Tricuspid Valve Anterior Leaflet Strains in Ovine Functional Tricuspid Regurgitation

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Functional tricuspid regurgitation (FTR) is thought to arise due to annular dilation and alteration of right ventricular (RV) geometry in the presence of normal leaflets, yet mitral leaflets have been shown to remodel significantly in functional mitral regurgitation. We set out to evaluate tricuspid valve anterior leaflet deformations in ovine FTR. Eleven animals (FTR group) underwent implantation of a pacemaker with high rate pacing to induce biventricular dysfunction and at least moderate TR. Subsequently, both FTR (n = 11) and Control (n = 12) animals underwent implantation of 6 sonomicrometry crystals around the tricuspid annulus, 4 on the anterior leaflet, and 14 on RV epicardium. Tricuspid valve geometry and anterior leaflet strains were calculated from crystal coordinates. Left ventricular ejection fraction and RV fractional area change were significantly lower in FTR animals versus Control. Tricuspid annular area, septo-lateral diameter, RV pressures were all significantly greater in the FTR group. Mean TR grade (+0-3) was 0.7 \pm 0.5 in Control and 2.4 \pm 0.5 in FTR (P = < 0.001). The anterior leaflet area and length increased significantly. Global radial leaflet strain was significantly lower in FTR mostly driven by decreased free edge leaflet strain. Global circumferential anterior leaflet strain was also significantly lower in FTR with more remarkable reduction in the belly region. Rapid ventricular pacing in sheep resulted in a clinically pertinent model of RV and annular dilation with FTR and leaflet enlargement. Both circumferential and radial anterior leaflet strains were significantly reduced with FTR. Functional TR may be associated with alteration of leaflet mechanical properties.

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Keywords: Trisuspid Valve, Functional tricuspid regurgitation, Sonomicrometry



Reconstruction of the geometric shape and strains of tricuspid valve anterior leaflet

Central Message

During the evolution of ovine functional tricuspid insufficiency, anterior leaflet remodeled and became stiffer. Altered leaflet mechanical properties may contribute to the pathogenesis of FTR.

Perspective Statement

Our experimental data suggest that leaflet enlargement may be a compensatory mechanism in functional tricuspid regurgitation, however, pathological stiffening may perturb this adaptive process. Further studies investigating biochemical pathways underlying leaflet remodeling may define targets for leaflet-specific therapy to improve treatment of functional tricuspid regurgitation

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Abbreviations: 3D, three-dimensional; TA, tricuspid annulus/tricuspid annular; TV, tricuspid valve; FTR, functional tricuspid regurgitation; RV, right ventricle/ventricular; LV, left ventricle/ventricular; RV-FAC, RV fractional area change; RVP, RV pressure; LVP, left ventricle pressure; CVP, central venous pressure; FMR, functional mitral regurgitation; ES, end systole; ED, end diastole; EIVC, end of isovolumetric contraction; EIVR, end of isovolumetric relaxation; S-L, septo-lateral

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INTRODUCTION

Functional tricuspid regurgitation (FTR) is thought to result from altered tricuspid annular (TA) size and right ventricular (RV) geometry in the setting of anatomically normal leaflet and chordal structure.^{1,2} The consequent leaflet tethering and reduced coaptation are recognized as the main pathomechanisms of FTR.^{2,3} However, experimental⁴ and clinical⁵ studies on ischemic mitral regurgitation bring into question a solely "functional" etiology of secondary tricuspid insufficiency. Our prior studies of ovine functional mitral regurgitation revealed that although valve tissue appears grossly normal, mitral leaflets remodel significantly during the disease process⁶ with changes in leaflet composition, structure, and valve cell phenotype.⁷ Furthermore, ex vivo mechanical tests conducted on human mitral leaflets and chordae from congestive heart disease showed significant alterations and fibrosis that could contribute to insufficient leaflet coverage of the valve orifice.⁵ Although valve interstitial cell stiffness⁸ and hemodynamic milieu differ between the mitral and tricuspid valves, it is not unreasonable to conjecture that similar processes are at work in the pathogenesis of FTR. Indeed, clinical studies have shown that tricuspid leaflet area increased by 49% in patients with pulmonary hypertension with those developing severe FTR demonstrating inadequate leaflet remodeling relative to annular and ventricular dilation.9 Similar echocardiographic findings have been reported in functional mitral insufficiency.¹ Addressing TA dilation with ring annuloplasty represents the current therapeutic approach of surgical FTR treatment,¹¹ yet leaflet remodeling may offer an adjunctive target. As little is known regarding leaflet tissue remodeling in FTR, we set out to investigate tricuspid valve leaflet mechanical behavior in an ovine model of tachycardia induced cardiomyopathy with FTR.

