MECHANICAL CHARACTERIZATION OF TRICUSPID BICUSPIDIZATION IN A PORCINE MODEL

by

Joshua Pataky

Georgia Institute of Technology
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SUMMARY

Tricuspid valve regurgitation currently affects over 1.6 million people in the US and largely uses annuloplasty ring deployment as the main method of correction for severe regurgitation. As this method inherently contains a number of risks, among others, the Kay bicuspidization procedure has been adapted for use as a transcatheter device. This procedure places anchors in the valve annulus on either side of the posterior leaflet and cinches them together, creating a bicuspid valve. The mechanics involved in this bicuspidization process, however, are poorly understood; this study looks to quantify those mechanics. Paired healthy and regurgitant porcine hearts were attached to a custom chamber, with regurgitation being induced through the topical application of 95% phenol. Tricuspid valve annular area, diastolic leakage, cinching tension, and annulus ellipticity are quantified at different cinching distances. As predicted, the use of phenol to induce tricuspid regurgitation is seen to be effective. The bicuspidization cinching reduces annular area and diastolic leakage in diseased case hearts to that of a “healthy” heart through altering the annulus geometry towards a more circular shape.

CHAPTER 1

INTRODUCTION

The heart contains four valves, the aortic, pulmonary, mitral, and tricuspid, which ensure unidirectional blood flow through the heart and thus the body. These valves are categorized as semilunar valves, the aortic and pulmonary, or atrioventricular valves, the mitral and tricuspid. The tricuspid valve (TV) separates the right atrium from the right ventricle and is made up of three leaflets, the anterior, posterior, and septal[1]. The TV annulus, the area surrounding the valve, is highly flexible and can lose its shape due to physical trauma, right ventricle dilation, or diseases such as rheumatic fever or infective endocarditis. This leads to improper valve closure, or coaptation of the leaflets, and a backflow of blood through the TV, known as tricuspid regurgitation (TR)[2]. TR presents itself in two forms: primary, where a lesion or damage to the valve structure causes the improper leaflet closure, or functional, where dilation of the annulus and right ventricle cause improper leaflet coaptation and thus regurgitant flow[3]. When left untreated, tricuspid regurgitation can cause significant cardiac remodeling which eventually leads to heart failure and death[4].

TR affects 1.6 million individuals in the United States and has a very poor one-year survival rate of 63.9% when at moderate to severe levels[5]. TR presents no visible symptoms until reaching severe levels, often resulting in late diagnosis. When this diagnosis does eventually come, patients are likely too high-risk to undergo the corrective surgery that is needed[3].

When tricuspid regurgitation becomes too severe to be corrected with medication, surgical procedures are employed. The current gold standard involves the implantation of an annuloplasty ring to bring the valve annulus back to a normal shape and reduce its area, allowing the leaflets to close properly[6,7]. While annuloplasty surgeries are effective at reducing regurgitation, there is an inherent amount of risk associated with open-heart surgery. Additionally, due to the late diagnosis of TR, patients are not approved to undergo this open-heart procedure. To combat this risk and treat these unapproved patients, several transcatheter devices are currently under development that are based on various corrective methods, including the surgical annuloplasty, edge-to-edge leaflet repair, and valve bicuspidization. The Kay bicuspidization procedure, which has been adapted for percutaneous use in the Trialign procedure[8] and is the method used here, cinches the TV at the posterior leaflet, turning the three-leaflet valve into a two-leaflet, or bicuspid, valve[9].

The bicuspidization procedure has been seen to be effective at reducing tricuspid regurgitation in preliminary clinical trials and compassionate use cases[4,8,10]. The mechanics involved of this procedure however have not been studied and it is important for medical professionals to have a full understanding of this corrective method. The goal of this study is to quantify the mechanics and planar geometry of the TV annulus involved in the Kay procedure. The bicuspidization will be replicated through the use of a novel *ex-vivo* testing technique and a custom-designed apparatus. To account for the lack of rhythmic contractions, hearts will be placed in contractile and relaxing solutions to simulate both active and passive contraction states. Cinching tension, tricuspid annulus area (TAA), diastolic leakage (DL), and ellipticity are all recorded during testing to be used in gaining a better understanding of this corrective method.

