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Redesign and Quantitative Assessment of an Accelerated Venous Valve Fatigue Apparatus

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Honors Thesis Project of
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Abstract

Chronic venous insufficiency (CVI) is a form of cardiovascular disease that is caused when valves in the leg become incompetent. Current treatment methods serve to manage symptoms, but there are currently no ways to treat the underlying cause of CVI. A venous valve prosthetic made from a xenograft of a bovine jugular vein is one possible treatment method currently in the research phase. Prosthetic valves must be tested with an accelerated wear tester prior to approval for clinical testing. Although such testers exist for heart valves, physiological differences between heart and venous valves restrict the use those testers on venous valves. An accelerated wear tester, or venous valve fatigue apparatus, was created by a student previously, but failed when the rubber syringe tips melted due to friction. The previous project ran for a total of 10 hours and no conclusive results were determined from subsequent mechanical testing of the valves. The goal of this project was to redesign and rebuild the fatigue apparatus to be more durable, in addition to obtaining quantitative data signifying the machine was working. The fatigue apparatus should create a pressure difference that would drive the valve to repeatedly open and close, wearing the valve out over time. The reconstruction of the apparatus was successfully completed by replacing the syringes used to pump water, with a pneumatic air cylinder connected to a diaphragm. The pneumatic air cylinder causes the diaphragm to expand and contract, moving water with it. Pressure measurements were obtained from the diaphragm, indicating that a maximum pressure 27.24 kPa was created by the diaphragm. Although pressure with a vein would be slightly less, valves close in response to a 1.33 – 5.33 kPa increase. Therefore, the apparatus should function as intended. Testing with a vein was not accomplished in this experiment due to complications from COVID-19 and can be conducted as part of future work.

Article I. Introduction

Section 1.1 Background and Motivation

Chronic Venous Insufficiency (CVI) affects 10-35% of adults over forty in the United States (1) Approximately 900,000 new patients are diagnosed annually in the United States (2). Despite its prevalence, there is currently no long-term treatment method that addresses the underlying cause of CVI (3). Current treatment methods work to manage symptoms, such as taking blood thinners, ligation, or bypass surgery, but do not address the problem directly (2). CVI occurs when venous valves in the leg become incompetent, leading to backflow of blood and subsequent pooling of blood in the lower extremities (3). CVI is exacerbated by high blood pressure, lack of exercise, and smoking (2). Untreated, CVI causes pain in the legs from swelling of calves and ankles due to enlarged veins from the clotting of blood. Economically, CVI constitutes 2% of the total Western society healthcare budget (4).

Venous valves are bicuspid valves located in the veins of the leg. Venous valves prevent retrograde flow of blood away from the heart. In other words, venous valves work to maintain one-direction blood flow within a vein. An example of venous valve function can be seen in **Figure 1**. The valve closure mechanism is pressure driven and will close in response to an increase in pressure (4). Pressure significantly increases upon standing, from a sitting position, breathing, and during exercise via muscle flexion (4). Because valve closure is dependent on physical activity, valve usage is variable.

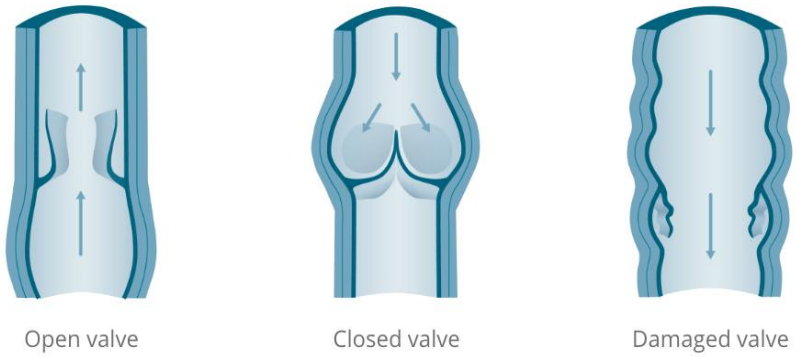

Figure 1*: Depicts normal and abnormal function of venous valves*

Source: Jobst Medical Canada

The creation of a venous valve prosthetic from a bovine jugular valve is a promising option for future treatment of CVI. A prosthetic would replace the invalid valve and maintain all functionality. A prosthetic valve can be created by using a xenograft, a tissue transplant from another organism (5). Prior testing has established that bovine jugular valves are most comparable to human femoral and iliac veins in the leg, based on size and performance at various pressures (5). Bovine jugular valves come from the jugular vein located in the neck of a cow. Jugular valves can be used as opposed to valves from the leg because the valves function the same way, opening and closing in response to pressure differentials. If successful, the xenograft would function in the human body in place of the incompetent venous valve.

