

Effect of variable annular reduction on functional tricuspid regurgitation and right ventricular dynamics in an ovine model of tachycardia-induced cardiomyopathy

Tomasz Jazwiec, MD,^{a,b} Marcin Malinowski, MD,^{a,c} Haley Ferguson, BS,^a Jeremy Wodarek, BS,^a Nathan Quay, BS,^d Jared Bush, BS,^d Matthew Goehler, BS,^d Jessica Parker, MS,^d Manuel Rausch, PhD,^{e,f,g} and Tomasz A. Timek, MD, PhD^a

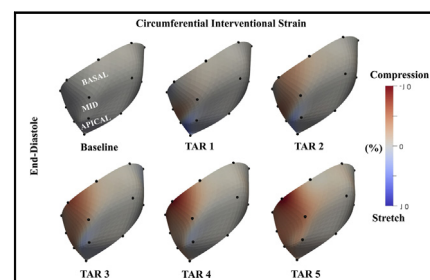
ABSTRACT

Objective: To investigate the effect of variable tricuspid annular reduction (TAR) on functional tricuspid regurgitation (FTR) and right ventricular (RV) dynamics in ovine tachycardia-induced cardiomyopathy.

Methods: Nine adult sheep underwent implantation of a pacemaker with an epicardial lead and were paced at 200 to 240 bpm until the development of biventricular dysfunction and functional TR was noted. During reoperation on cardiopulmonary bypass, 6 sonomicrometry crystals were placed around the tricuspid annulus (TA) and 14 were placed on the RV epicardium. Annuloplasty suture was placed around the TA and externalized to an epicardial tourniquet. After weaning from cardiopulmonary bypass, echocardiographic, hemodynamic, and sonomicrometry data were acquired at baseline and during 5 progressive TARs achieved with suture cinching. TA area and RV free wall strains and function were calculated from crystal coordinates.

Results: After pacing, changes in left ventricular (LV) ejection fraction and RV fractional area decreased significantly. Mean TA diameter increased from 25.1 ± 2.9 mm to 31.5 ± 3.3 mm ($P = .005$), and median TR (range, 0-3+) increased from 0 (0) to 3 (2) ($P = .004$). Progressive suture cinching reduced the TA area by $18 \pm 6\%$, $38 \pm 11\%$, $56 \pm 10\%$, $67 \pm 9\%$, and $76 \pm 8\%$. Only aggressive annular reductions (67% and 76%) decreased TR significantly, but these were associated with deterioration of RV function and strain. A moderate annular reduction of 56% led to a substantial reduction of TR with little deleterious effect on regional RV function.

Conclusions: A moderate TAR of approximately 50% may be most advantageous for correction of functional TR and simultaneous maintenance of regional RV performance. Additional subvalvular interventions may be needed to achieve complete valvular competence. (J Thorac Cardiovasc Surg 2019; ■:1-10)



Color maps of right ventricular free wall interventional strains.

CENTRAL MESSAGE

Tricuspid annular reduction of approximately 50% is most advantageous for correction of functional tricuspid regurgitation and maintenance of right ventricular function in ovine tachycardia-induced cardiomyopathy.

PERSPECTIVE

Current data offer insight into the effect of variable degrees of tricuspid annular reduction (TAR) on right ventricular (RV) dynamics and valvular competence in a clinically pertinent animal model. Our findings suggest that a moderate degree of TAR may achieve an optimal balance between adequate correction of functional tricuspid regurgitation and preservation of RV myocardial performance.

See Commentary on page XXX.

From the ^aDivision of Cardiothoracic Surgery and ^dResearch Department, Spectrum Health, Grand Rapids, Mich; ^bDepartment of Cardiac, Vascular and Endovascular Surgery and Transplantology, Medical University of Silesia in Katowice, Silesian Centre for Heart Diseases, Zabrze, Poland; ^cDepartment of Cardiac Surgery, Medical University of Silesia, School of Medicine in Katowice, Katowice, Poland; Departments of ^eAerospace Engineering and Engineering Mechanics, and ^fBiomedical Engineering, and ^gOden Institute for Computational Engineering and Science, University of Texas at Austin, Austin, Tex.

This study was supported by internal grants from Meijer Heart and Vascular Institute at Spectrum Health.

Read at the 45th Annual Meeting of the Western Thoracic Surgical Association, Olympic Valley, California, June 26-29, 2019.

Received for publication June 21, 2019; revisions received Oct 11, 2019; accepted for publication Oct 27, 2019.

Address for reprints: Tomasz A. Timek, MD, PhD, Spectrum Health, Michigan State University College of Human Medicine, 100 Michigan Ave NE, Grand Rapids, MI 49503 (E-mail: tomasz.timek@spectrumhealth.org).

