Effects of Cinching Force on the Tricuspid Annulus: A Species Comparison

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Abstract

Purpose: Tricuspid annuloplasty rings are commonly used to cinch an enlarged tricuspid annulus back to its original shape and size in patients with severe functional tricuspid regurgitation. However, the invasive operation is contraindicated for patients at risk for reoperation. Fortunately, transcatheter repair procedures, currently in the development process, are minimally invasive alternatives to current repair techniques. This study aims to determine the species-dependence of cinching force with the potential of informing transcatheter repair design by quantifying the minimum required cinching force necessary to reduce tricuspid regurgitation.

Methods: The cinching force necessary to reduce the septal-lateral diameter of a dilated annulus was quantified and compared in ten ovine hearts and nine porcine hearts. Additionally, a deparaffinization protocol and Verhoeff-Van Gieson stain were used to compare the microscopic structure of tissue samples at different stages of the experimental procedure in the two species.

Results: The maximum annulus dilation observed for the porcine was 11.2%, and the maximum cinching force was 0.40 ± 0.12 N. As previously demonstrated, ovine hearts yielded a maximum annulus dilation and cinching force of 8.82% and 0.38 ± 0.09 N respectively. Histological stains revealed no gross tissue differences between ovine and porcine septal or free wall tissues.

Conclusion: The cinching force was not species dependent between ovine and porcine models. This study is an essential first step for determining which animal model should be utilized for the development of transcatheter devices.

Keywords: Cardiac mechanics; Tricuspid valve; Transcatheter repair; Species comparison

Introduction

Functional tricuspid regurgitation (FTR) is a form of heart valve disease that has been linked with morbidity when in conjunction with mitral, aortic, or pulmonary valve complications [1]. FTR commonly occurs as a result of circumferential dilation of the tricuspid annulus. The dilation becomes concerning when coaptation between the three leaflets of the tricuspid valve is insufficient in prevent regurgitation [2-5]. Surgical treatment is often undertaken when the annulus dilates to an area greater than 40 mm² [2,6,7]. The treatment options for FTR which include DeVega-suture, Kay bicuspidization, and tricuspid annuloplasty rings require open-heart surgery and are typically done only in adjunct to mitral valve repair [2,6,7]. Currently, the most widespread treatment for FTR is the annuloplasty ring. A tricuspid annuloplasty is used to cinch the enlarged tricuspid annulus back to its original shape and size with the aim of halting regurgitation [8]. Notably, the first annuloplasty operation is low risk for patients who qualify for open heart surgery. However, recurrent regurgitation is seen in 20% of the population and reoperation yields a morbidity rate up to 37% [9,10]. Tricuspid annuloplasty is contraindicated in patients due to the invasive procedure and high risk of reoperation [11]. Fortunately, transcatheter repair procedures such as TRAIPTA, TRcinch, and Mitraling are in the development process and are minimally invasive alternatives to current tricuspid repair techniques [12-14]. For further development of transcatheter repair techniques, animal studies are necessary to insure efficacy and safety of these treatments.

Aim

The aim of this study is to determine if cinching force is species-dependent. Specifically, we will 1) compare the cinching force necessary to reduce the area of a dilated annulus and 2) compare microscopic structure of tissue samples at different stages of the experimental procedure in both ovine and porcine models. This study has the potential to inform the minimum cinching force that a transcatheter treatment should produce to reduce regurgitation.

Materials and Methods

Cinching of the annulus—the methodology used to defrost, dilate, cinch, and pressurize the porcine heart was previously established in this lab for the ovine model [15]. The same conditions of non-pressurize (NP) (control), pressurize (P), and dilated-pressurize (DP) were used on the porcine model. When sizing the annulus in the porcine hearts, the T32 sizer was used to normalize the tricuspid annulus (Figure 1). Additionally, the pressure was increased to 32 mmHg due to the size of the porcine hearts. Statistical analysis was conducted to determine statistical differences between models, conditions, and pulling distances using SPSS (version 22.0, IBM).