MATERIALS AND METHODS

The study was approved by our local Institutional Animal Care and Use Committee. All animals received humane care in compliance with the Principles of Laboratory Animal Care formulated by the National Society for Medical Research and the Guide for Care and Use of Laboratory Animals.

Twenty-three healthy male sheep were used in the experiment. Eleven animals (FTR Group) underwent pacemaker implantation with subsequent high rate pacing to induce biventricular cardiomyopathy and FTR. After completion of the pacing protocol, animals underwent sonomicrometry crystals implantation on cardiopulmonary bypass and subsequent data collection. Remaining 12 animals underwent sonomicrometry crystals implantation only and served as controls (Control Group).

Pacing Protocol

FTR sheep underwent pacemaker implantation according to the surgical protocol previously described in detail.¹² A monopolar pacing lead was sutured onto the lateral LV wall and exteriorized through the thorax to a subcutaneous

pacemaker (Medtronic Consulta CRT-P, Minneapolis, MN). After 4–5 days of recovery, high rate pacing was initiated as previously described.¹² Animals were paced for 15.5 \pm 3.5 days at a rate of 200–240 beats/min until left ventricular dysfunction (left ventricular ejection fraction <30%) and at least moderate FTR were both seen on surveillance transthoracic echocardiography.

Terminal Surgery

The terminal surgery was performed on both groups. The animals were anesthetized and mechanically ventilated. While on the cardiopulmonary bypass and with the heart beating, each animal underwent implantation of 24 sonomicrometry crystals (Sonometrics Corporation, London, Ontario, Canada) as described in our previous studies.^{12,13} Six (2 mm) crystals were implanted around the TA and 4 (1 mm) were sutured on the anterior leaflet in a diamond shape (Fig. 1). The anterior leaflet was used due to its largest surface area and most consistent anatomy. Additional 14 crystals were implanted along 3 equators on the right ventricle (RV) free wall epicardium. Pressure transducers (PA4.5-X6; Konigsberg Instruments, Inc, Pasadena, CA) were placed in the left ventricle (LV) and RV through the apex and in the right atrium. The atriotomy was subsequently closed and the crystal wires externalized. Due to severe LV dysfunction after rapid pacing, FTR animals received epinephrine and milrinone for weaning from cardiopulmonary bypass and epinephrine (0.2 mcg/kg/min) was maintained during data acquisition. Data collection was performed with the chest open, 30 minutes after achieving the stable hemodynamic state in all animals. At the conclusion of the experiment, the animals were euthanized by administering sodium pentothal (100 mg/kg IV). The heart was excised and proper placement of annular and anterior leaflet crystals was confirmed. Next, the tricuspid valve was excised and prepared for anterior leaflet area measurement.



Figure 1. Location of the sonomicrometry crystals implanted during terminal surgery on the tricuspid annulus and anterior tricuspid leaflet.

Sonomicrometry Data

Sonomicrometry data were acquired at 128 Hz with simultaneous LV, RV, and right atrial pressure and electrocardiographic recordings. Three consecutive cardiac cycles during normal sinus rhythm were used for data analysis. Threedimensional crystal coordinates acquired from the SonoSoft software (Sonometrics Corporation) were subsequently analyzed in MATLAB (MathWorks, Natic, MA) using custom written code. Methodology described in our previous work¹³ was applied to approximate the mean shape of the tricuspid valve leaflets from the crystal coordinates. The mean data set for each group was computed based on eleven animals. The cardiac cycle of each animal was divided into 4 segments: (1) enddiastole (ED) to end-isovolumic contraction, (2) end-isovolumic contraction to end-systole (ES), (3) ES to end-isovolumic relaxation, and (4) end-isovolumic relaxation to ED of the next cardiac cycle. Subsequently, the linear interpolation was applied to all crystal positions segment-wise throughout the cardiac cycle. Finally, the resampled data between all animals from each group was averaged. To create smooth representations of the native anterior leaflet surfaces, the modified loop subdivision algorithm¹⁴ and an iterative optimization procedure were applied.¹⁵ ED was defined as the peak of the R-wave on the electrocardiographic recording and ES as time of maximum negative dP/dt of LV pressure.