0022-5223/\$36.00

Copyright © 2019 by The American Association for Thoracic Surgery

<https://doi.org/10.1016/j.jtcvs.2019.10.194>

Abbreviations and Acronyms

CSA	= cross-sectional area
ED	= end-diastole
ES	= end-systole
FTR	= functional tricuspid regurgitation
IV	= intravenous
LV	= left ventricle/ventricular
MR	= mitral regurgitation
RV	= right ventricle/ventricular
RVP	= right ventricular pressure
TA	= tricuspid annulus
TAR	= tricuspid annular reduction
TR	= tricuspid regurgitation
TV	= tricuspid valve



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

The tricuspid valve (TV) has recently become a focus of renewed clinical interest¹ due to the increasingly recognized deleterious effect of functional tricuspid regurgitation (FTR) on right ventricular (RV) function, mechanics, and geometry.^{2,3} Prosthetic ring annuloplasty provides surgical correction of FTR, but frequently has suboptimal results when severe tricuspid regurgitation (TR) or RV dilation are present preoperatively.⁴⁻⁷ These outcomes may be related in part to annuloplasty prosthesis sizing,⁶ with undersized annuloplasty shown to provide effective and durable TV repair.^{8,9} However, aggressive tricuspid annulus (TA) reduction (TAR) raises concerns about tricuspid stenosis¹⁰ and deleterious effects on myocardial function,⁹ as has been demonstrated experimentally in an ovine ischemic mitral regurgitation (MR) model.¹¹ Owing to more compliant myocardial structure, it is reasonable to conjecture that prosthetic TAR may have a greater effect on chamber geometry and function compared with left-sided annuloplasty. As such, the optimal degree of annular reduction to abolish FTR and affect ventricular geometry while maintaining myocardial function remains to be determined.

We recently showed in healthy sheep hearts that stepwise TAR with an adjustable suture annuloplasty favorably altered RV geometry but had a deleterious effect on RV myocardial performance when area reduction exceeded 50%.¹² In the present study, we set out to investigate the effect of variable degrees of TAR on valvular insufficiency and RV geometry, function, and strain in a

chronic ovine model of tachycardia-induced cardiomyopathy with FTR.

METHODS

All surgical and experimental procedures were performed in accordance with principles of laboratory animal care formulated by the National Institutes of Health Institute for Laboratory Animal Research *Guide for Care and Use of Laboratory Animals*. The study was approved by our local Institutional Animal Care and Use Committee.

Experimental Protocol

Pacemaker implantation. Twenty adult male sheep were used in the study. The surgical protocol has been described in detail previously.¹³ In brief, after a 7-day acclimation period, all animals had an external right jugular intravenous (IV) catheter placed under local anesthesia with 1% lidocaine and were subsequently anesthetized with propofol (2-5 mg/kg IV), intubated, and mechanically ventilated. General anesthesia was maintained with inhalational isoflurane (1%-2.5%) and fentanyl (5-20 µg/kg/minute). Arterial blood pressure measurements were performed through an 18-gauge left carotid artery catheter (Teleflex, Morrisville, NC). Using a left lateral mini-thoracotomy approach (10-15 cm, fifth/sixth intercostal space), a monopolar pacing lead was sutured onto the lateral LV wall (Figure 1, A). The lead was exteriorized through the thorax to a pacemaker (Consulta CRT-P; Medtronic, Minneapolis, Minn) placed in the subcutaneous pocket near the spine. Control epicardial echocardiography was performed through the mini-thoracotomy. The surgical incision was approximated in standard fashion, and intercostal nerves in the region were infiltrated with 0.25% bupivacaine. The animal was returned from the recovery area to the pen when breathing spontaneously, standing up, and eating. Prophylactic antibiotics (cefazolin 2 g IV every 12 hours and gentamicin 240 mg IV every 24 hours) were given for 10 days postoperatively starting with the preoperative dose.

Pacing protocol. After a 4- to 5-day recovery period, high-rate pacing was initiated as described previously.¹³ Animals were paced for a mean of 15.5 ± 3.5 days at a rate of 200 to 240 bpm until both LV dysfunction (LV ejection fraction <30%) and at least moderate FTR were seen on surveillance transthoracic echocardiography. Subsequently, the animals were returned to the operating room for the terminal study.

Terminal procedure. After sedation (with ketamine 2-3 mg/kg IV and fentanyl 100 µg IV) and additional local anesthesia (1% lidocaine subcutaneously), a tracheotomy was performed, and the mice were intubated and mechanically ventilated. General anesthesia was maintained with isoflurane (1%-2.5%) and fentanyl (5-20 µg/kg/minute), and muscle paralysis was achieved with vecuronium (0.1 mg/kg IV). The heart was exposed via sternotomy, the animal was fully heparinized, and the right carotid artery and right jugular vein were cannulated for cardiopulmonary bypass. Caval snares were placed around the superior and inferior vena cava. Once activated clotting time exceeded 480 seconds, normothermic cardiopulmonary bypass was initiated, both venae cava were snared, and the right atrium was opened. With the heart beating, each animal underwent implantation of 20 2-mm sonomicrometry crystals (Sonometrics, London, Ontario, Canada) using a 5-0 polypropylene suture (Figure 1, B and C). Six crystals were implanted around the TA (Figure 1, B), and an additional 14 crystals were implanted along 3 equators on the RV free wall epicardium defining 3 separate regions: basal, mid, and apical (Figure 2). Two layers of 2-0 polypropylene sutures were sewn around the TA anchored at the anteroposterior commissure and mid-septal annulus (Figure 1, B). The sutures, representing a DeVega-like annuloplasty, were externalized through the anteroposterior annulus to an epicardial tourniquet to allow for subsequent stepwise suture cinching and TAR. Pressure transducers (PA4.5-X6; Kongsberg Instruments, Pasadena, Calif) were placed in the LV and RV through the apex and in the right atrium. The atriotomy was subsequently closed, and the animal was weaned from cardiopulmonary bypass.

