5-1-2018

BIOMECHANICAL CHARACTERIZATION OF THE NEONATAL PORCINE VENTRICULAR SEPTUM

Chidalu Mozie

BIOMECHANICAL CHARACTERIZATION OF THE NEONATAL PORCINE VENTRICULAR SEPTUM

by

CHIDALU MOZIE

Presented to the Faculty of the Honors College of

The University of Texas at Arlington in Partial Fulfillment

of the Requirements

for the Degree of

HONORS BACHELOR OF SCIENCE IN BIOMEDICAL ENGINEERING

THE UNIVERSITY OF TEXAS AT ARLINGTON

May 2018

ACKNOWLEDGMENTS

This material is based upon work supported and funded by Biomedical Engineering Department of University of Texas at Arlington. I would like to acknowledge Dr. Liao, Dr. Nair and Dr. Alexandrakis, for their continued guidance throughout the course of this project; my team members, Shaz Akhtar and Sandra Miller for their cooperation and dedication to the successful completion of this project; Katherine McGrath Copeland, Sarah McMahan and Tom Manuel for the mentorship they provided

May 4, 2018

ABSTRACT

BIOMECHANICAL CHARACTERIZATION OF THE NEONATAL PORCINE VENTRICULAR SEPTUM

Chidalu Mozie, B.S Biomedical Engineering

The University of Texas at Arlington, 2018

Faculty Mentor: Jun Liao

Defects in the interventricular septum are the most common congenital cardiac defect in infants. The pressure difference between the two ventricles causes increased blood flow to the right ventricle, which leads to septal deformation. Given the difficulty of imaging the interior of the intact heart, the mechanics of this interventricular septal deformation has not been determined in situ. My project entails the creation a motor-controlled pressurization system to deform the neonatal porcine left ventricle for the characterization of the interventricular septal mechanical properties. The pressurization system comprises of a motor controlled piston pump, run by a personalized LabVIEW program that deformed the left ventricle at varying pressures. The corresponding displacement of the septum was characterized by tracking septal marker movement,calculating the equivalent biaxial strains (εX And εY) and areal strain (εareal)

using MATLAB, and plotting data curves of pressure vs εareal, pressure vs. εX , and pressure vs. εY.

TABLE OF CONTENTS

Appendix

LIST OF ILLUSTRATIONS

CHAPTER 1

INTRODUCTION

1.1 Background and Significance

The heart septum is a muscular wall that separates the left and right sides of the heart from one another. The septum, although continuous, is classified into two parts, the first being the interatrial septum; this section is located in the superior region of the heart, and it separates the left and right atria. The second section located in the inferior region is the interventricular septum; this section separates the left and right ventricles from one another. The main function of the septum is to prevent the mixing of deoxygenated blood (right heart) from the oxygenated blood (left heart), although this is not always attainable. The following are examples of congenital heart septal defects/diseases.

1.1.1 Hypertrophic Cardiomyopathy (HCM)

HCM is a heterogeneously expressed familial disorder which is estimated to affect 0.2% of the world population with 200,000 new cases in the US per year; 85% of the cases go undiagnosed due to the lack of apparent symptoms [1]. Due to the fact that many cases of HCM go undiagnosed, it is the leading cause of sudden cardiac death in young athletes. HCM occurs when there is an enlargement of the heart muscle specifically the interventricular septum; this enlargement reduces the volume of the left ventricle, in turn reducing the amount of oxygenated blood that can be pumped out of the heart. This reduction of oxygenated blood being pumped can lead to: shortness of breath, dizziness, arrhythmia, and sudden cardiac death.

There are two main types of HCM [1]:

1. Obstructed- During obstructed HCM the mitral valve will hit against the enlarged septum, this causes further blockage of the heart and the possibility for blood regurgitation into the left atria.

2. Unobstructed- In unobstructed HCM the mitral valve does not further impede the flow of blood, but the enlarged septum does cause lowered blood flow.