Echocardiographic Protocol

All study animals underwent epicardial echocardiography during pacemaker implantation to evaluate baseline biventricular function and valvular competence as described previously.¹² Transthoracic echocardiography was performed every 3 days during the pacing protocol to assess heart failure progression. The final epicardial echocardiography was performed during the terminal surgery for both groups. Tricuspid regurgitation was assessed before initiation of cardiopulmonary bypass and crystal implantation and subsequently during sonomicrometry data acquisition. The degree of valvular insufficiency was assessed using American Society of Echocardiography criteria. The grading included comprehensive evaluation of color flow and continuous-wave Doppler. Tricuspid and mitral regurgitation was graded accordingly and categorized by an experienced cardiologist as none or trace (0), mild (+1), moderate (+2), or severe (+3).

Data Analysis

Tricuspid Valvular Geometry and Kinematics

TA area was calculated based on 3D coordinates of the 6 annular crystals using splines¹⁶ while the septo-lateral (S-L) annular diameter was determined as the distance between the mid-septal and anteroposterior commissural crystals (Fig. 1). Anterior leaflet length was computed based on spline fit of the mid-anterior annular crystal, mid-belly crystal, and free edge crystal. Anterior leaflet angles were calculated as an angle between annular plane and a vector leading from mid-anterior

crystal to the free edge crystal. Leaflet excursion angle was calculated as a difference between maximal opening and minimal closing angles. Anterior leaflet tenting height was calculated as a perpendicular distance from the least-squares TA plane to the leaflet-free edge crystal. RV volume was calculated using the convex hull method based on 3D coordinates of all annular and RV epicardial crystals.

Anterior Leaflet Strains

Anterior leaflet strains in the beating ovine heart were calculated based on anterior leaflet crystal coordinates using methodology formerly described.¹³ In particular, Green-Lagrange circumferential, longitudinal and areal strains were calculated for global leaflet area, leaflet belly, and leaflet free edge. Areal strains combine changes in circumferential and longitudinal directions and thus represent the directionally independent total deformation. Average anterior leaflet strains were calculated for each leaflet region with ED as the reference state.

Anterior Leaflet Area

To measure anterior leaflet area, all tricuspid valves were excised immediately after euthanasia, laid flat on a cutting board with a calibration grid, and floated on saline before acquiring images. Using a custom Matlab program, we loaded all images and manually selected approximately 100 points on the anterior leaflet annulus, free edge, and along the commissures. Subsequently, cubic spline segments were fit through these discrete points and computed their inscribed area (Fig. 2).

Statistics

Statistical analysis was performed using SAS Enterprise Guide software, Version 7.1 of the SAS System for Windows



Figure 2. Tricuspid valve anterior leaflet on the cutting board with calibration grid. The blue line outlines anterior leaflet border used for computation of inscribed area.

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(copyright 2014 SAS Institute Inc., Cary, NC). Descriptive statistics are provided as mean \pm standard deviation for normally distributed numeric variables while median [25th,75th percentile] is reported for non-normally distributed numeric variables. Normally distributed numeric variables were analyzed using a 2-sample independent t-test. If the normality assumption was not met a Wilcoxon rank sum test was used. Tricuspid valve and mitral valve regurgitation were analyzed using a Fisher's Exact test and expressed as frequency (percent). Due to technical acquisition problems, hemodynamic and sonomicrometry data were not usable in one Control animal.

RESULTS

The average weight of the animals was 61 ± 3 kg and 62 ± 5 kg for Control and FTR sheep, respectively, and did not differ significantly (*P* = 0.559). At the time of the terminal study, degree of tricuspid insufficiency in Control and FTR sheep did not differ before and after crystal implantation.