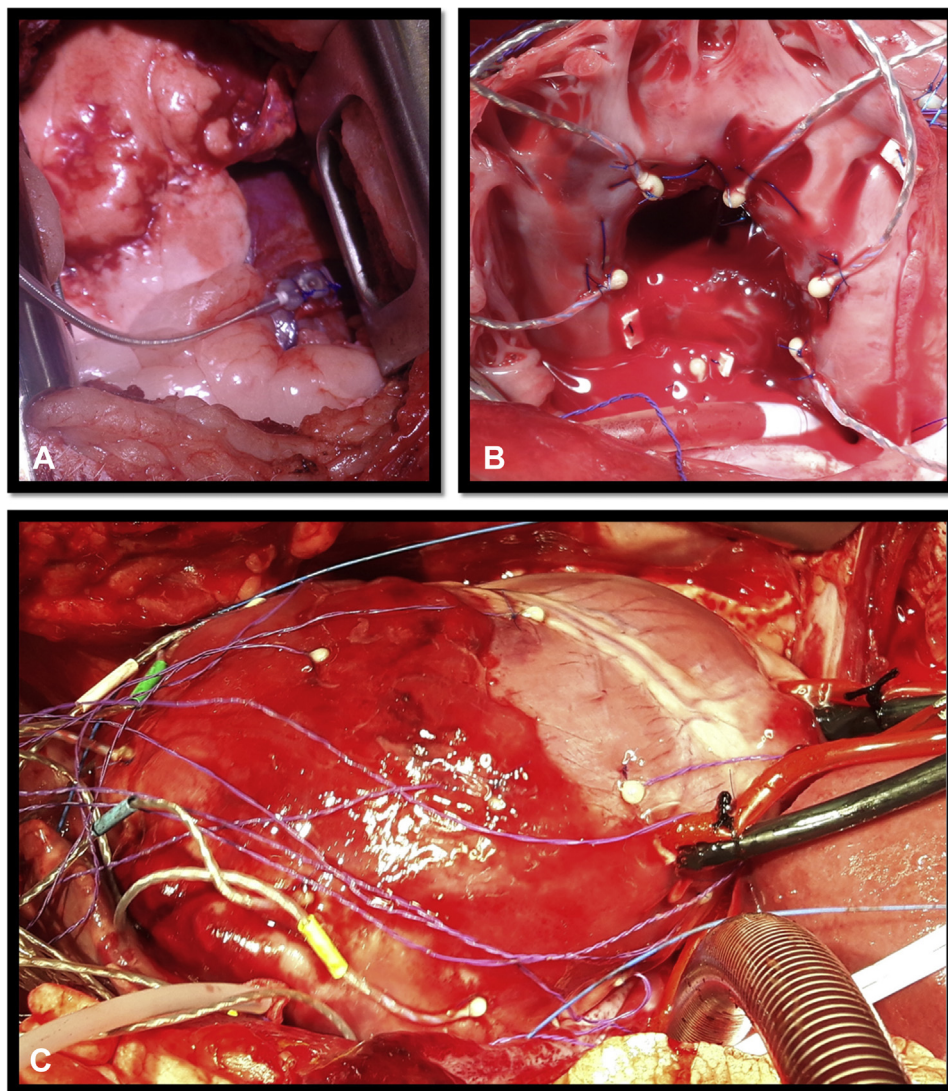


FIGURE 1. Intraoperative view of pacemaker lead implantation on the left ventricular lateral wall (A), tricuspid annular crystal arrangement (B), and sonomicrometry crystal placement on the right ventricular epicardium (C).

Postoperatively, a lidocaine IV drip (0.03 mg/kg/minute) was given to prevent ventricular ectopy. Epinephrine and milrinone were used for weaning from cardiopulmonary bypass, and epinephrine (0.2 μ g/kg/minute) was maintained during data acquisition. Data collection was performed with the chest open. All animals were observed for 30 minutes to allow for achievement of a stable hemodynamic state before echocardiographic and sonomicrometry data collection.

Echocardiographic Protocol

All animals underwent epicardial echocardiography during pacemaker implantation to evaluate baseline biventricular function and valvular competence. Subsequently, transthoracic echocardiography was performed every 3 days during the pacing protocol to assess the progression of heart failure. Pacing was paused 1 hour before each echocardiographic study and resumed once the study was completed. The final epicardial echocardiography study to evaluate biventricular function and valvular insufficiency was performed during the terminal procedure at baseline. Echocardiographic examination during TAR

was focused on measuring TR only. All images were acquired with a 1.5- to 3.6-MHz transducer and Vivid S6 ultrasound machine (GE Healthcare, Chicago, Ill). The degree of valvular insufficiency was assessed using American Society of Echocardiography criteria. The grading included a comprehensive evaluation of color flow and continuous-wave Doppler. TR was graded accordingly and categorized by an experienced cardiologist as none or trace (0), mild (+1), moderate (+2), or severe (+3). MR was categorized correspondingly. The flow across the TV was acquired to measure valvular gradients during progressive TAR (TAR 1-5).

Data Acquisition

The pacemaker was inactivated 12 hours before the terminal procedure. During the terminal procedure, sonomicrometry data were acquired using a digital ultrasonic measurement system (DS3; Sonometrics) after weaning from cardiopulmonary bypass and 30 minutes of hemodynamic stability as described previously.^{12,14} Sonomicrometry measurements were collected during three consecutive cardiac cycles in normal sinus rhythm