1.1.2 Ventricular Septal Defect (VSD)

VSD is the most common congenital heart defect in newborns affecting an estimated 0.6% of the population with 200,000 new cases in the US per year. VSD occurs when there is an improper joining of the superior and inferior regions of the ventricular septum, leading to holes or defects usually less than 5mm. These defects cause a leaking effect from the higher pressure left ventricle toward the lower pressured right ventricle. This leads to oxygenated blood in the right heart thus causing an increase of blood volume in the right heart, which leads to pulmonary hypertension. Normally the VSD if below 5mm will self-heal. If the VSD is larger than 5mm, then a surgically implanted mesh would need to be implanted to facilitate the closing of the defect.

Critical Congenital Heart Defects (CCHDs), such as those mentioned above, are present at birth and have the potential negatively impact the daily lives of those affected. Many of these conditions are not diagnosed until the child in much older, since the current screening techniques quite often include the use of prenatal ultrasounds, which tend to properly diagnose CCHDs fewer than half the time. Since many of the current screening techniques are based on visual cues, this can more than often be misleading and cause a false negative. These false negative results lead to the discharge of newborn babies from

the hospital who later succumb to the negative impact of these CCHDS. Currently, with the help of the American Academy of Pediatrics, there is a push to include screening via pulse oximetry during the first 24-48 hours of life if the oxygen saturation is found to be less than 90%, then the CCHD screen is positive, and an echocardiogram is requested for the patient. This push for screening has helped substantially increase the number of CCHDs to be correctly diagnosed leading to better long-term health for patients [2].

Since there are not many resources regarding the characterization of the human neonatal heart muscles, specifically the septum, there is a demand for a system that can map out the characteristics of the neonatal heart. This would have to be done first with the porcine heart, since the porcine heart is comparable to the human heart. There currently exists a handful of systems that can stimulate the heart externally, but these systems all deal with the adult porcine hearts and are currently limited to the study of the internal heart and the heart valves via endoscopy.

CHAPTER 2

METHODOLOGY

2.1 Ideal Device Function Description

The ideal device was designed to use a LabVIEW controlled syringe pump and motor to push water through the left ventricle of a neonatal heart. During the data acquisition process, the heart was to be kept in clear chamber filled with PBS solution. A catheter pressure sensor was to be placed in the center of the left ventricle, and a LabVIEW software was to record the pressure in the ventricle as it was deformed. The camera and LabVIEW software was to recognize each marker on the septum and track their movement as the septum was deformed. The raw data was then to be analyzed in a LabVIEW and MATLAB software and generate pressure-strain graphs for the x, y, and areal strains.