Hemodynamics

Table 1 summarizes hemodynamic, echocardiographic, and sonomicrometry data in Control and FTR animals. Left ventricular ejection fraction and RV fractional area change were significantly lower in FTR animals consistent with biventricular failure induced by rapid pacing. RV pressures and RV volumes

Table 1. Hemodynamics				
Group	Control (n = 11)	FTR (n = 11)	P Value	
HR (min ^{-1})	115.5 [111.5, 120.0]	128.0 [120.0, 132.0]	0.049	
LVP _{MAX} (mm Hg)	95.9 ± 9.6	96.7 ± 16.3	0.892	
LV EF (%)	55.2 ± 3.8	23.4 ± 7.0	<0.001	
RVP _{MAX} (mm Hg)	$\textbf{29.1} \pm \textbf{4.9}$	50.6 ± 11.0	<0.001	
RVP _{ED} (mm Hg)	4.6 ± 2.3	16.7 ± 7.6	<0.001	
RV-FAC (%)	$\textbf{50.8} \pm \textbf{5.3}$	40.3 ± 7.4	0.002	
RV-Vol _{ED} (cm ³)	113.5 ± 14.8	163.2 ± 24.4	<0.001	
RV-Vol _{ES} (cm ³)	87.9 ± 12.3	138.6 ± 26.9	<0.001	
TR _{GRADE} (0-3)			<0.001	
0 -none/trace	3 (27.2)	0 (0.0)		
1 - mild	8 (72.7)	0 (0.0)		
2 - moderate	0 (0.0)	7 (63.6)		
3 - severe	0 (0.0)	4 (36.4)		

Values are means \pm standard deviation, median [25th,75th percentile] or frequency (percent); EF, ejection fraction; ES, end-systole; FTR, functional tricuspid regurgitation; HR, heart rate; LVP, left ventricle pressure; MAX, Maximum; RVP, right ventricle pressure; ED: end-diastole; RV-FAC, right ventricle fractional area change; RV-Vol, right ventricle volume (includes myocardium); TR, tricuspid regurgitation.

Variables were analyzed using a two-sample independent t-test or a Wilcoxon rank sum test. Tricuspid regurgitation grade was analyzed using a Fisher's Exact test.

at both ED and ES were significantly higher with FTR, while maximal LV pressure remained unaffected. Tachycardiainduced cardiomyopathy was associated with significant increase in FTR and mitral regurgitation.

TA Geometry and Leaflet Kinematics

TA geometry and anterior leaflet length and area in both groups are summarized in Table 2. Sonomicrometry derived TA area and S-L diameter increased significantly at both ED and ES in FTR animals as did tricuspid anterior leaflet length. Planimetry calculated anterior leaflet area also increased with development of tachycardia-induced cardiomyopathy. Anterior leaflet angles were substantially altered with decreased leaflet excursion suggesting depressed mobility (Fig. 3). Moreover, compared to Control, tenting height of anterior leaflet was significantly increased with FTR confirming leaflet tethering as a clinically observed pathophysiological phenomenon (Fig. 4).

Anterior Leaflet Strains

Mean tricuspid valve anterior leaflet strains are presented in Figure 5. Anterior leaflet areal strains did not differ between the groups, but global radial leaflet strain was significantly lower in FTR animals mostly due to the decreased free edge leaflet strain. Global circumferential anterior leaflet strain was also significantly lower in FTR with more remarkable reduction in the belly region. Figure 6 presents reconstruction of the mean geometric shape of the anterior leaflet. The color maps illustrate areal, radial, and circumferential leaflet strains at ES relative to ED. These data reveal decreased leaflet strain and suggest increased stiffness of the leaflet tissue (Fig. 7).