CHAPTER 2

METHODS AND MATERIALS

Heart Preparation

Adult porcine hearts (n = 12) were obtained from a local slaughterhouse (Holifield Farms, Covington, GA) and placed in a 100mM KCl (n = 6) or passive EDTA (n = 6) solution until testing could be performed, replicating active and passive states of the heart respectively. To perform the bicuspidization procedure, the tricuspid valve was first prepared before the heart was attached to the testing chamber. The tricuspid valve was exposed by removal of the atria, and optical markers were placed around the tricuspid annulus for area tracking. Two cinching sutures were implanted in the tricuspid annulus, 3 cm apart on either side of the posterior leaflet, 5 mm superior to the leaflet attachment edge, as per the Trialign procedure[8].

Chamber Design

The chamber design used was custom-built to prevent any alteration to the natural geometry of the TV or compromise the pressurization of the right ventricle. As can be seen in figure 1, the heart was mounted to the chamber through the left ventricle and was hydrostatically pressurized to 25 mmHg through the pulmonary artery to close the TV. After the heart was mounted inside the chamber, the cinching lines were anchored to a unidirectional slider with a coupled force sensor to measure the tension over the cinching distance. When attaching the cinching lines to the slider, care was taken to ensure the force applied was acting uniaxially when cinching. As porcine heart sizes vary, the pulley system used was made to be adjustable, allowing it to sit as close to the cinching lines as possible and obtain accurate tension results regardless of heart size and shape. One camera was placed with its lens in plane with the TV annulus to track annular area, while another was used to track DL by the water volume drop used to pressurize the right ventricle over the course of the bicuspidization.

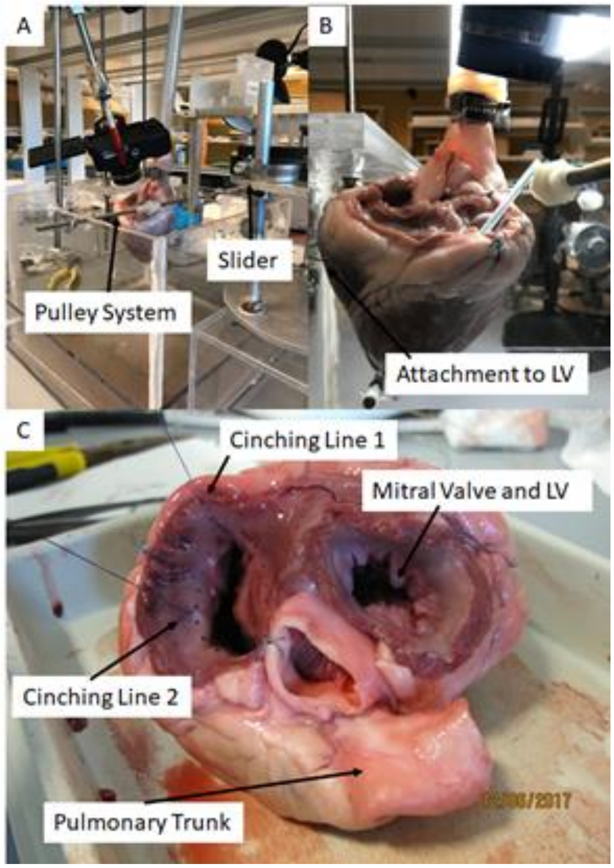

Figure 1: Testing set-up and heart before and after mounting to the chamber. **A**. The heart mounted in the chamber. The bar used to vary the location of the pulley can be seen along with the slider to ensure a unidirectional force is applied. **B**. Close-up view of the heart mounted to the chamber. Wires used to mount the heart are connected to the left ventricle (LV) to maintain integrity of the right ventricle. **C**. The heart before mounting. The two cinching lines implanted in the annulus and the graphite markers can clearly be seen. The pulmonary trunk, which is used for hydrostatic pressurization, is also visible.

Cinching Procedure

Over the course of the bicuspidization cinch, annular area was measured through recording of the optical markers around the annulus. Additionally, diastolic leakage was measured by quantification of the change in volume in the water column over time. As the cinching distance increased, the force applied to the cinching lines was recorded through a custom LabView VI. After initial pressurization, measurements were taken at cinching distances of 1, 2, 3, and 4 cm. After the experiment was completed in the healthy porcine heart, 95% phenol, which has been shown to effectively induce TR[10], was topically applied and the procedure was repeated for the diseased, regurgitant case. Video analysis was again performed to capture TAA and DL measurements at each cinching distance. Matlab and Excel were used to quantify the annular area, diastolic leakage, and cinching tension.