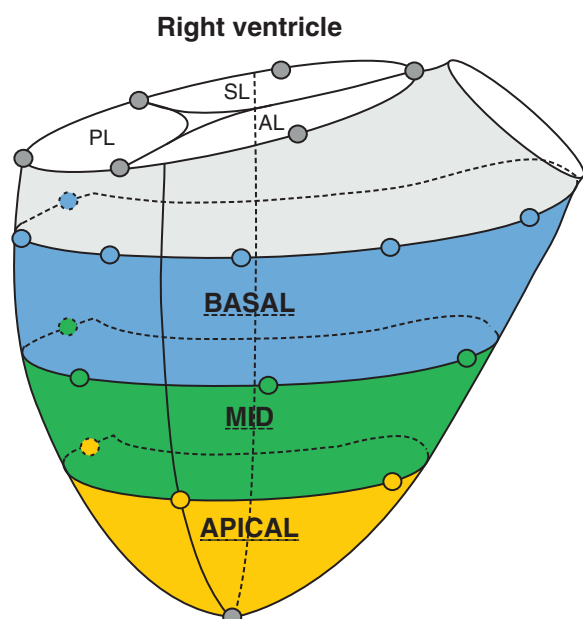


FIGURE 2. Schematic representation of the location of sonomicrometry crystals implanted around the tricuspid annulus and on the epicardium of the right ventricular (RV) free wall defining 3 RV free wall regions. PL, Posterior leaflet; SL, septal leaflet; AL, anterior leaflet.

before (Baseline) and after each of the 5 progressive TARs (TAR 1-5) induced with stepwise annuloplasty suture cinching. Data were acquired at 128 Hz with simultaneous LV, RV, and right atrial pressure and electrocardiographic recordings. The 3-dimensional crystal coordinates acquired using SonoSoft software (Sonometrics) were subsequently analyzed in MATLAB (MathWorks, Natick, Mass) using custom written code. To create smooth surface representations of the RV epicardial surfaces, the modified loop subdivision algorithm was applied.¹⁵ End-diastole (ED) was defined as the peak of the R-wave on the electrocardiographic recording, and end-systole (ES) was defined as the time of maximum negative dP/dt of LV pressure.

Data Analysis

TA area was calculated based on 3-dimensional coordinates of the 6 annular crystals as described previously.¹² The septolateral (S-L) annular diameter was calculated as the distance between the mid-septal and anteroposterior commissural crystals. As shown in Figure 2, blue, green, and yellow crystals were used to calculate basal, mid, and apical RV cross-sectional area (RV-CSA), respectively. RV-CSA change was calculated as $(RV-CSA_{ED} - RV-CSA_{ES})/RV-CSA_{ED} \times 100\%$. The RV radius of curvature was calculated as the radius of epicardial crystal curvature for the RV epicardium at each ventricular level (basal, mid, and apical). RV volume was calculated using the convex hull method based on all annular and epicardial crystals. RV epicardial strain was calculated based on epicardial RV crystal coordinates using a previously described methodology.^{16,17} Green-Lagrange strains were calculated for basal, mid, and apical regions of the RV free wall (Figure 2) in the circumferential and longitudinal directions (Figure 3). Average cardiac cycle strain, a measure of RV free wall regional function, was calculated for each ventricular region, with ED as the reference state. Areal cardiac strain, which combines both circumferential and longitudinal deformations of the RV epicardium, at baseline and during progressive TARs is shown in Video 1. Interventional strain, assessing the direct effect

of annular size reduction on RV function, was calculated at ED and ES for all interventions (TAR 1-5), with the same time points at baseline serving as the reference.

Statistical Analysis

Descriptive statistics are provided as mean \pm standard deviation for normally distributed numeric variables and as median (interquartile range [IQR]) for non-normally distributed numeric variables. Statistical analysis was performed using SAS Enterprise Guide 7.1 for Windows (SAS Institute, Cary, NC). Echocardiographic data at the time of pacemaker implantation (healthy animals) were compared with the data from the terminal study using the paired *t* test or Wilcoxon signed-rank test if the assumption of normality was not met. Baseline (heart failure) data were compared with annular cinching steps (TAR 1-5) using repeated-measures analysis of variance, and if the *P* value was $<.05$, then pairwise comparisons were done using Bonferroni correction. For non-normally distributed data, Friedman's analysis was used.

RESULTS

Nine animals (mean weight, 64 ± 5 kg) completed the pacing protocol and terminal procedure with successful acquisition of sonomicrometric, hemodynamic, and echocardiographic data. Two sheep died during the pacing period, and another 9 sheep were excluded due to pacemaker failure ($n = 1$), sonomicrometry crystal damage ($n = 2$), lack of significant heart failure and FTR at the completion of pacing protocol ($n = 1$), or inability to wean from cardiopulmonary bypass ($n = 5$).

After pacing, the mean LV ejection fraction on echocardiographic imaging decreased from $59 \pm 4\%$ to $28 \pm 6\%$ ($P < .001$), and the median RV fractional area decreased from 52 (3)% to 43 (4)% ($P = .003$). The mean LV chamber volume increased from 36.1 ± 6.8 mm to 46.1 ± 5.6 mm at ED ($P = .013$), and mean RV chamber volume increased from 25.6 ± 4.4 mm to 31.8 ± 3.5 mm at ED ($P = .021$). The mean TA S-L diameter increased from 25.1 ± 2.9 mm to 31.5 ± 3.3 mm ($P = .005$), and FTR (0-3+) increased from 0 (0) to 3 (2) ($P = .004$). Similarly, MR (0-3+) increased from 0 (0) to 2 (1) ($P = .008$). These echocardiographic parameters were consistent with the bi-ventricular dysfunction and FTR seen clinically.

Hemodynamics

Table 1 summarizes hemodynamic data at the time of the terminal study in sheep with tachycardia-induced cardiomyopathy before (baseline) and after 5 progressive TARs (TAR 1-5). Hemodynamic parameters remained stable with all annular cinching steps, except for a decrease in maximum LV pressure with the most aggressive annular reduction (TAR 5).