Histology

Tissue was isolated, fixed using 10% formalin for 24 hours, washed using physiological bath solution (PBS), and dehydrated using
progressive alcohol concentrations. Samples were sent to the UT Health Science Center at San Antonio Histology/Immunohistochemistry Lab to be embedded in paraffin wax, sectioned to a thickness of 3mm and placed onto slides. Once the slides were prepared, they were subjected to a deparaffinization protocol and Verhoeff-Van Gieson stain applied for histological analysis [16].

Statistical analysis

All measurements are shown as mean ± standard deviation (SD). Two way ANOVAs were used to test for interactions between the two independent variables on each of the five dependent variables. The two factors in this study were pulling distance (0 mm to 24 mm) and condition of the valve (NP, P, DP). The dependent variables were force, area, leakage, septal-lateral diameter, and anterior posterior diameter. In addition, a Tukey post hoc test was used to determine significance for all dependent variables according to pulling distance and condition. A 2-tailed t-test for two samples with unequal variance was used to determine statistical difference in the percent reduction in the septal-lateral diameter divided by force between ovine and porcine hearts. After standardizing the cinching force with the area of the tricuspid valve, a two-sample t-test assuming equal variances was implemented to determine if there was a significant difference between the ovine and porcine models.

Results

This study utilized nine porcine hearts and ten ovine hearts. Data is displayed with a mean ± standard deviation. While the pulling distance increased for all three conditions (NP, P, DP), the cinching force increased and the annulus area, anterior posterior, and septal-lateral distances decreased (Figure 2). Reduction in leakage of the porcine specimen was only observed in relation to the pulling distance when the valve was in the DP condition.

After chemical dilation by phenol, an increase in annulus area and leakage was observed in both ovine and porcine species. Porcine valve area increased from the P to DP state by 11% (6.5 cm² ± 0.9 cm² to 7.2 cm² ± 0.7 cm²) (Figure 3). Leakage increased by 275% (8 L/min ± 5 L/min to 30 L/min ± 10 L/min) with dilation of the valve. Additionally, phenol increased the septal-lateral dimension by 11% (2.8 cm ± 0.3 cm to 3.1 cm ± 0.3 cm) and the anterior posterior dimension by 3.1% (3.2 cm ± 0.3 cm to 3.3 cm ± 0.2 cm). As pulling distance increasing from 0 mm to 24 mm the septal-lateral and anterior posterior diameters decreased in both species. An 18% decrease (2.8 cm ± 0.3 cm to 2.3 cm ± 0.3 cm) was observed in the P condition and 23% (3.1 cm ± 0.3 cm to 2.4 cm ± 0.3 cm) in the DP condition in the porcine specimen. Similarly, the anterior posterior dimension decreased 25% (3.2 cm ± 0.3 cm to 2.4 cm ± 0.3 cm) for the P condition and 27% (3.3 cm ± 0.2 cm to 2.4 cm ± 0.2 cm) in the DP condition. While the leakage in the DP condition was reduced by 56% (1.8 cm ± 0.7 cm to 0.8 cm ± 0.3 cm) with pulling distance, the leakage in the P condition stayed constant at 0.41 L/min ± 0.05 L/min.

Notably, in the ovine specimen a similar pattern was seen with a reduction in leakage of the DP condition with pulling distance but no decrease in leakage in the P condition with pulling distance [15]. Overall, the histological stains revealed no gross tissue differences between ovine and porcine septal or free wall tissues (Figures 4 and 5). The difference in the integrity of tissues that are not cinched, cinched, and are dilated with phenol and cinched can be observed in Figure 6.