Data Analysis

Data obtained for TAA, DL, and cinching tension is reported as mean ± standard deviation, with statistical significance determined by the analysis of variance test and a post-hoc t-test. TAA was obtained through video recorded of the TV annulus, DL by measuring water drop in the pressurization tube through the valve, and tension recorded by the load cell on the unidirectional slider. To analyze the planar geometry of the valve during the bicuspidization, the ellipticity was tracked by relating the valve's large and small radii through the equation: $e = \sqrt{1 - \frac{large\ radius}{small\ radius}}$ (**Equation 1**). When *e* approaches 0 the geometry is more circular than elliptical.

CHAPTER 3

RESULTS

Tested hearts were split into four distinct groups: Active Healthy (n = 6), Active TR (n = 6), Passive Healthy (n = 6), and Passive TR (n = 6) depending on whether they were placed in KCL or EDTA solutions and if testing was done before or after phenol application. To ensure TR was effectively induced by topical phenol application, TAA dilation was evaluated, with the target being a 25% increase. For the passive hearts, the are increased by 22.5 ± 6.1%, while in the active hearts area increased by 27.2 ± 3.0%. When looking at the DL increase between healthy and TR hearts, it increased by a factor of 4.34 ± 0.74 and 4.44 ± 1.8 for the passive and active hearts, respectively.

The cinching was performed at 1 cm increments over a total distance of 4 cm, resulting in 5 points of data collection for each heart in the four groups. As can be seen in figure 2, the maximum cinching tension was comparable between all cases, resulting in no statistically significant difference between the groups. There was, however, a statistically significant increase in TAA at all cinching distances but one between the healthy and TR cases in the active and passive states. Over the 4cm cinch, normalized annular area decreased in the active TR cases by 21.1% and in the passive TR cases by 19.0%, bringing the TAA to not significant differences when compared to the uncinched hearts in the healthy cases. This decrease in annular area over the course of the cinch led to a decrease in recorded diastolic leakage in both the active and passive TR cases, reductions of 52.0% and 43.6% respectively (Fig. 3).