TA Geometry and TR

TA geometry data obtained from sonomicrometry crystals and echocardiographically determined TR grade and transvalvular gradients are presented in Table 2. Each TAR significantly reduced TA area and S-L diameter, but

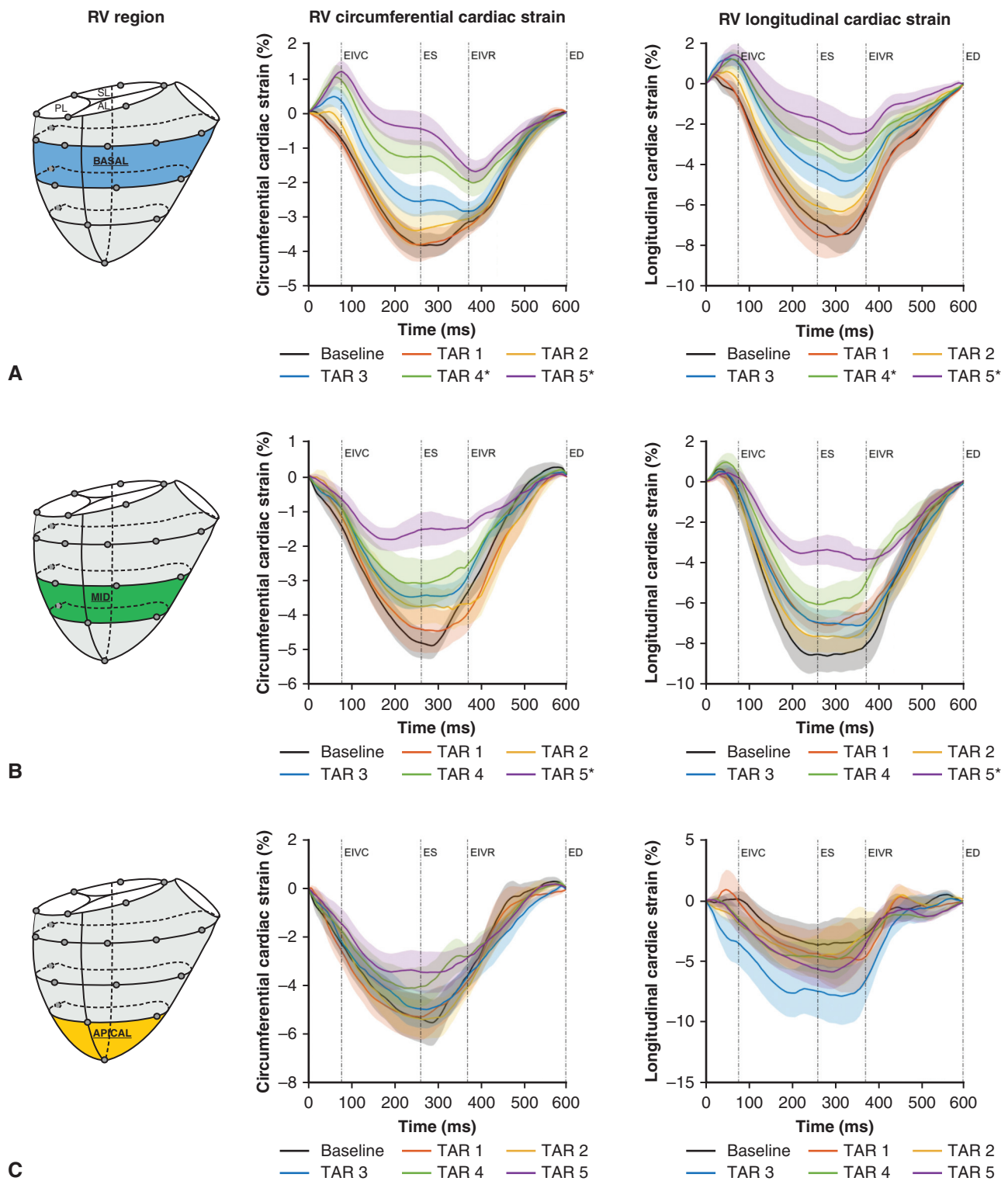
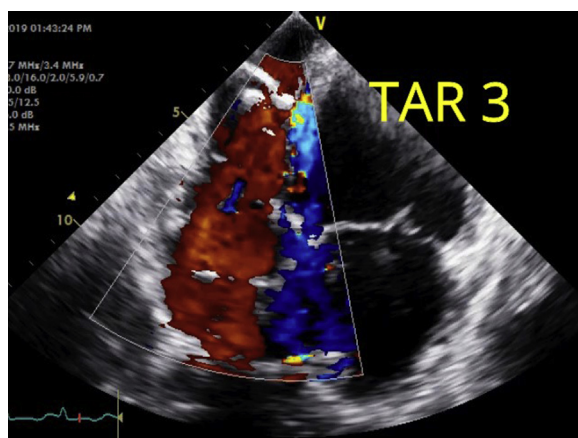


FIGURE 3. Right ventricular (RV) free wall average regional epicardial strains. The circumferential and longitudinal cardiac strains are presented for baseline and each tricuspid annular reduction (TAR 1-5) throughout the heart cycle. The RV free wall was divided into 3 regions: basal (A), mid (B), and apical (C). The strain was calculated referenced to end-diastole (ED) and is presented as mean \pm standard error of the mean during the averaged cardiac cycle ($n = 9$). * $P < .05$, repeated-measures analysis of variance with Bonferroni correction vs baseline at end-systole (ES). EIVC, End of isovolumic contraction; EIVR, end of isovolumic relaxation.



