintaining leaflet closure throughout the duration of the scan.

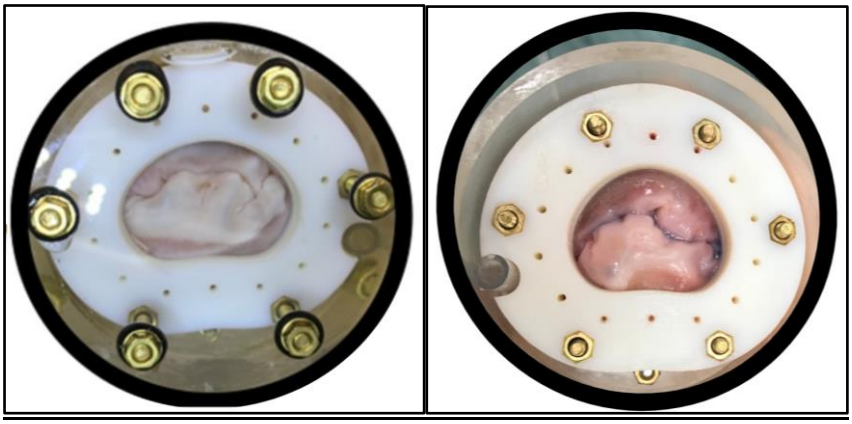
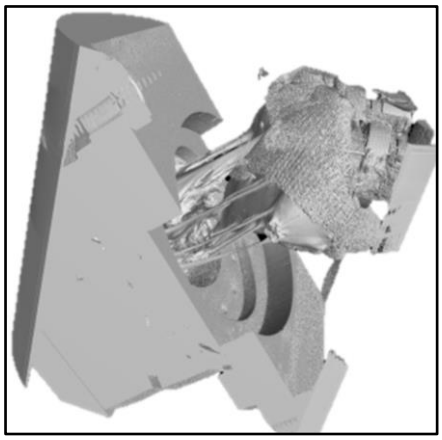


Figure 5A. MV leaflet closure for MRI using fluid pressure (5). **Figure 5B:** MV leaflet closure using air pressure with Vetbond adhesive for µCT.

Micro CT scanning resulted in a voxel resolution of 29 microns, with a scan time of approximately 1.5 hours. Data was reconstructed using a MATLab code where 1300 images were input into MATLab function (Appendix A) where the file type .tiff is transformed using the 'double' function. The code normalizes the intensities of the images from a range of 0 to 1. The intensities values of the background and customized hardware are removed to isolate the mitral valve (Figures 6 and 7).



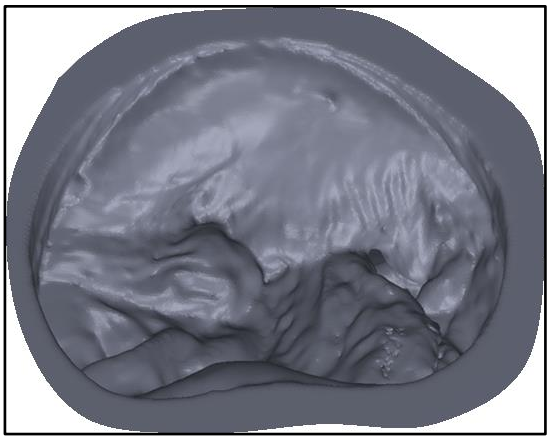


Figure 6. Reconstructed 3D μCT scan data of MV from ventricular side with hardware. **Figure 7.** Reconstructed 3D μCT scan data of closed MV leaflets from atrial side.

Discussion

The 3M Vetbond (98% N-butyl cyanoacrylate) surgical adhesive was found to have the highest strength in maintaining the closure of the leaflets. This is actually contrary to other research where butyl cyanoacrylates were found to have the least bursting and tensile strength when used on in vivo porcine wound sites (7). It should also be noted that this portion of the study was limited by the number of porcine hearts available. The strength in maintaining the closure of the MV leaflets decreased with the use of the tissue preparatory adhesives. The adhesive barriers are used for easy and painless removal of adhesives when used on top of the wound sites (8). Even though the tissue prep appears to have decreased the strength, it still proved to be advantageous when attempting to remove the adhesive from the leaflets. The adhesive was easily removed as thin film whereas all the cyanoacrylate adhesives could only be removed in small brittle fragments when used alone. Use of the tissue prep has the potential to be advantageous when extracting the layer of adhesive from the Micro CT images.