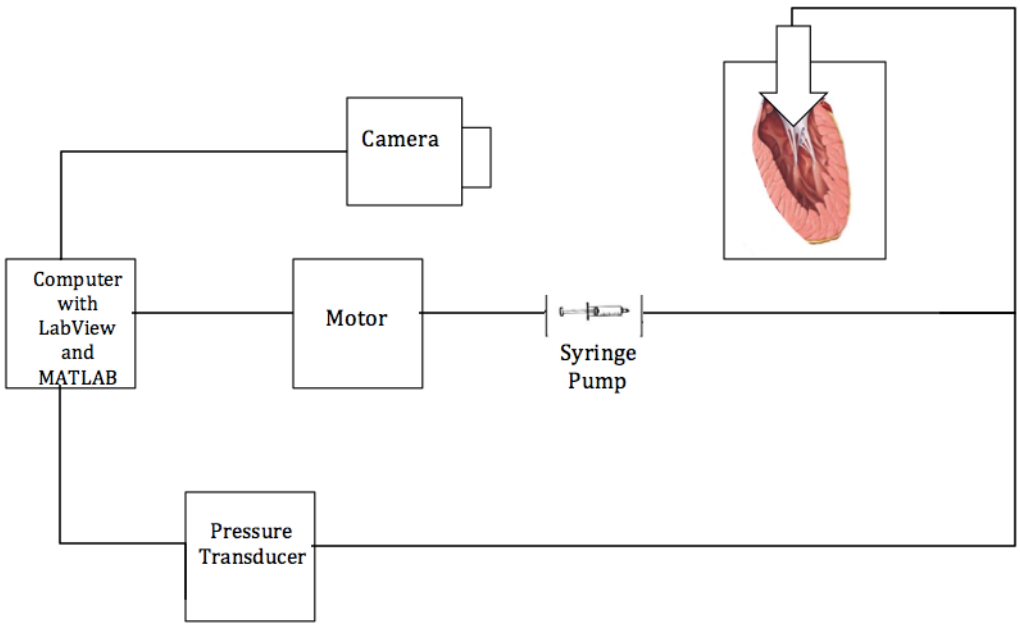


Figure 2.1: Ideal/Current Design Approach

2.1.1 LabVIEW Marker Tracking Program

The image capturing system captured the live video feed of the heart and recognized either light or dark markers. Image threshold, marker size limits, and marker color detection could be initialized and modified for each run. When the image capturing process began, the time, pressure, and coordinate location of each marker was recorded every 500 ms. A separate LabVIEW program operated the motor on the syringe pump, and the volume of liquid displaced each run could be modified. The data was then compiled into a string and saved as a text file that could be accessed through MATLAB.

2.1.2 MATLAB Data Analysis Process

The data was imported into MATLAB using a user input function. The program analyzed each of the four marker's x and y coordinates at time zero to determine the location of each marker relative to each other. The program then calculated the distance between the makers at time zero and at each time point thereafter. The x, y, and areal strain were then calculated for each time point. The equations used for this purpose can be seen in Appendix A. Graphs were generated that plotted time versus strain for each type of strain calculated.

2.2 Description of Prototype

Since the neonatal porcine heart was relatively small in size, the initial thought process was to maintain the entire heart structure in order to maintain the overall structure and integrity of the neonatal porcine heart.

2.2.1 Alternative Concept Analysis

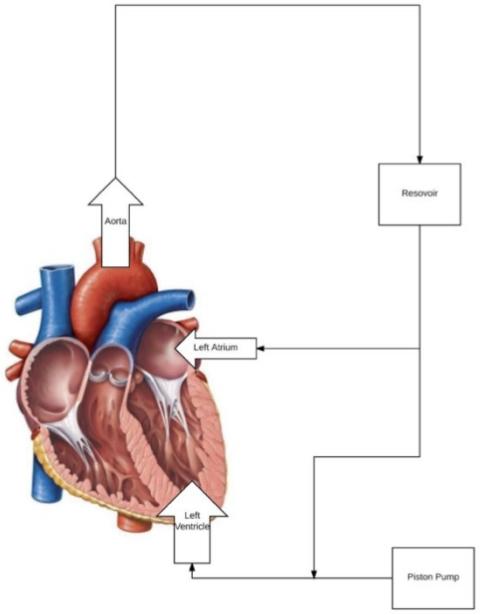


Figure 2.2: Design Approach 1

The system that would feed the heart with the solution was composed of two main components:

1. Reservoir: This reservoir would have two functions:
    1. The reservoir would feed the heart's left atrium passively via gravity.
    2. The reservoir would collect the fluid that was pumped out of the aorta.
2. Motor Controlled Syringe Pump: The pump was to be connected to the heart via tubing on the inferior region of the heart in the middle of the left ventricle, and the pump would be controlled via a LabVIEW program to mimic relevant cardiac output values.

This approach was realized to be flawed when the neonatal heart was extracted from the piglet. In order for the characterization of the neonatal ventricular septum to even begin, the septum had to be observable. Another flaw with this method would have been the difficulty to place markers on the septum in a precise manner. With the entire heart intact, this would not be doable without the use of an endoscope.