For valves to be biocompatible, they must meet certain criteria. Valves must be easily implantable, non-thrombogenic or non-clotting, have preserved leaflet strength and flexibility, and must remain open when there is no pressure (5). In addition, valves must reestablish prevention of reflux flow and remain functional for a set, minimum period of time (2). The mechanical properties of a valve, which include elasticity, Young's modulus, and yield strength, are important in assessing the lifetime of a prosthetic. A venous valve prosthetic must be reliable so that it doesn't break down

again and lead to another case of CVI within the same valve (5). Although several valve designs have been proposed in the early 21st century, long-term durability and thrombosis are the major hurdles to a viable prosthetic (4).

Accelerated wear testers (AWT) are devices currently used to test prosthetic heart valves prior to approval for clinical testing. The Food and Drug Administration (FDA) recommends that bioprosthetic heart valve designs be tested up to 200 million cycles using an AWT, the equivalent of six years *in vivo*, to give a better understanding of device safety over time (6, 7). These requirements are for heart valve replacements, including mitral and aortic valves, but nothing has been specifically stated by the FDA for venous valves which are not used at as high a rate as heart valves. A previous patent for an implantable prosthetic vascular valve indicated that a prosthetic valve should maintain those conditions to be biocompatible, up to 500,000 cycles (8). For heart valves, *Dalgliesh et al.* determined that 1,400 cycles per minute is the optimal acceleration to maintain physiologic pressure and boundaries at an accelerated rate (7). For that experiment, it would take about 4.96 days to run 10 million cycles, so 200 million would require approximately 100 days (7). After simulation, the most common methods to assess the presence of wear is visual inspection using a magnified camera, such as scanning electron microscopy, and mechanical testing. Valve durability is dependent on the mechanical properties of the leaflets.

Although AWTs exist for heart valves, such devices cannot be used for venous valves due to physiological differences between heart and venous valves. Testing of a venous valve prosthetic would require the construction of a novel device. This project is a continuation from previous work to construct a fatigue apparatus for venous valves. The design from the previous project is shown in **Figure 2**. The first design was made to accommodate five veins. It utilized plastic syringes attached to linear actuators that moved back and forth, subsequently moving the syringe heads and

pulling and pushing water through the valve. The device ran at 4 cycles per second and was intended to run continuously for more than one day. Upon testing the device, the rubber seal of the plastic syringes melted due to friction, creating an open system allowing water to leak out. The first design didn't last long enough to properly fatigue the valve, could only be used a single time, and had no way of confirming whether the valves were closing. Improvements in these aspects would work towards a functional accelerated fatigue apparatus.

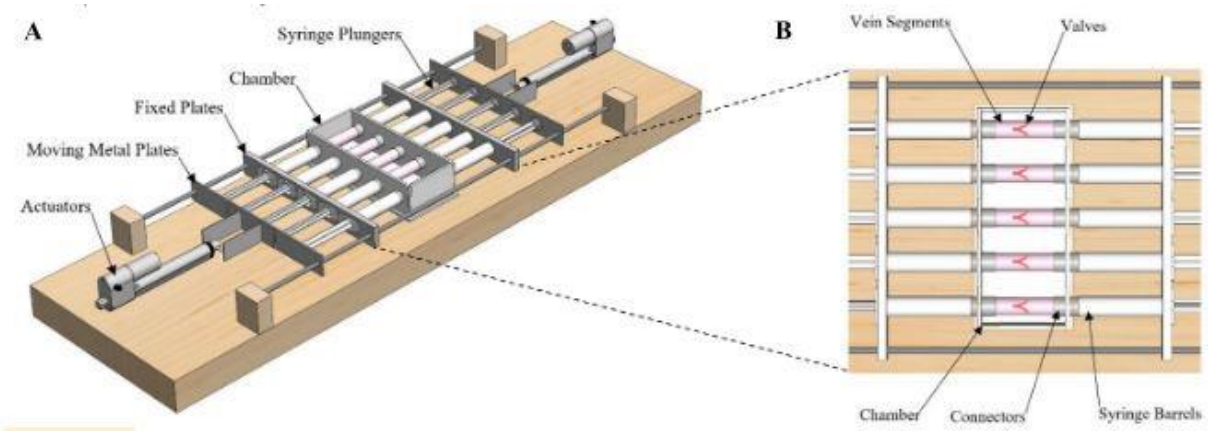

Figure 2*: SolidWorks rendering of the original fatigue apparatus design.*

Section 1.2 Objectives

Objective 1

The first objective was to redesign the fatigue apparatus to increase durability. Plastic syringes with rubber tipping can no longer be used, so a viable replacement that doesn't contain frictional elements needs to be constructed. As shown with the original model, friction caused the rubber sealing of the plastic syringes to melt. Water present inside the syringes subsequently leaked out the top of the syringe and created an open system within the vein.