Discussion

In this study, the cinching force required to bring a dilated annulus back to its original size was not dependent on species. The cinching force for the porcine model was determined in the same manner as the ovine model, as a combination of the tissue resistance force and the transvalvular pressure force [15]. The resultant of these two forces is demonstrated in both the P and DP conditions of the valve. The NP condition, in which no transvalvular pressure was applied, represents tissue resistance force. For both the ovine and porcine models, the force due to tissue resistance is significantly smaller (p < 0.05) than the transvalvular pressure force at peak systolic pressure. With the addition of phenol to the porcine annulus, an increase in septal-lateral (S-L) diameter of 6.2% was observed as well as an increase of 14.6% to the
the valve. For our experiment, ovine and porcine heart models were
265% to 56% allocating more of the pressure force from the leakage to
from 82% to 26% of the original dilation, the pig was reduced from
as pulling distance was increased. While the ovine leakage was reduced
be as a result of the larger leakage decrease in the dilated porcine valve
similar until approximately 0.1N, where there is diversion. This may
area between the pig and sheep for a given cinching force are very
ventricle. Notably, it was found that there was no significant difference
between the two models (p=0.29) when normalizing the cinching force
Comparison to human tricuspid valves can be made. This was a quasi-
comparison study looking at differences in cinching force. Studies have
selected due to having a tricuspid annulus physiologically similar to
that of humans. Thus, it can be inferred that the data from porcine and
ovine models will have similar cinching forces and reductions in
area to humans. To the best of our knowledge, this is the first species
comparison study looking at differences in cinching force. Studies have
been conducted to determine the biaxial mechanical properties of heart
tissues in human, porcine, and ovine models [18]. The study was done
on coronary sinus tissue in which a significant difference was found
between the animals and humans. In the animal model, tissue was more
compliant and provided a lower interaction force than that of the human
model. Given that the average human heart was 85 ± 10 years, stiffness
observed may be explained by the patients’ elderly age [18]. Knowing
the difference between animal models is important in the development
of new surgical techniques and interventions, which can be effected
by the mechanical properties of the tissue. New developments of
transcatheter techniques such as TRclinch, and Mitraling have taken
this technique to human tests; however, no data has been produced
yet. Both of these methods work by introducing a cinching force inside
of the right atrium to reduce the tricuspid area, leading to a decrease
in regurgitation and restoration of the coaptation depth of the leaflets
[14] TRAIPTA conversely works on the exterior of the heart by placing
customized tension along the atrioventricular groove compressing
both the tricuspid and mitral valve. While TRIPITA is less invasive than
open-heart surgery it still ruptures through the right atrium to extend
to the outside of the heart [19].

This study has some limitations that should be addressed. Only two
animal models were compared; neither mode was human, thus no direct
comparison to human tricuspid valves can be made. This was a quasi-
static experiment where we only looked at the 2D area of the annulus in
peak systole pressure, meaning that no systemic loading was simulated
in the heart. While FTR is commonly diagnosed with an enlargement
of the annulus, the 3D area also has an effect on leaflet function. For
future studies the coaptation depth would be an important experiment
to determine how well treatment bring the leaflets back together as
well as conducting this study on human hearts in order to have a direct
comparison. However, this study, which was the first study comparing
species differences in cinching force, was an essential first step in
understanding the minimum required cinching force a transcatheter
treatment must produce to reduce regurgitation.

Acknowledgments

The authors would like to thank their sources of funding: National Center for
Advancing Translational Sciences, National Institutes of Health, through Grant UL1
TR001120. Institute for Integration of Medicine & Science/Clinical & Translational
Science Award (IIMS/CTSA) grant, St. Mary’s Research grant, and Maximizing
Access to Research Careers (MARC) fellow training aid. This work would not have
been possible without the support of the the Engineering Department at St. Mary’s
University, Dr. Tim Raabe, Ray Jaszcz, Dr. Anna Lurie, Rey Balli, Evelia Salinas,
and Miguel Pelayo for their help in this work. The Authors would also like to thank Dr.
Haimanti Banerjee (University of Pittsburgh) for help in finding the relevant papers.

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