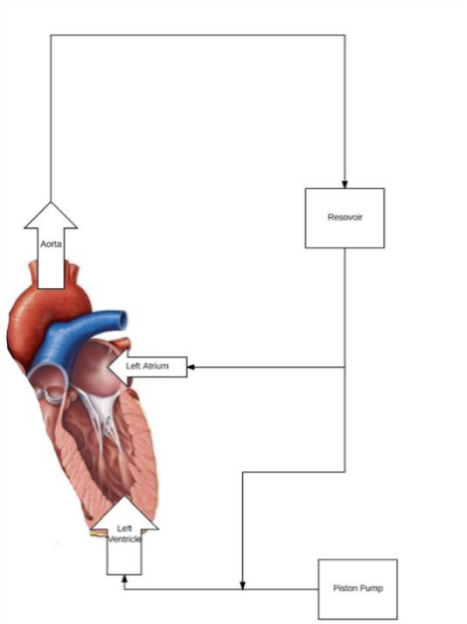


Figure 2.3: Design Approach 2

Design 1 was modified into design 2, where instead of the entire heart being intact, the right side of the heart would be removed in order to expose the interventricular septum. With the interventricular septum exposed, markers could be placed in a square 2X2 pattern. This pattern was chosen due to the testing standard of using square patterning and due to the limited region. If the septum was larger, a larger pattern would have been implemented. The components (reservoir and motor) remained the same for Design 2, but there was an

addition of a pressure sensor that would be incorporated ideally in the tubing leading into the heart from the inferior region.

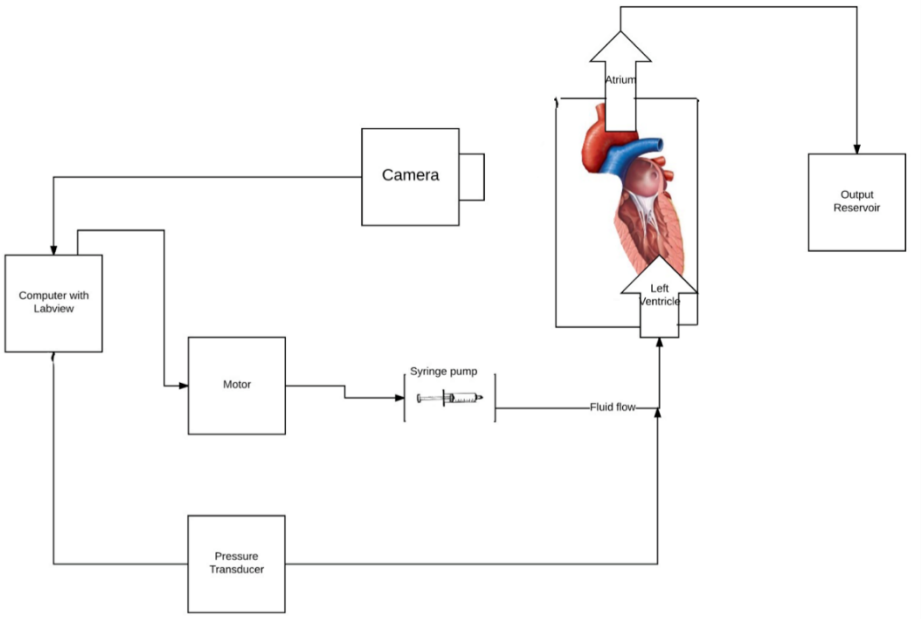


Figure 2.4: Design Approach 3

Design 3 differed from the first two designs primarily in the way that the liquid was pumped into the heart. In the previous designs, the liquid was to be pumped into the ventricle and the atrium, while design three only had liquid pumping into the ventricle and then out through the atrium into a reservoir. The only other change was that a syringe pump was to be used instead of a piston pump. This change was primarily made as a LabVIEW compatible syringe pump and motor was already available to us, and it was able to displace liquid within our desired parameters.