Objective 2

The second objective was to quantitatively evaluate the effectiveness of the model. The previous design had no way to assure the user of its functionality. Because valves respond to changes in pressure, adding a pressure sensor in line is critical in evaluating performance.

Article II. Materials and Methods

2.1 Design Criteria

The main consideration for this project was the improvement of the previous design. The use of plastic syringes to drive the movement of water had to be abandoned. The new construction must not have frictional components that will wear down with use. In addition, all previous design criteria should be considered. The device must fatigue valves at an accelerated rate compared to physiological conditions. A pressure gradient greater than or equal to physiologic conditions must also be created.

2.2 Specifications

Physical

The final design included six key components- testing chamber, diaphragm, pneumatic cylinder, actuator, pressure transducer, and electrical components as indicated in the computer animated design shown in **Figure 3**. The computer animated design is shown with a similar representation of the original setup to emphasize the changes that have been made to the original design. The current design focuses on initially testing one vein to evaluate the concept of the diaphragm.

The testing chamber is a 12 by 5- inch acrylic box that contains five holes on either side to accommodate a maximum of five veins. The box was adapted to accommodate one vein by plugging up unused holes with rubber stoppers. The diaphragm was intended to act as a membrane

to prevent the pneumatic cylinder from getting wet. An expanded view of the diaphragm made in SolidWorks is shown in **Figure 4a** and **4b**. Acrylic spacers and an acrylic end piece were made using the laser-cutter. The two grey pieces were 3D printed and are intended to clamp the rubber membrane. The rubber membrane is intended to separate liquid and air, and to expand and contract to push and pull water through the vein with the extension and retraction of the pneumatic cylinder. The diaphragm is a key design change. The pneumatic cylinder (Tailonz Pneumatic Air Cylinder SC 63 x 150 with 2.5" bore 6" stroke) cannot be used to push water directly through the vein to prevent the metal bore of the cylinder from corroding from water and saline use. Having water in the pneumatic cylinder may also remove any lubrication present, leading to additional problems. The actuators (Progressive Automations PA-14P-4-50 with 4" stroke) are connected to the pneumatic cylinder bore. The pressure transducers (AdInstrument disposable blood pressure transducers) were stripped to connect to an NI-max setup.

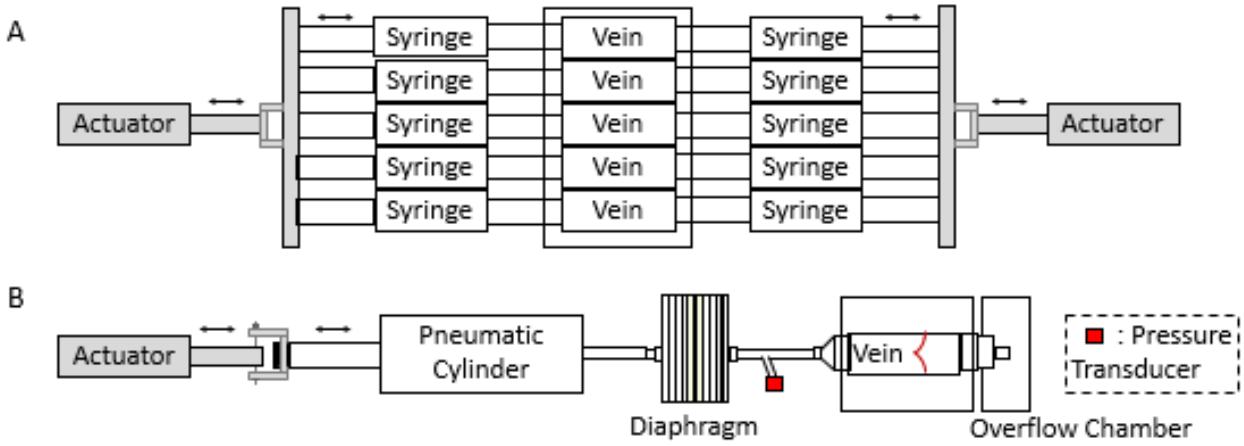

***Figure 3**: Compares the original fatigue apparatus model (A) to the current design (B). Both plates and syringe plungers were removed from the original design, and a pneumatic cylinder in addition to a diaphragm were added to the current design. A pressure sensor was also added.*