VIDEO 1. Average right ventricle free wall areal cardiac strain ($n = 9$) at baseline and during TAR 1-5. Video available at: [https://www.jtcvs.org/article/S0022-5223\(19\)33119-8/fulltext](https://www.jtcvs.org/article/S0022-5223(19)33119-8/fulltext).

only aggressive TAR (TAR 4 and 5) significantly decreased FTR (Video 2).

RV Geometry and Function

Regional RV radius of curvature did not differ from baseline during TAR 1-5 at any level of the ventricle, but RV ED volume decreased significantly after TAR 5 (Table 3). Local RV function, represented by RV-CSA change, began to initially deteriorate at the basal level after a 56% TAR (TAR 3). Continued narrowing with TAR 4 and TAR 5 led to further progressive RV dysfunction within both basal and midventricular regions. The apical RV region remained unaffected by annular cinching.

Strain

Cardiac strains throughout the cardiac cycle in all 3 ventricular regions are summarized in Figure 3. Both RV circumferential and longitudinal cardiac strains at ES were significantly affected at the basal level after a 67% TAR (TAR 4), while further narrowing resulted in decrease at the basal and mid RV levels. Areal cardiac strain of the RV epicardium at baseline and during progressive TARs is presented in Video 1. Figure 4 presents color maps of RV

interventional circumferential and longitudinal strains at both ED and ES relative to baseline. RV free wall myocardial compression gradually increased with progressive annular reductions and become most evident with TAR 4 and 5 in both longitudinal and circumferential strains. The most pronounced compression was noted in the basal and mid regions of the posterior and lateral RV free wall at ED.

DISCUSSION

Our experimental study in sheep with biventricular dysfunction and FTR-induced rapid pacing revealed that annular reduction effectively abolished valvular insufficiency but had a deleterious effect on regional myocardial function and strain when the tricuspid area was reduced beyond 50%.

Modern clinical approaches to restore the dilated TA in FTR to its physiological dimensions are centered around prosthetic or suture annuloplasty.^{5,6} Rigid, semirigid, flexible, planar, and 3-dimensional annular prostheses are available to reshape and stabilize the TA, yet optimal sizing remains a topic of considerable controversy.^{5,6,8,18} In the present study, echocardiographically measured TA diameter increased from 25.1 mm to 31.5 mm after induction of heart failure with rapid pacing, consistent with measurements of 31.2 mm obtained after the implantation of piezoelectric crystals. It is noteworthy that TA diameter was nearly normalized with TAR 2 (S-L diameter of 25.6 mm, area reduction of 38%), but TR was still significant. Assuming that healthy size of the native annulus was achieved when S-L diameter was normalized, these data imply that true size reduction of TA is inadequate to effectively control FTR.

As recent studies have suggested, the pathophysiology of FTR is not only restricted to the annulus, but is also coupled with alterations in RV function and geometry.^{1,19} Therefore, perturbations of subvalvular geometry might have been responsible for the persistent valvular insufficiency seen with annular size normalization observed in our study. Initial TA undersizing with TAR 3, associated with a mean $56 \pm 10\%$ area reduction, resulted in substantial decrease in FTR with only a slight deleterious effect on

TABLE 1. Hemodynamic data

Parameter	Baseline	TAR 1	TAR 2	TAR 3	TAR 4	TAR 5	P value
HR, bpm	129 \pm 15	133 \pm 20	132 \pm 21	131 \pm 22	132 \pm 22	132 \pm 22	.999
LVP _{MAX} , mm Hg	100.3 (5.5)	98.9 (4.3)	96.0 (8.2)	92.3 (7.3)	83.3 (13.2)	77.3 (26.5)*	.012
LVP _{ED} , mm Hg	15.8 \pm 3.1	15.0 \pm 3.4	14.3 \pm 2.8	13.6 \pm 3.0	13.7 \pm 3.1	13.1 \pm 4.0	.489
RVP _{MAX} , mm Hg	52.2 \pm 11.9	51.4 \pm 10.0	50.7 \pm 9.6	49.0 \pm 9.7	46.8 \pm 8.1	44.3 \pm 8.6	.571
RVP _{ED} , mm Hg	16.2 \pm 6.7	15.6 \pm 6.1	15.6 \pm 7.0	15.7 \pm 7.1	16.6 \pm 8.0	16.1 \pm 7.9	.999
CVP, mm Hg	12.9 \pm 1.9	12.4 \pm 2.4	12.4 \pm 2.3	12.6 \pm 2.2	14.4 \pm 2.5	15.1 \pm 2.4	.081

Values are mean \pm SD or median (interquartile range). Significant values are in bold type. TAR, Tricuspid annular reduction; HR, heart rate; LVP, left ventricular pressure; MAX, maximum; ED, end-diastole; RVP, right ventricular pressure; CVP, central venous pressure. * $P < .05$ vs baseline.