2.2.2 Final Design Prototype Construction

One of the main changes on the final design (see Figure 1) is the absence of the output reservoir. We instead decided to cut both the right heart and the atrium, and pump directly into the top of the left ventricle and not provide an output reservoir. The other

major change was the incorporation of a MATLAB code into the data analysis, as MATLAB allowed for easier manipulation of the data and graph creation

The hearts used were extracted from stillborn neonatal and the right portion of the heat and the left atrium were then removed. Tubing was attached to the opening on the left ventricle, where the atrium had been removed using super glue. The pulmonary artery was closed using suture and super glue. Black markers were made by cutting black duct-tape into small, uniformly sized squares (approximately ¼ inch by ¼ inch). The markers were secured to the exposed ventricular septum using super glue. The chamber used to contain the heart had been previously constructed from Plexiglas and glue. The chamber was filled with PBS solution, and the heart was placed into the chamber. The tubing in the heart was connected to a syringe pump filled with PBS solution, with a motor controlled by the LabVIEW program. The camera and motor were connected to the computer with the LabVIEW software, and data analysis was run with the MATLAB and LabVIEW software.

CHAPTER 3

TESTING AND VALIDATION

Before the neonatal porcine septum was attached to the pressurization system and monitored using the LabVIEW marker tracking system, the following components were tested: optimal size and color of the markers, LabVIEW marker tracking, and MATLAB analysis. The optimal maker size was determined to be approximately ¼ inch by ¼ inch, which was determined to be the limit the LabVIEW program could visualize. Regarding marker color black and white markers were tested, since the heart was placed in the liquid filled chamber and the marker visualization system treated liquid as a white background, black colored markers were chosen. Multiple trial runs were performed by placing markers in a 2 X 2 grid on a balloon of equal size and volume of the left ventricular. The balloons were then pressurized with the pumping system, and markers were tracked and analyzed using LabVIEW and MATLAB. Adjustments that enabled more efficient marker tracking and data analysis were made to both programs.

CHAPTER 4

RESULTS

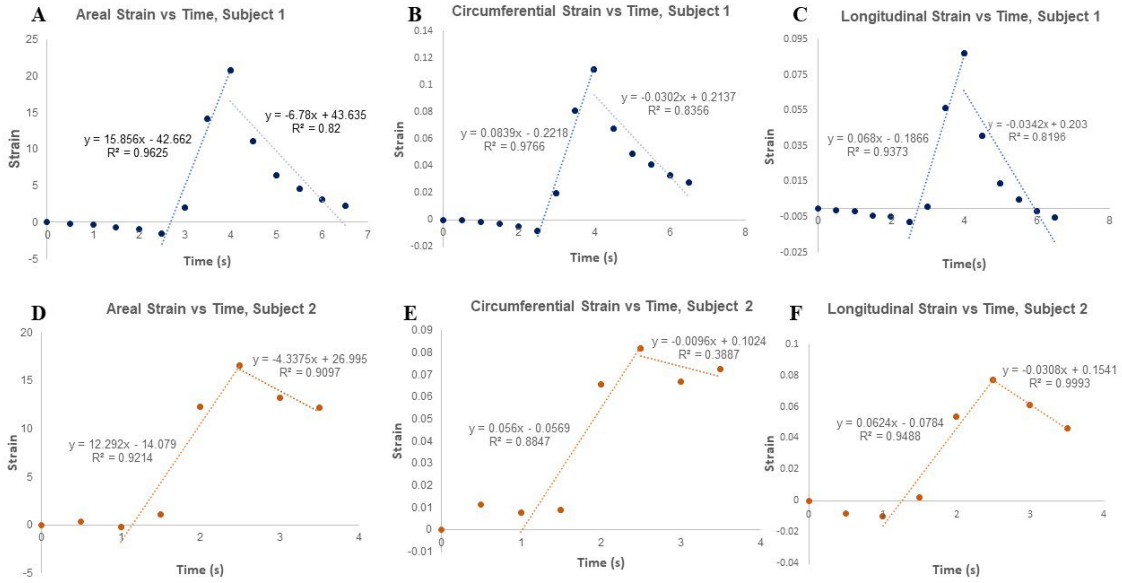


Figure 3.1: Graphs Showing Areal, Circumferential (x), and Longitudinal (y) Strain with Respect to Time (note: parts A, B and C were generated using the heart from subject one. Parts D, E and F were generated using the heart from subject two)

The highlighted equations were derived from the trend lines that correspond to the pressurization and depressurization of the ventricle. The positive and negative slopes of the equations indicate the strain rate of the septum during diastole and systole, respectively.