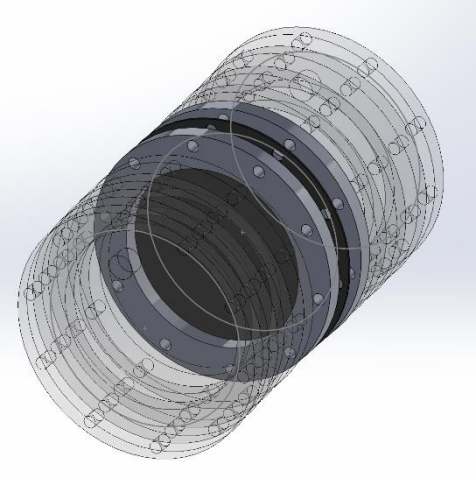

***Figure 4a**: Diagonal, expanded view of diaphragm created in SolidWorks*

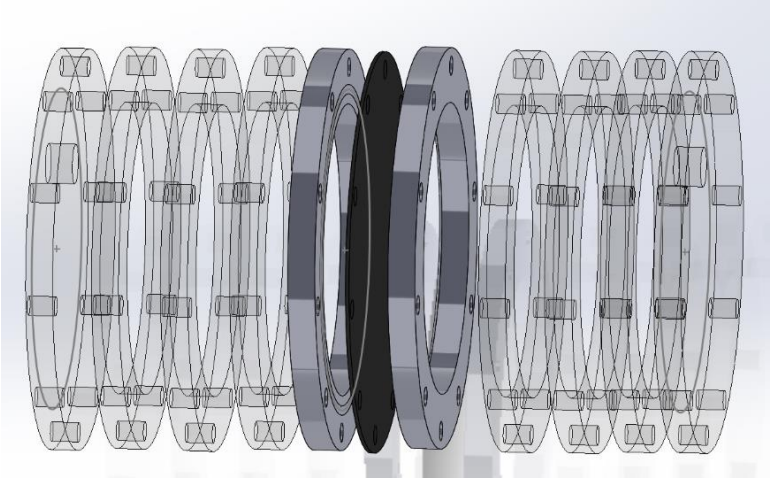

***Figure 4b**: Side, expanded view of the diaphragm. The clear panels were laser-cut from acrylic, the grey panels were 3D printed, and the black piece was cut out of a piece of rubber.*

Software

Because an Arduino Uno was used, the corresponding software was used to write a code to control the actuator movement. Two scripts were used from the previous project. One for calibrating the position of the actuators, and the second for dictating the movement of the actuators during testing. The NI-Max app was also used concurrently to acquire the pressure measurements.

Electrical

The electrical components include a breadboard, Arduino Uno, and a Songle 4-port power relay. This is used to power and control the movement of the actuator. The electrical setup can be seen in **Figure 5** seen below.