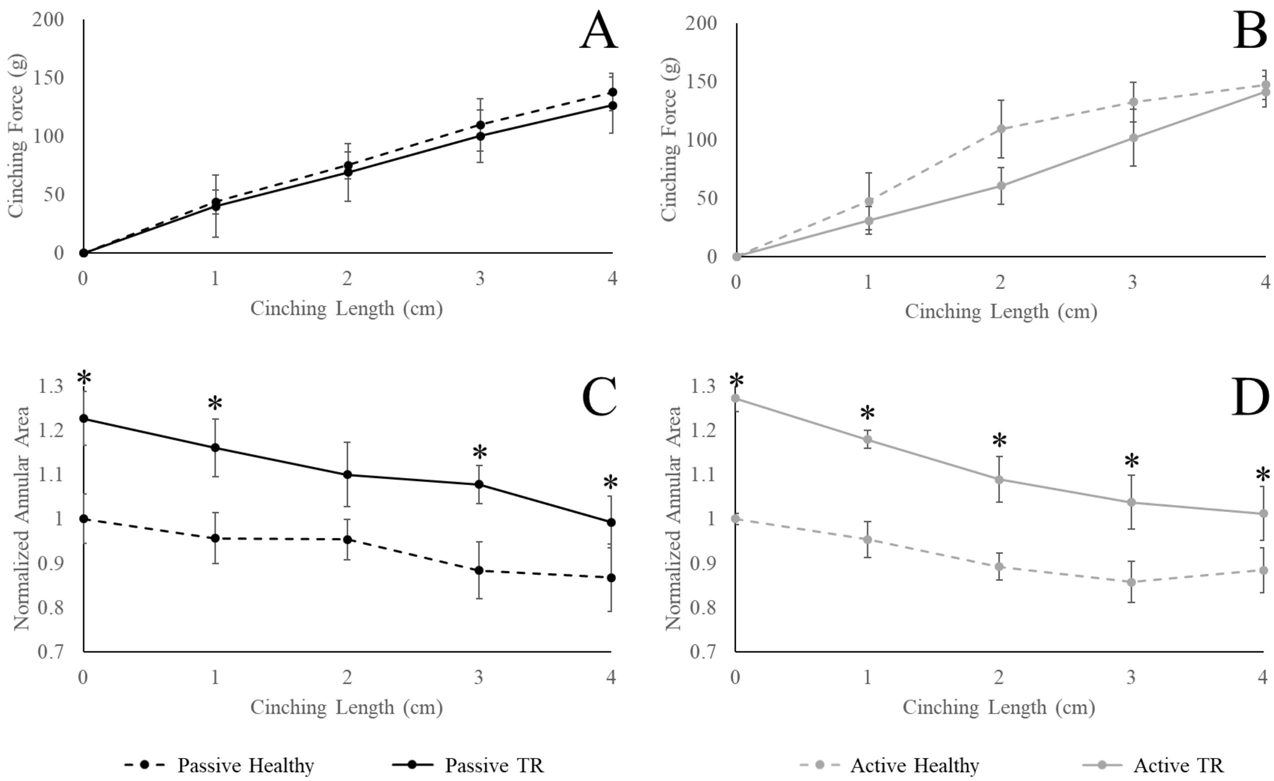

Figure 2: Cinching tension and annular area measurements at each cinching distance over the 4cm cinch used in bicuspidization of the TV. (*) indicated a statistically significant difference between the healthy and TR cases ($p<0.05$). **A:** Cinching tension of the passive hearts at cinching lengths. **B:** Cinching tension of the active hearts at cinching lengths. **C:** Annular area of the passive hearts normalized by the healthy uncinched area. **D:** Annular area of the active hearts normalized by the healthy uncinched area.

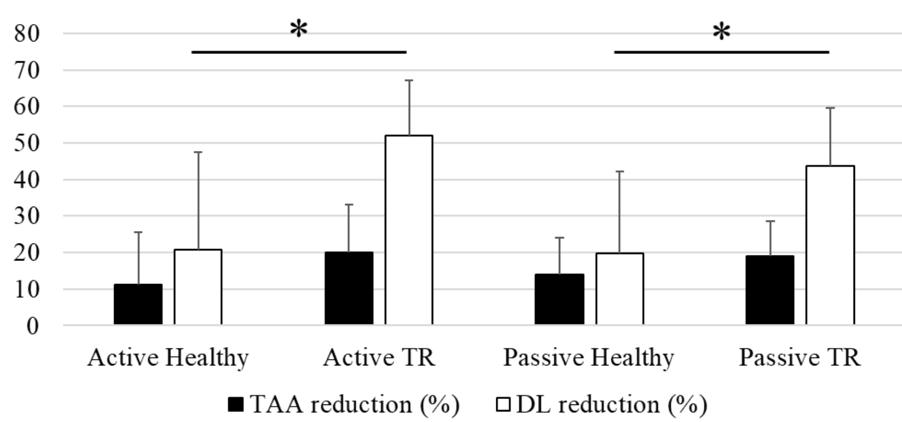

Figure 3: Tricuspid annulus area and diastolic leakage reduction after bicuspidization of TV. (*) indicate $p<0.05$,

Data from one heart sample in each of the active and passive cases is shown in figure 4 as a representation of the TAA data obtained during the bicuspidization cinching procedure. Plotted is the annular area of the uncinched and max cinched annulus area in both the healthy and TR states.

Figure 4: Plots of representative TV annular area at uncinched and maximum cinched distances. A) Active KCl case annular area. B) Passive EDTA case annular area.

While bicuspidizing the TV it was noticed that the shape of the valves' annulus become more circular and the cinching distance increased. The ellipticity (Fig 5) at the maximum cinching distance was significantly lower than when uncinched ($p = 0.04$ for passive healthy, $p = 0.01$ for passive TR, and $p = 0.01$ for active healthy) for all groups but the active TR case ($p = 0.10$). Topically applying phenol to induce TR did not significantly change the ellipticity of the annulus, with $p = 0.27$ for passive states and $p = 0.40$ for active states.

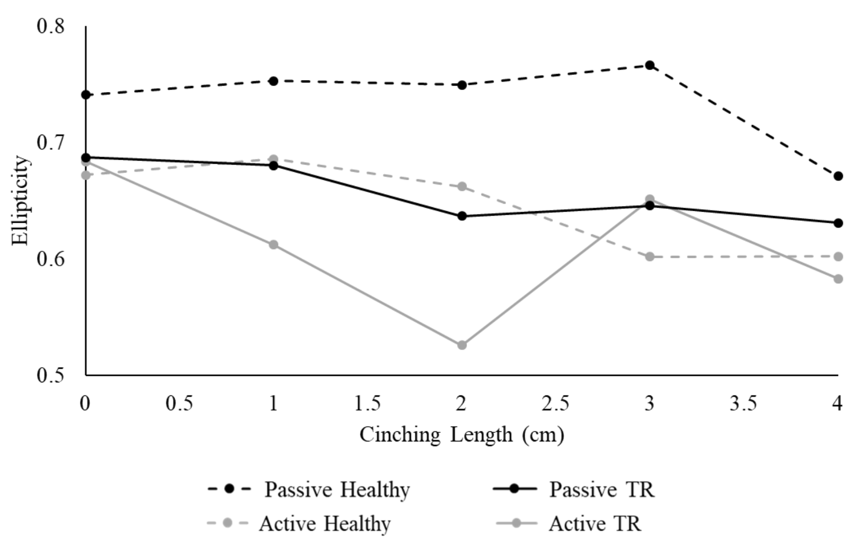

Figure 5: Ellipticity values calculated with equation 1 at each cinching length for all heart groups.