For subject 1 Figure 5A shows an initial increase in the areal strain at a rate of 15.85/s, and a second strain rate of -6.78/s shows a decrease in the strain rate. Circumferential strain for subject 1 is observed in Figure 5B, which shows the initial rate of 0.084/s and the second rate of -0.030/s. The longitudinal strain for subject 1 is shown in

Figure 5C, indicating an initial rate of 0.061/s and the negative second rate of -0.0304/s.

For subject 2 figure 5D exhibits the areal strain, an initial rate of 12.292/s, and a secondary strain rate of -4.338/s indicates systole. Figure 5E exhibits the circumferential strain in subject 2, an initial rate of 0.056/s indicates diastole, and the negative secondary rate of -0.0096 indicates systole. Figure 5F exhibits the longitudinal strain in subject 2, an initial rate of 0.0624/s indicates diastole, and the negative secondary rate of -0.0308/s.

CHAPTER 5

DISCUSSION

The goal of the project was to create a motor controlled pressurization system in order to monitor and analyze strain in the interventricular septum of neonatal porcine hearts. We successfully completed this goal, and the observed result indicated a roughly linear relationship between septal strain and time. This linear relationship is classified as strain rate (1/s). From this data, it can be inferred that the induced increase in ventricular pressure yielded an increase in septal strain. Likewise, the decrease in ventricular pressure yielded a decrease in septal strain. Accordingly, this increase and decrease in ventricular pressure is pertain to diastole (ventricular filling) and systole (ventricular contraction) respectively. Thus, the slopes of positive and negative trendlines in Figure 5A-F indicate the strain rate of the septum during diastole and systole, respectively. Since a similar characterization of the neonatal septum is yet to be performed, standard values of the longitudinal and circumferential systolic and diastolic septal strain rate can only be determined after testing a large population of neonatal hearts. Seeing as the two subject hearts we tested yielded similar results, our system has good potential to be used for this purpose. Also, there are studies that have determined the global longitudinal and circumferential systolic and diastolic septal strain of adults through echocardiography (1), as thus future work could entail the pressurization of adult hearts so we could compare our derived values to present literature values. To optimize our pressurization system, we could incorporate a marker system that consists of a 3 X 3 array, this would allow for data points

and a more comprehensive strain rate determination. In addition, utilizing a pressure sensor inside the heart, would allow for the calculation and graphing of parameters such as strain vs pressure, and stress vs pressure, and stress vs strain.

5.1 Conclusion

In conclusion, our designed system was able to pressurize the isolated left ventricle of the neonatal porcine heart. The LabVIEW program that was created was able to track the movement of the markers placed on the exposed interventricular septum, and the MATLAB program was able to analyze the marker movement and display a relationship between strain and time. As seen in Figure 5 A-F, the strain value increases overtime during ventricular pressurization followed by a decrease in the strain values during ventricular depressurization. This same trend can be seen in both heart models indicating a reproducible methodology.

5.2 Future Work

Future work on this project would entail the use of other parameters such as pressure, stress, young modulus, and compressive and tensile forces that would enable a more comprehensive characterization of the septum. We would also simulate a more physiological environment for determining these parameters, possibly through the use of biological fluids for heart immersion and fluid flow that would give us more realistic results. Also, to ensure we obtain the standard characteristics for healthy hearts, in the future we would use a larger sample size of healthy and diseased neonatal hearts. This would provide data that could be used to compare and analyze the change in the aforementioned parameters of hearts with and without certain pathologies. With regards to our methodology, we would use more biocompatible markers that would better preserve

the septal tissue integrity. Also using more markers, specifically a three by three array, will enable more sensitive detection of septal deformation, resulting in more data points obtained per parameter. To achieve this, we would have to utilize a camera with a higher frame rate that can track minute marker movement and also modify the LabVIEW and MATLAB program, to allow for the use of this 3 by 3 array of markers.