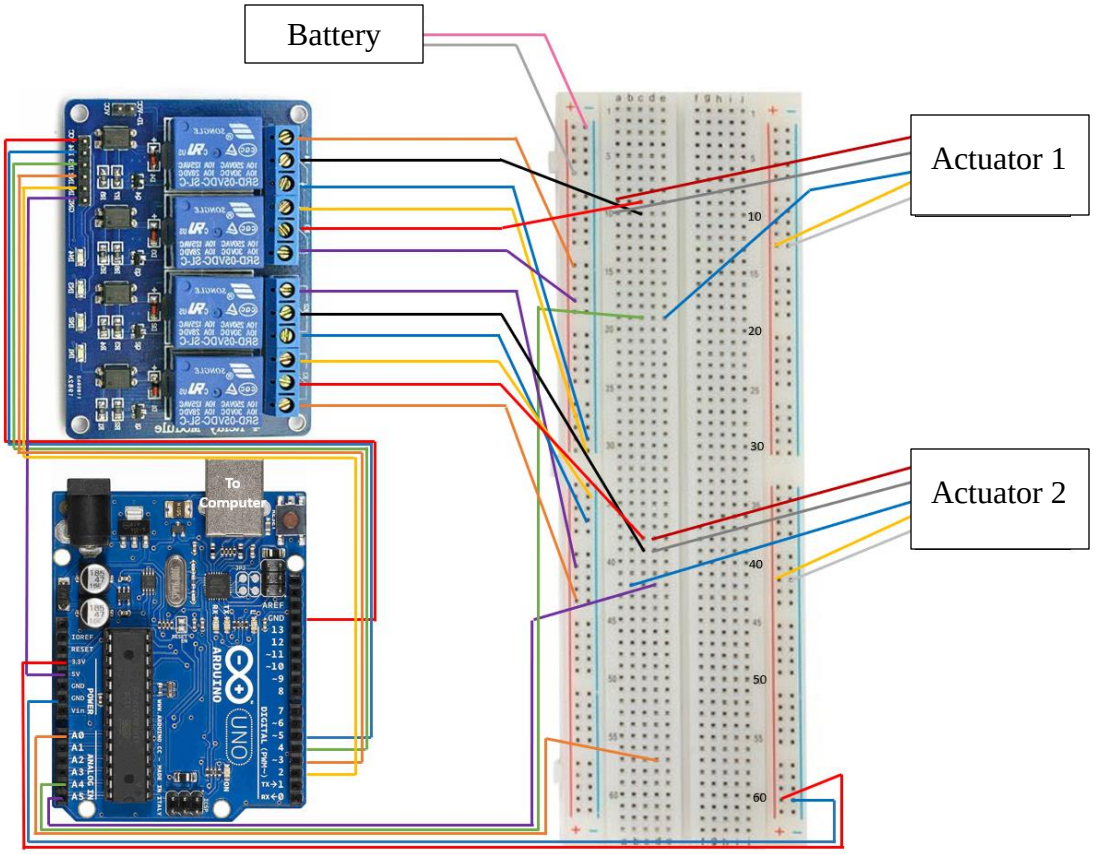

***Figure 5**: Image of the electrical setup that powered the actuator movement. The setup includes an Arduino Uno, a relay, and a breadboard.*

2.3 Processes

The outlined processes were intended for completion in March of 2020, but due to complications from COVID-19, was not completed. The procedures are still included for reference.

Vein Preparation

Bovine jugular veins were used for testing the fatigue apparatus. After obtaining fresh veins from a local meat processing plant, the veins were dissected to remove any muscle, fat, and tissue surrounding the vein. The vein was then trimmed down to a 1.5-inch section containing a valve at least .3 inches away from the edge. Valve formation is variable, because it is dependent on changes in blood pressure within the vein during development. The location of the valves within the veins

are not uniform. Valves can be located by running water through the vein. The presence of a valve is indicated by a bulge in the vein from the prevention of water flow through the valve. The presence of a valve can be confirmed by turning the vein inside out to observe the valve leaflets.

The sectioned vein was then attached to heat-shrink wrap. Prior to vein attachment, the heat shrink wrap was cut into 1.5-inch pieces. One inch was placed around the PVC connection on the fatigue apparatus and shrunk to fit. The other half inch was shrunk to match the diameter of the vein using a 5/16- inch metal rod. The vein was then pulled around the 5/16-inch end of heat shrink and attached using a running suture. This was repeated for both ends of the vein.

Fatigue Testing

After vein preparation, the fatigue apparatus was prepared for testing. The side of the diaphragm facing the testing chamber was filled with .6% *v/v* saline solution and all tubing was secured after filling. The heat-shrink wrap attached to the vein was loaded into the testing chamber and attached to the PVC pipe within. The acrylic chamber was then filled with .6% *v/v* saline solution so that the vein was submerged during testing. The saline solution is intended to mimic an *in vivo* environment.

After the physical setup was completed, the electrical components were plugged in following the electrical specifications. The battery was plugged into an electrical outlet and the Arduino and NI-Max were plugged into the computer. First, the calibration script was uploaded, and the output recorded and used to update the actuation script. Next, the actuation script was uploaded, allowing the actuators to move. The NI-Max can be started at this time as well. Both will run continuously.

The fatigue apparatus can then be ran for the required time, 14.5 days. Further discussion on the required length of operation is explored in *Section 3.2*.

2.4 Pressure Measurements

For official testing, the pressure transducers would be connected to a National Instruments device (NI-cDaq 9174) that would record and compile the data into an Excel spreadsheet. Because the corresponding software couldn't be loaded onto a personal laptop, the pressure transducer was adapted to work with an Arduino Uno. The pressure transducer was connected to the Arduino with the black wire to ground, the red wire to 5V, the white wire to A0, and the green wire to A1. A code to read the analog input from A1 was used to obtain pressure values.