DISCUSSION

It is generally accepted that functional TR results from alterations in TA size and RV dimension and function which in turn produce valve tethering and impair leaflet coaptation.^{1,2} Tricuspid valve leaflets in FTR have long been considered to be

Table 2. Tricuspid Annular and Anterior Leaflet Geometry					
Group	Control (n = 11)	FTR (n = 11)	P Value		
Tricuspid annular					
geometry					
TA _{area ED} (cm ²)	$\textbf{6.8} \pm \textbf{1.0}$	$\textbf{8.9} \pm \textbf{1.2}$	< 0.001		
TA _{area ES} (cm ²)	$\textbf{6.5} \pm \textbf{1.3}$	$\textbf{8.8} \pm \textbf{1.3}$	< 0.001		
TA _{S-L diameter ED} (mm)	$\textbf{27.4} \pm \textbf{2.1}$	$\textbf{32.9} \pm \textbf{2.6}$	< 0.001		
TA _{S-L diameter ES} (mm)	24.9 ± 2.5	$\textbf{31.9} \pm \textbf{3.0}$	<0.001		
Anterior leaflet length					
Leaflet length ED (mm)	17.2 ± 4.8	21.4 ± 3.0	0.021		
Leaflet length _{ES} (mm)	$\textbf{19.8} \pm \textbf{3.8}$	$\textbf{23.6} \pm \textbf{3.2}$	0.017		
Anterior leaflet area					
Leaflet area (mm ²)	333.8	470.9	0.039		
	[310.5, 367.0]	[359.9, 584.6]			

Values are means \pm standard deviation or median [25th,75th percentile]; ED, end-diastole; ES, end-systole; FTR, functional tricuspid regurgitation; TA, tricuspid annulus/annular; S-L, septo-lateral.

Variables were analyzed using a two-sample independent t-test or a Wilcoxon rank sum test.



Figure 3. (A) Schematic representation of the tricuspid valve anterior leaflet opening and closing angle at end-diastole (ED) and end-systole (ES). (B) Tricuspid valve anterior leaflet angle presented as mean \pm standard error of the mean during the heart cycle in Control and FTR animals.; (C) Anterior leaflet angles at end-diastole (ED), end-systole (ES) and excursion angles in Control and FTR. Box and whisker charts: Box indicates range, 25th-75th percentile; vertical bar, median; square, mean; whiskers, max and min; points, individual data. Control: healthy animals under baseline conditions; *P* values were determined using a two-sample independent t-test. EIVC: end of isovolumic contraction; EIVR: end of isovolumic relaxation; FTR: study animals with tachycardia induced functional tricuspid regurgitation.

intact and unaffected, and thus possible tissue alterations ignored.¹ However, recent studies suggest that leaflet tissue is a contributor to the pathophysiology of functional mitral regurgitation (FMR),^{4,6} raising questions about its right-sided counterpart. This study is the first to investigate in-vivo tricuspid valve anterior leaflet strains in the setting of a clinically pertinent ovine model of FTR encompassing annular enlargement (approximately 30%) and RV dilatation and dysfunction as known pathophysiological triggers of FTR.^{1,2} Our data revealed that anterior leaflet enlarged while circumferential and radial leaflet strains were significantly reduced during evolution of FTR suggesting altered mechanical properties of leaflet tissue.

An ex vivo cadaveric study of mitral leaflets in patients with cardiomyopathy revealed larger leaflet areas than those of

patients without cardiac disease.¹⁷ This evidence of adaptive mitral leaflet remodeling has been confirmed by experimental in-vivo ovine studies¹⁸ and clinical echocardiographic reports.¹⁰ Furthermore, perturbation of normal mitral valvular loading patterns by pacing cardiomyopathy has been shown to affect valvular microstructure⁷ and human cadaveric mitral valves in congestive heart failure revealed significantly modified leaflet material properties suggesting valve remodeling.⁵ These data imply that FMR in patients with heart failure might not be purely functional, and leaflet tissue should not be considered intact. Anatomic and biochemical data are exposing the fallacy of such assumptions as normal mitral valvular tissue has been demonstrated to be richly innervated,¹⁹ and to have heterogeneous biochemical composition²⁰ and non-homogeneous deformation.²¹ These investigations remind us that



Tricuspid valve anterior leaflet tenting height

Figure 4. Schematic representation of the tricuspid valve anterior leaflet tenting height and comparison of this parameter between Control and FTR groups. The tenting height was calculated as a perpendicular distance from the tricuspid annular plane to the free edge crystal. Box and whisker chart: Box indicates range, 25th-75th percentile; vertical bar, median; square, mean; whiskers, max and min; points, individual data. Control: healthy animals under baseline conditions; FTR: study animals with tachycardia induced functional tricuspid regurgitation. *P* value was determined using a two-sample independent t-test.