It is possible that viscosity may have played a role in the measured strength of maintaining leaflet closure. This was demonstrated in the results when comparing between the

adhesives LiquiVet and Vetbond. Although they had similar compositions, the LiquiVet had a higher viscosity than the Vetbond and was not as effective at maintaining leaflet closure. Additionally, Dental Lab super glue had the highest viscosity and displayed the poorest performance when closing the leaflets. However, there is no statistical significance that demonstrates that viscosity definitively affects the strengths of the adhesives (7). Low viscosity was also found to be advantageous when distributing an even layer adhesive across the leaflets.

In comparison of the systole conformation achieved by the trans-mitral fluid pressure for 7T MRI (5), this alternative approach was also effective in closing the leaflets and providing images of the MVs in the systole conformation. A drawback stemmed from a visible downward displacement of the leaflets once the air pressure was turned off. This however was significantly reduced when the adhesive was applied uniformly across the leaflets as opposed to applying the adhesive only along the coaptation zone (6). Upon initial trials it was measured that the leaflets were displaced by 0.9 mm after the removal of the air pressure from the ventricular chamber (6). It should also be noted that is was not verifiable how much air pressure was required to close the leaflets. However, literature has shown that the porcine blood pressure during systole ranges from 73 mmHg to 230 mmHg (9).

In the last iteration, there were some challenges with regards to isolating the mitral valve from the mounting hardware in the images. The contrast settings were lowered during the scan caused the intensity values of the mounting hardware to be very close to the intensity

values of the mitral valve. This suggests that removal of the adhesive from the leaflets would be more difficult to isolate.

Conclusions

This study presents an alternative method for obtaining high resolution imagery of the closed mitral valve utilizing Micro CT imaging. The use of individually customized mounting hardware permits valves to be mounted in a physiological geometry in the systole conformation by closing the leaflets using a surgical grade adhesive permits the scanning of the closed valve without the difficulty of having to maintain a constant pressure across the valve (6). 3M Vetbond (98% N-butyl cyanoacrylate) was found to be the most effective surgical adhesive with regards to strength and had the most uniform application on mitral valve leaflets. By obtaining these high resolution images, computational models will be more accurate at capturing MV behavior for the potential to diagnose and develop surgical plans for patients with mitral valve disease.

Future Directions

Further work could be done to measure the mitral valve leaflet displacement when air pressure is removed from the ventricular chamber. The thickness of the adhesive distributed across the leaflets could be measured with the potential to isolate the mitral valve leaflets from the Micro CT scan data. Further tests could be done in using other tissue adhesion barriers across leaflets and working to extract from mitral valve leaflets from Micro CT scan data. This has the potential to be done by improving the contrast

images in Micro CT to allow for the adhesive to be extracted from the leaflets. Additionally, improved contrast settings would allow for easier extraction of the case hardware.

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I would like to thank Dr. Morten Jensen for his continuous support and advice. I would like to thank Sam Stephens for his constant support and mentorship. Additionally, I would like to thank undergraduates Hudson Surber, Kaylee Henry, and Joseph Berryman for their help in this project along the way.

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Appendix

Contents


```
% Created by Kaylee Henry
% April 22, 2019
clc
clear
```

```
Error using evalin
Undefined function 'MV' for input arguments of type 'char'.
```

IMPORTING THE FILE WITH ALL IMAGES

Below we are identifying the file name that holds the images, and importing all images.

```
tic
D = 'Jensen_CT';
S = dir(fullfile(D,'*.tif')); % pattern to match filenames.
S = S';
for k = 1:length(S)
    F = fullfile(D,S(k).name);
    I = imread(F);
    J = double(I)/255;
    CTdudes{k} = J;
end
toc
```

Multi-thresholding each image

```
tic
for i=1:size(CTdudes) % looking through every image
    originalpic=CTdudes(i);
    picture=cell2mat(originalpic);
    thresholds=multithresh(picture,3);
    mask=(picture>thresholds(3));
    newpic{i}=picture.*(1-mask);%Extracts mounting hardware and background.
end
tic
```

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