The pressure tests conducted were not performed with any veins in the testing chamber. Rather, the pressure transducer was connected directly to the tube extending from the diaphragm to get a direct pressure reading. Therefore, the pressure reading shown in *section 3.2* represents the maximum pressure possible. The analog output from the Arduino was converted into a voltage value using equation 1. The voltage value was then converted to pressure using values obtained from a three- point calibration. To calibrate the transducer, the analog output was recorded at three known pressures, and the voltage (y) was graphed against the known pressure values (x) to obtain a line of best fit. The inverse slope and y-intercept were then plugged into equation 2.

$$Voltage = (analog\ input) * \frac{5}{1023} \quad (1)$$

$$Pressure = \big(Voltage - (Calibration\ y - int)\big) * \frac{1}{Calibration\ slope} \quad (2)$$

$$Pressure\ = (Voltage - 1.72193) * 138.2488$$

Article III. Results

The main product of this project was the construction of the accelerated venous valve fatigue apparatus. This included a complete redesign and re-construction from the previous model. The final product is pictured in **Figure 6** with all the parts labeled. This image of the final apparatus can be compared to the computer animated design depicted in **Figure 3**. The pressure transducer can be easily connected between the diaphragm and testing chamber, and the overflow chamber is not shown to the right of the testing chamber. The diaphragm was measured to push approximately 180 mL.

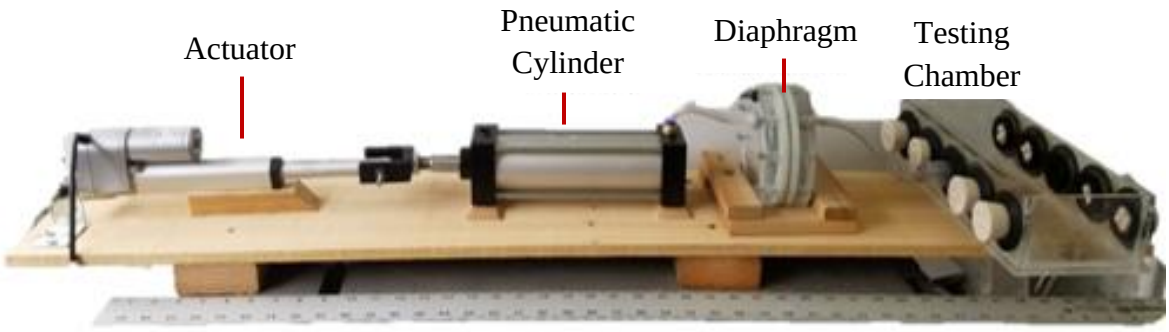

***Figure 6**: Final assembled product of the accelerated venous valve fatigue apparatus.*

3.1 Data

The data from this experiment consisted of pressure readings obtained using the Adinstrument pressure transducer connected to an Arduino Uno. **Table 1** depicts the pressure reading, actuator position, and pressure difference values at specific times across three cycles. **Figure 7** shows the same information, but as a continuous graph. The information from **Table 1** is derived from the data shown in **Figure 7**.

***Table 1**: Comparison of pressure measurements based off actuator position.*

Time (s)	Actuator Position	Pressure (kPa)	Pressure Difference (kPa)
0	Retracted	74.119	27.181
22	Extended	100.47	.828
32	Retracted	70.065	31.235
44	Extended	101.150	.1524
57	Retracted	70.741	30.559
67	Extended	97.769	3.5309