atrioventricular valve leaflets are not inert flaps but rather active components of the valvular-ventricular complex capable of regulating valvular function in health and disease. Although no major differences in porcine mitral and tricuspid leaflet mechanics and structure have been demonstrated recently,²² the extrapolation of mitral findings to the tricuspid



Figure 5. Tricuspid valve anterior leaflet average strains in Control and FTR. Areal, radial, and circumferential strains are presented for global leaflet area (A), leaflet belly (B) and leaflet free edge (C). Diamonds with the green color filled visualize the region from where the leaflet strain was analyzed. Strain was referenced to end-diastole and is presented as mean ± standard error of the mean during the averaged cardiac cycle for all animals in each group. *P* values were determined using a two-sample independent t-test or a Wilcoxon rank sum test at end systole. Control, healthy animals under baseline conditions; ED, end-diastole; EIVC, end of isovolumic contraction; EIVR, end of isovolumic relaxation; ES, end-systole; FTR, study animals with tachycardia induced functional tricuspid regurgitation. (Color version of figure is available online.)



Figure 6. Reconstruction of the mean geometric shape of the anterior leaflet of the tricuspid valve. The color maps illustrate areal, radial, and circumferential leaflet strains at end-systole relative to end-diastole in Control and FTR. Red color indicates stretch whereas blue color indicates compression. Control, healthy animals under baseline conditions; FTR, study animals with tachycardia induced functional tricuspid regurgitation. (Color version of figure is available online.)

valve requires appropriate caution considering their different anatomy, physiology, and cells phenotypes.^{8,19} The presence of 3 leaflets of varying origins, dynamic TA folding,²³ and 3 papillary muscles with septal attachment yield a much more intricate valvular complex.^{23,24} In our study, anterior leaflet opening and closing angles were significantly altered indicative of subvalvular remodeling leading to leaflet tethering and increased tenting height. Similar observations were reported by Fukuda et al in their clinical study,² and together these data imply perturbation of forces acting on the tricuspid leaflets in the pathophysiology of FTR. Merryman⁸ showed that tricuspid interstitial cells are significantly less stiff than those from mitral valves suggesting that cells respond to local tissue stress by altering cellular stiffness and collagen biosynthesis. Our recent biomechanical studies on normal ovine tricuspid valves revealed that leaflet strains were largest in the anterior leaflet



Figure 7. The graphical presentation of the methods, results, and implications of the present study. Left side of the figure: simplified scheme of the methods. Upper central part of the figure: The tricuspid valve anterior leaflet tenting height in Control and FTR groups. Lower central part of the figure: Tricuspid valve anterior leaflet average strains in Control and FTR animals. Radial and circumferential strains are presented for global leaflet area. Upper right corner: Reconstruction of the mean geometric shape of the tricuspid valve anterior leaflet strains at end-systole relative to end-diastole in Control and FTR. *P* values were determined using a two-sample independent t-test or a Wilcoxon rank sum test at end systole. Box and whisker chart: Box indicates range, 25th-75th percentile; vertical bar, median; square, mean; whiskers, max and min; points, individual data. Control: healthy animals under baseline conditions; FTR: study animals with tachycardia induced functional tricuspid regurgitation. ED, end-diastole; EIVC, end of isovolumic contraction; EIVR, end of isovolumic relaxation; ES, end-systole.