TABLE 2. TA geometry and TR

Parameter	Baseline	TAR 1	TAR 2	TAR 3	TAR 4	TAR 5	P value
TA area at ED, cm ²	8.2 ± 1.4	6.7 ± 1.3*	5.1 ± 1.5*	3.6 ± 1.2*	2.7 ± 1.0*	1.9 ± 0.7*	<.001
TA area reduction, %	—	18 ± 6	38 ± 11	56 ± 10	67 ± 9	76 ± 8	—
TA S-L diameter at ED, mm	31.2 ± 2.7	28.7 ± 2.8*	25.6 ± 4.6*	20.9 ± 4.2*	18.0 ± 3.7*	14.1 ± 2.7*	<.001
TR grade (0-3)	3 (2)	2 (2)	2 (2)	1 (2)	0 (2)*	0 (2)*	.040
TV mean gradient, mm Hg	—	0.9 ± 0.2	1.2 ± 0.4	2.3 ± 1.0	2.8 ± 1.7	3.2 ± 0.8	—

Values are mean ± SD or median (IQR). Significant values are in bold type. TAR, Tricuspid annular reduction; TA, tricuspid annulus/annular; ED, end-diastole; S-L, septolateral; TR, tricuspid regurgitation; TV, tricuspid valve. **P* < .05 vs baseline.

regional RV function and no effect on RV cardiac strain. To achieve statistically significant reduction in FTR, aggressive undersizing with TAR 4 (67 ± 9% area reduction) was required. No further improvement in control of valvular insufficiency was induced with TAR 5, but continued deterioration of regional RV function and cardiac strains was observed.

Aggressive annular reduction has been demonstrated to reduce myocardial performance of the basal segments of the LV,¹¹ and we previously reported similar findings with TAR in normal sheep hearts, with regional RV myocardial performance declining with annular reduction beyond 50%.¹² The foregoing findings reflect the clinical concept first introduced by Bolling and colleagues²⁰ of undersized ring annuloplasty for the treatment of functional MR as an “annular treatment of a ventricular problem.” Our experimental data corroborate clinical experience showing that aggressive annular reduction can overcome annular and subvalvular geometric perturbation to treat valvular insufficiency, but with possible compromise of regional myocardial performance (Figure 5).

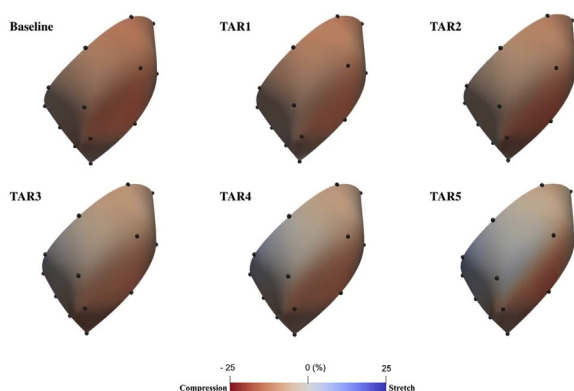
Navia and colleagues⁶ found that use of a larger tricuspid annuloplasty ring increased the risk of early and late recurrence of regurgitation, whereas Ghoreishi and colleagues⁸ reported good immediate efficacy of undersized tricuspid

annuloplasty with 26-mm or 28-mm rings and satisfactory mid-term results. Late recurrent TR was associated mainly with the evolution of RV dysfunction, perhaps due in part to overly aggressive annular reduction in accordance with our experimental data. However, Huffman and coworkers¹⁰ used identical-sized annuloplasties (26 mm or 28 mm) for simultaneous repair of FTR and mitral insufficiency with good control of valvular regurgitation and without deleterious effects on RV function at 4 weeks. Owing to very limited follow-up, it is difficult to surmise the influence of this strategy on long-term RV function and TR recurrence.

Although clinical data favor prosthetic versus suture annuloplasty for distant outcomes of FTR repair,^{5,21,22} a recent study demonstrated that a well-standardized and tight suture annuloplasty provides equivalent results to flexible ring prostheses.²³ These investigators performed “overcorrection” of the TV orifice to a diameter of 20 mm, very similar to that observed with TAR 3 in our study, although the degree of annular reduction in the study of Shinn and colleagues²³ is impossible to determine. Among 148 patients repaired with suture annuloplasty, significant RV dysfunction was present in 3 patients preoperatively but in 11 patients at hospital discharge, possibly due to aggressive annular reduction influencing RV performance.

Our data suggest that annular reduction alone may be inadequate to most effectively treat FTR, and that additional subvalvular interventions should be considered to achieve complete valvular competence without compromising myocardial function. Such a multilevel approach to functional MR has already demonstrated encouraging early results.²⁴ In the right heart, papillary muscle approximation has been shown to correct residual TR that persists after annuloplasty²⁵ and improve severe leaflet tethering.²⁶ Ex vivo studies in isolated pig hearts revealed that a combination of tricuspid annuloplasty and papillary muscle approximation provided the best control of functional valvular insufficiency.²⁷

Alterations in cardiac strains observed in the study with progressive TAR may be explained by the structural relationship of the tricuspid valvular-ventricular complex. Detailed anatomic studies have revealed that much of the anterior annulus originates from the supraventricular crest,



VIDEO 2. Exemplary echocardiographic evaluation of tricuspid regurgitation by color flow Doppler at baseline and during TAR 1-5. Video available at: [https://www.jtcvs.org/article/S0022-5223\(19\)33119-8/fulltext](https://www.jtcvs.org/article/S0022-5223(19)33119-8/fulltext).