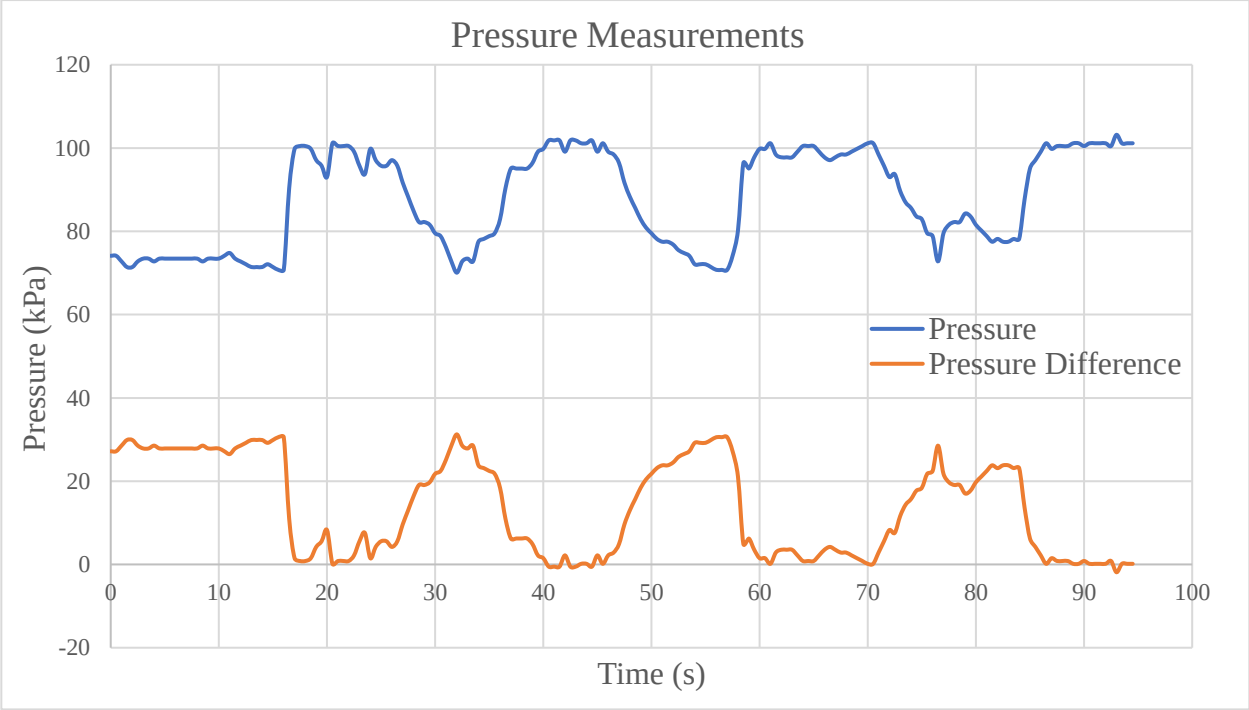

***Figure 7**: Graph of pressure measurements and calculated pressure differences across the valve.*

3.2 Discussion

The use of a diaphragm driven by a pneumatic cylinder was a novel pursuit for this application. Mechanical diaphragm pumps are positive displacements pumps that are used in most industries requiring fluid transfer. The diaphragm was intended to separate the saline solution that would flow through the vein, from the pneumatic cylinder. Traditionally, pneumatic cylinders are used

to push air. Using the pneumatic cylinder to push water directly through the vein may lead to oxidation of the metal and subsequent contamination of the testing fluid. In addition, use of liquid in the pneumatic cylinder could also remove any lubrication that resides within. It was shown that the diaphragm could push a maximum of approximately 180 mL.

The pressure tests show that an average pressure difference of 27.24 kPa was created when the actuator was in the extended position. Venous valve studies researched implemented pressure differential ranges from approximately 10 mmHg to 40 mmHg, or 1.33 to 5.33 kPa, while all were very vague about the specific pressure required for valve closure (4, 2). Most papers simply refer to a significant increase in pressure which causes the valve to close. Nevertheless, the pressure created by the apparatus greatly exceeds what might be required for the valve to close. In addition to causing the valve to close, the valve must also open when the actuator is retracted. Specifications for a prosthetic venous valve require that the valve be open at pressure gradients less than 5 mmHg or .667 kPa (9). The data indicates that the apparatus is able to create a low enough pressure gradient but is not consistent.

The pressure measured is the maximum pressure from the diaphragm created at the full extension of the pneumatic cylinder, six inches. If a vein were to be attached to the machine, then a small drop in the maximum value should be expected. **Figure 8** depicts this relationship. Leakage through the valve can be expected due to the delay between the increase in pressure and time it takes for the valve to close in response. The leakage rate should not be expected to be greater than 1 mL per minute (9).