APPENDIX A

PICTURES PROVIDING FURTHER DETAIL ON PROJECT

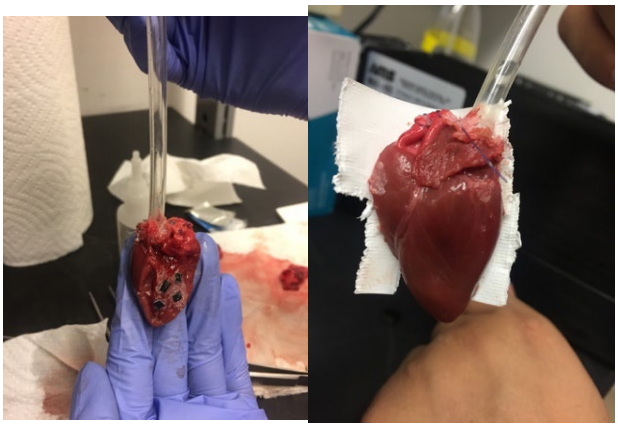


Figure 7: Front and back view of the isolated left ventricle from fetal pig heart with tubing attached.

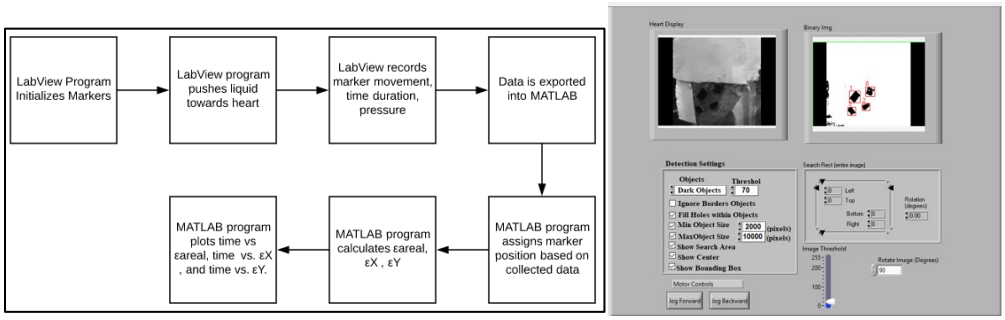
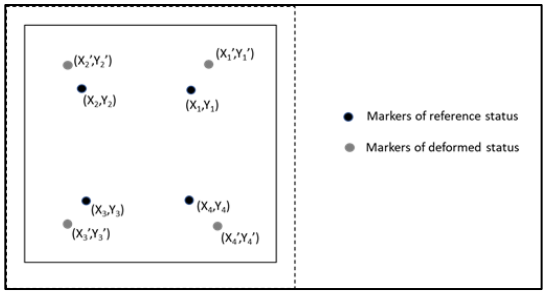


Figure 8: Data Collection and Analysis Process (left) LabVIEW marker tracking program interface (right).



Original:

$$L_X = \frac{L_{X_{12}} + L_{X_{34}}}{2} = \frac{\sqrt{(x_1-x_2)^2+(y_1-y_2)^2}+\sqrt{(x_4-x_3)^2+(y_4-y_3)^2}}{2}$$

$$L_Y = \frac{L_{Y_{23}} + L_{Y_{14}}}{2} = \frac{\sqrt{(x_3-x_2)^2+(y_3-y_2)^2}+\sqrt{(x_4-x_1)^2+(y_4-y_1)^2}}{2}$$