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with greater magnitude in radial than circumferential direction,¹³ and that differences in leaflet microstructure correlated with varying biaxial mechanics among leaflets.²⁵ Anterior leaflet belly was found to have highest collagen concentration in normal ovine valves,²⁵ and this region showed reduced strain after development of FTR in our current model. Our study revealed that with development of FTR, anterior leaflet elongated and increased its area suggesting active tissue remodeling during the evolution of valvular insufficiency. Anterior leaflet was less prone to radial deformation especially in the edge region, and global circumferential strain was significantly lower in FTR group with more remarkable reduction in the belly region. These data imply tricuspid anterior leaflet remodeling corroborating clinical findings in patients with FTR associated with pulmonary hypertension9 and postmortem studies of FMR.¹⁷ Indeed, the anterior tricuspid leaflet lengthened by approximately 19% at ES in the current experiment which is similar to the 15% anterior and 19% posterior mitral leaflet lengthening reported previously in the same ovine model.⁶ Merryman⁸ hypothesized that leaflet interstitial cells react to local stress with increased collagen biosynthesis and tissue stiffness consistent with our findings of decreased radial leaflet strain with FTR. Moreover, the reduction in circumferential strain was more remarkable in the belly region possibly due to increasing stretching forces induced by annular dilatation as reported in finite element modeling of the mitral valve.²⁶ There are only few reports in the literature analyzing tricuspid leaflet strains. In normal porcine tricuspid leaflets in-vitro, Spinner et al²⁷ reported 21% areal strain for the anterior leaflet which is below our values of 65% for healthy ovine hearts and 37% for FTR. In a finite element analysis of healthy human valves, Kong²⁸ reported average strain values in the radial direction of 19%-26% for the anterior tricuspid leaflet. Strain in the circumferential direction appeared to be higher near the coaptation region while some compressive circumferential strains were observed near the annulus and commissural regions. We also observed strains in the anterior leaflet to be higher in the radial rather than the circumferential direction, although we did not report compressive strains. Overall, our study is consistent with prior findings in the ovine mitral valve.²⁹ Whether the above disparities are due to species differences or experimental conditions is unclear.

Surgically, the tricuspid valve has been the "forgotten" valve as it was widely held that most cases of significant TR would resolved by correcting left-sided valvular lesions.³⁰ However, this has been shown to be an unreliable strategy, leaving many patients with untreated significant TR.³¹ Prosthetic ring tricuspid annuloplasty represents the contemporary surgical approach for correcting FTR, yet offers suboptimal results in patients with severe TR,³² and aggressive annular reduction may be deleterious to regional RV function.¹² Our experimental data suggests leaflet lengthening in FTR may be a compensatory mechanism, and it has been shown clinically to reduce valvular insufficiency in patients with pulmonary hypertension.⁹ Leaflet augmentation³³ has been performed surgically to improve tricuspid valve repair, yet the ultimate target should be at the tissue level. Innovative studies of postinfarction ovine mitral valves have shown this to be a possibility as Losartan treatment was found to modulate fibrotic changes in the valve while maintaining adaptive growth through inhibition of TGF-B.³⁴ Such biochemical pathways remain to be studied in FTR but hold promise of an alternative therapeutic approach.

Conclusion

In conclusion, rapid ventricular pacing in sheep resulted in a clinically pertinent model of RV and annular dilation with FTR. During evolution of tricuspid insufficiency, anterior leaflet remodeled and became stiffer in both radial and circumferential direction. Observed leaflet growth may be a compensatory mechanism in FTR, however, pathological stiffening may perturb this adaptive process. These data suggest that altered leaflet mechanical properties may contribute to the pathogenesis of the FTR.

Limitations

The results of our research must be interpreted in the context of important limitations. This was an acute study performed open-chest with inherent effects of anesthesia on RV and valvular dynamics²³, and extrapolation of these data into clinical practice should be performed cautiously. Only anterior leaflet of tricuspid valve has been studied, therefore, in the context of heterogenous kinematics, biomechanics, and tricuspid valve leaflet structure^{13,25} further investigations are needed to fully understand the complexity of valvular remodeling. Sonomicrometry crystals themselves may have affected leaflet dynamics due to their weight and bending stiffness of their wires, but to minimize this effect we used smaller 1-mm crystals softer wires for leaflet sonomicrometry. Furthermore, no difference in valvular insufficiency was observed before and after crystal implantation in each group. Histologic and biomechanical data of the anterior leaflet are yet to be performed by our group, and at this time we cannot present a tissue correlation to the depicted sonomicrometry findings. These detailed data will be forthcoming in the near future.

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SUPPLEMENTARY MATERIAL

Scanning this QR code will take you to the article title page to access supplementary information.



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