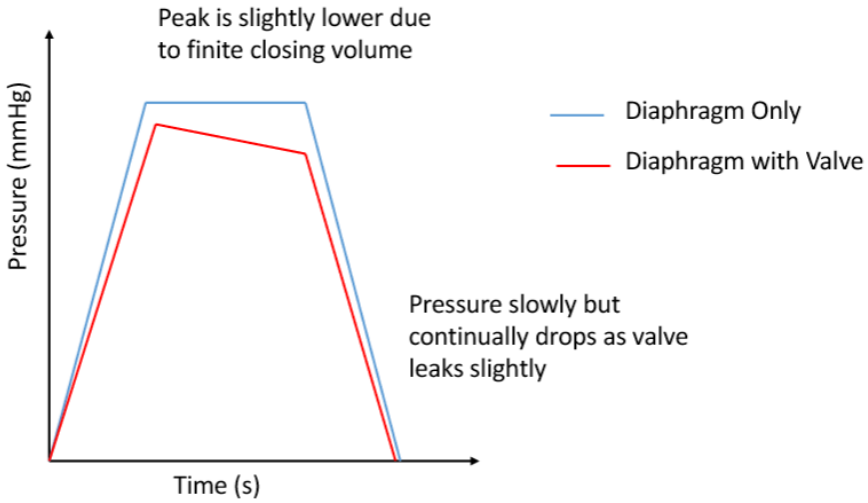

***Figure 8**: Relationship between pressure measured from diaphragm only compared to pressure measured with vein*

A venous valve prosthetic would need to be tested for 500,000 cycles of opening and closing (8, 9). Although the previous fatigue apparatus claimed to run at 4 cycles per second, the actuators only completed one cycle of movement every 6 seconds. The actual rate was likely less than the estimated. The rate is limited by the speed at which the actuator moves. By decreasing the distance the actuator is required to move, the cycles per minute can be increased. If the actuator were to move 2 inches for one vein, it would take about 2.5 seconds per cycle and 14.47 days to complete 500,000 cycles. 14 days may seem long, but it is a reasonable time frame compared to the 100 days required for heart valve testing. Improvements to the fatigue apparatus to increase speed are discussed in *Article V. Future Work*.

Article IV. Conclusion

A prosthetic venous valve from a bovine jugular valve is a promising treatment method for Chronic Venous Insufficiency currently being researched. Prosthetic valves require accelerated wear

testing prior to clinical trial approval. The goal of this project was to both redesign a venous valve fatigue apparatus and conduct testing of the apparatus to quantify its effectiveness. A diaphragm driven by a pneumatic cylinder, replaced the syringes that failed in the previous experiment to successfully reconstruct the apparatus. It was proven that the diaphragm was able to create a maximum pressure difference averaging about 27.24 kPa, enough to force the valve to close. In theory, the apparatus should function as intended based on the pressure measurements taken. Overall, all design criteria were met. Unfortunately, the experiment was cut short, so testing of the apparatus with a vein wasn't conducted to provide further evidence.

Article V. Future Work

As the search for a viable venous valve prosthetic is ongoing, it is important to continue further studies on possible candidates that can be used as a prosthetic. This project set out to improve on a previous design and can still be improved further. The current setup could be adapted to accommodate more veins to maximize efficiency. The current size of the diaphragm allows a maximum of two to three veins, based on the pressure created versus the pressure required to close the valve. Increasing the size of the diaphragm would allow for more veins to be accommodated. If the size of the diaphragm was increased without increasing the number of veins, the distance the actuator would be required to move to create the same pressure would decrease. This would increase the possible number of cycles per minute. Another possible future direction is the conversion of the current horizontal setup into a vertical one to better simulate the constant blood pressure that venous valves experience.

The second objective of this project was to establish quantitative data that proves that the apparatus is functional. Although pressure is what drives the valves to open and close, further testing should

be done to characterize the effects of the fatigue apparatus. As mentioned in *Section 1.1*, mechanical testing, microscopic surface inspection, and a measurement of the leakage are examples of tests that can be conducted. The effects of the fatigue apparatus could also be compared to *in vivo* fatigue in animal models. *Iwasaki et. al* indicates that fracture points are different when comparing an accelerated fatigue apparatus to animal valves in vivo, although both cases consistently fractured in areas of high strain concentration (10). This difference can be accounted for by the changes in viscoelastic properties of the membrane in physiological versus testing environments. A protocol would need to be developed to account for the difference in order to provide a more accurate understanding of long-term performance.

Another ongoing aspect of the project is the testing of different chemical fixation methods, comparing glutaraldehyde with another chemical, Chemical X. The venous valve fatigue apparatus constructed in this project, can be used to additionally characterize the effects and effectiveness of each fixation method over the long-term. Other tests that would further classify the effects of chemical fixation on a valve prosthetic include looking at collagen content, testing the valve under different blood pressures, and evaluating thrombogenicity and may be outside the scope of this experiment.

Article VI. Acknowledgements

Special thanks to Dr. Morton Jensen and Dr. Hanna Jensen for the guidance and support they have provided. I am grateful for the opportunity and experience these professors have extended to me through my participation in the Cardiovascular Biomechanics Lab. I would like to extend my gratitude to Megan Laughlin and Sam Stephens, for their continued help with troubleshooting and providing additional input in addition to Maxwell Bean and Evan Anderson for helping me despite working on different projects. I would also like to thank Olga Brazkhina for starting the project

and providing the foundation of the initial design. Thank you to Cockrums Meat Processing for always providing test specimens when needed, without them, previous testing would not have been possible. Thank you all.

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