Deformed:

$$L_{X'} = \frac{L_{X'_{12}} + L_{X'_{34}}}{2} = \frac{\sqrt{(x_1'-x_2')^2+(y_1'-y_2')^2}+\sqrt{(x_4'-x_3')^2+(y_4'-y_3')^2}}{2}$$

$$L_{Y'} = \frac{L_{Y'_{23}} + L_{Y'_{14}}}{2} = \frac{\sqrt{(x_3'-x_2')^2+(y_3'-y_2')^2}+\sqrt{(x_4'-x_1')^2+(y_4'-y_1')^2}}{2}$$

$$\varepsilon_{areal} = \left(\frac{L_X}{L_{X'}} * \frac{L_Y}{L_{Y'}} - 1\right) * 100\%$$

$$\varepsilon_X = \frac{L_X - L_{X'}}{L_{X'}} = \frac{L_X}{L_{X'}} - 1$$

$$\varepsilon_Y = \frac{L_Y - L_{Y'}}{L_{Y'}} = \frac{L_Y}{L_{Y'}} - 1$$

Figure 9: Equations used for determining distance between markers (top left and right). Equations used for determining areal, circumferential and longitudinal strain (bottom left to right).

REFERENCES

[1] Huang, TingTing, et al. “Hypertrophic Cardiomyopathy in Neonates with Congenital Hyperinsulinism.” Archives of Disease in Childhood. Fetal and Neonatal Edition, *U.S. National Library of Medicine*, 5 July 2013.

[2] Gersh, Bernard J., et al. “2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: Executive Summary.” *Journal of the American College of Cardiology*, vol. 58, no. 25, 2011, pp. 2703–2738., doi:10.1016/j.jacc.2011.10.825.

[3] Richards, AL et al. “A Dynamic Heart System to Facilitate the Development of Mitral Valve Repair Techniques.” *Annals of Biomedical Engineering* 3(4) 651-660

[4] Leopaldi AM, Wrobel K, Speziali G, van Tuijl S, Drasutiene A, Chitwood WR. The dynamic cardiac bio-simulator: A method for training physicians in beating-heart mitral valve repair procedures. *The Journal of Thoracic and Cardiovascular Surgery*. 2017 September 18

[5] Russo, Allison, and Anne Elixhauser. “Hospitalizations for Birth Defects, 2004.” *Healthcare Cost and Utilization Project*, 7 Jan. 2007, pp. 1–9

[6] Kobayashi T, Popovic Z, Bhonsale A, Smedira NG, Tan C, Rodriguez ER, et al. Association between septal strain rate and histopathology in symptomatic hypertrophic cardiomyopathy patients undergoing septal myectomy. *American Heart Journal*. 2013 September 1, 166(3): 503-11.

BIOGRAPHICAL INFORMATION

Chidalu Mozie decided she was going to be a doctor because of the outdated and ineffective health care system in her home county. She realized the need for good doctors and took it upon herself to be a contribution to an improved health care system.

Upon her admission into UTA, she chose biomedical engineering as her major because she was interested in the challenges engineering could present. During her junior year, she became aware of the importance of research, specifically in medicine. Sequentially, she made a long term goal to partake in research that would lead to a breakthrough in medicine.

Chidalu also discovered her love of teaching at UTA. She became a math tutor in the second semester of her freshman year. By the end of her junior year, she had mastered tutoring skills in the areas of Math, Physics, Biology, and Chemistry.

Chidalu determined the best way to integrate her passion for teaching, research, and medicine was to do an MD-PhD program. She intends on obtaining her Ph.D. in Biomedical Engineering; concerning her research experience garnered from the McNair Scholars Program, the Undergraduate Research Assistant Program, and some of her courses. She streamlined her research interests to tissue engineering and cancer. After her graduation, she will have two gap years, during which time she will work in a research institution. After she obtains her MD-PhD, she intends continuing on to a clinical residency, as she would be able to partake in research while interacting with patients. She also envisions becoming an academic medical school faculty years into her career.