CHAPTER 4

DISCUSSION

The increase in TAA seen in both the active and passive TR cases shows that this method of regurgitation induction is effective and can be used when creating a porcine model of moderate TR, seen as an increase of 25%. The resulting increase in DL due to this increase in annular area in both the active in passive states was substantial. By topically applying phenol to dilate the annulus, functional TR was induced, rather than using trauma to increase regurgitant flow and causing primary TR. As FTR is the more common type of regurgitation, this model will be more impactful when used in developing corrective devices.

Porcine hearts used in this study varied greatly in size, making it crucial to normalize the annular area between all samples for an accurate comparison. Uncinched annular area ranged from 7cm^2 to 13cm^2 in size. The normalization factor used was the annular area of the uncinched healthy case of each heart. At maximum cinching distance in the TR cases, TAA was decreased to levels that are seen in normal healthy hearts, showing that this method of FTR correction is effective at reducing the dilation causing the regurgitation. This decrease in area also resulted in a significant decrease in leakage through the valve. Not only was the annular area decreased by the cinch, but the volume leaking through was also reduced, showing the effectiveness this method has in correcting FTR.

Despite the various sizes of the hearts and TV annulus areas that were seen in the hearts tested, the cinching tension needed to bicuspidize the annulus over a maximum distance of 4 cm had no significant difference between the healthy and TR cases. While this was done outside the body without heart contractions, by replicating the active and passive states seen in the cardiac cycle, it is believed that these tension values obtained would remain comparable when the bicuspidization is performed in a living, contracting heart.

While the change in annular geometry was noticeable visually during the bicuspidization, calculating the ellipticity showed the annulus becoming significantly more circular in all groups tested but the active TR hearts. The natural shape of the TV annulus is elliptical in the 2D plane, which this procedure is drastically changing. It is important to note the topical application of phenol did not significantly alter the geometry of the annulus, further proving this is a good method of inducing FTR in a porcine model.

CHAPTER 5

CONCLUSION

The approach used in this study creates an effective model of functional tricuspid regurgitation in porcine hearts by increasing the annular area and the diastolic leakage through the tricuspid valve by topical application of 95% phenol to the annulus. The application of phenol effectively increased the annular area to the threshold of a 25% increase for what is considered moderate functional tricuspid regurgitation. Additionally, the custom device setup used to replicate the bicuspidization procedure not only accurately functions but does so in both the passive and active states of the heart, as replicated by the use of contractile KCl and relaxing EDTA solutions to soak the hearts in pre-cinching. In both these states, the force needed to reach maximum cinching is comparable, meaning this procedure will not differ when performed *in* vivo. At maximum cinch of the TR case, annular area was brought back to the range of a healthy heart before cinching, showing the effectiveness of this method in eliminating the annulus dilation seen in TR. The DL was significantly reduced as well at the maximum cinching distance. The geometry of the TV annulus however was greatly altered in shape, becoming more circular than the natural elliptical shape, which could alter the flow of blood through the valve *in vivo*.

CHAPTER 6

FUTURE WORK

The sample size used in this study was relatively small, so more samples would increase the statistical power. Observing the coaptation of the newly bicuspidized valve is crucial for fully understanding the resulting valve anatomy from this procedure. μCT imaging can be used to observe and measure leaflet coaptation before and after cinching of the TV with pre and post scan comparisons. This will also show the 3D shape of the valve, rather than simply looking at the planar geometry as done here. Additionally, while porcine hearts are a good stand-in for human hearts, more impactful and clinically relevant results could be obtained if this bicuspidization procedure is replicated in a human heart model. Finally, while topical application of phenol increased TAA to levels seen in moderate TR, the mechanical properties of the tissue could have been altered, potentially skewing results. Testing hearts with naturally occurring TR would eliminate the need for inducing it and thus preventing this limitation. As seen by the results presented here, either the passive or active state could be used to test in a human heart model, so long as consistency is maintained throughout testing.

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