TABLE 3. RV geometry and regional function

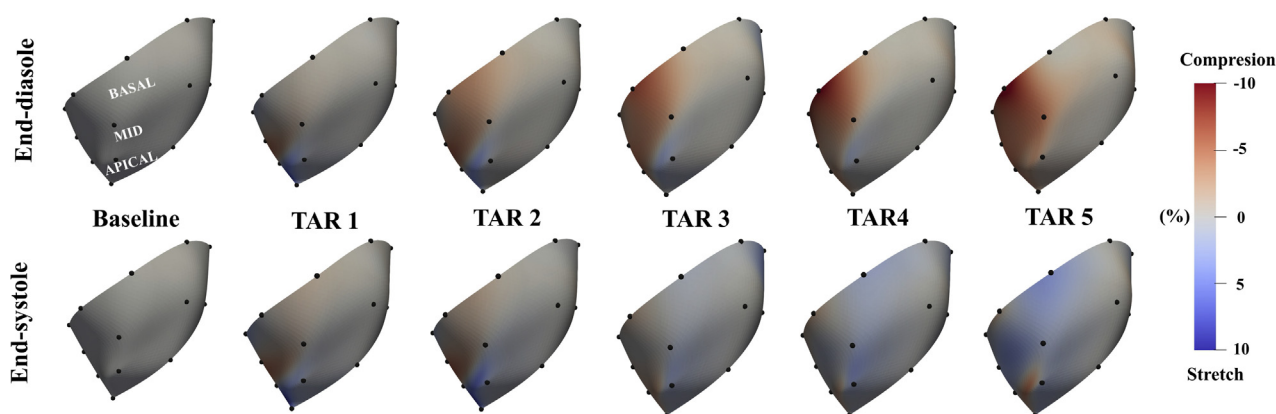
Parameter	Baseline	TAR 1	TAR 2	TAR 3	TAR 4	TAR 5	P value
RV radius of curvature, mm							
Basal ED	48.7 ± 2.4	48.1 ± 2.3	47.7 ± 2.2	47.3 ± 2.4	46.7 ± 2.7	46.0 ± 3.1	.279
Mid ED	39.8 ± 2.2	39.5 ± 2.1	39.5 ± 2.2	39.1 ± 2.3	39.0 ± 2.0	38.8 ± 2.6	.930
Apical ED	26.6 ± 2.8	26.8 ± 3.3	26.6 ± 3.5	26.6 ± 3.5	26.4 ± 3.5	25.6 ± 3.0	.983
RV volume, mL							
RV vol ED	146.3 ± 14.4	141.7 ± 11.2	136.1 ± 16.0	130.2 ± 15.9	126.6 ± 20.5	118.5 ± 18.5	.009
RV cross-sectional area change, %							
Basal	15.7 ± 5.0	13.8 ± 4.8	11.2 ± 4.7	6.8 ± 4.6*	4.9 ± 4.3*	2.6 ± 4.1*	<.001
Mid	19.9 ± 4.1	18.7 ± 4.3	17.1 ± 3.8	15.0 ± 3.7	12.6 ± 5.1*	6.7 ± 4.8*	<.001
Apical	17.5 ± 6.0	18.4 ± 6.3	15.8 ± 9.5	16.8 ± 5.8	12.6 ± 8.4	13.4 ± 3.9	.245

Values are mean ± SD. Significant values are in bold type. TAR, Tricuspid annular reduction; RV, right ventricle/ventricular; ED, end-diastole. *P < .05 vs baseline.

whereas the posterior portion of the annulus arises from the RV free wall.²⁸ Accordingly, the most pronounced changes in interventional strains with the progressive annular

reductions were found in the basal and mid regions of the posterior and lateral RV free wall, as shown in the color map in Figure 4. Our preliminary study in healthy animals

Interventional Circumferential Strain



Interventional Longitudinal Strain

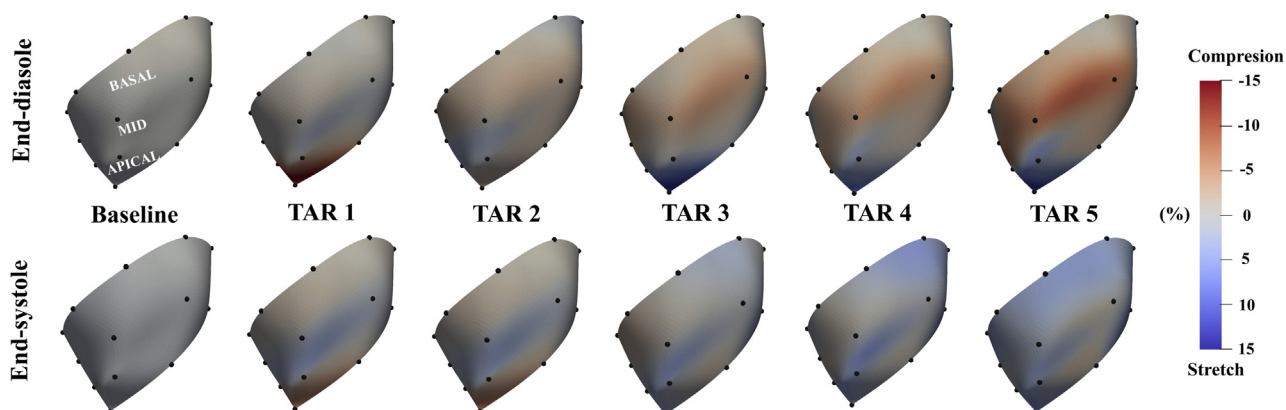


FIGURE 4. Color maps of right ventricular (RV) free wall interventional strains with progressive tricuspid annular reductions (TAR 1-5). Circumferential and longitudinal epicardial deformations of the right ventricle are presented at end-diastole and end-systole for each intervention (TAR 1-5) and referenced to baseline. Red on the RV color maps indicates myocardial compression, and blue indicates myocardial stretch. Color tone bars indicate the range of the RV deformation.

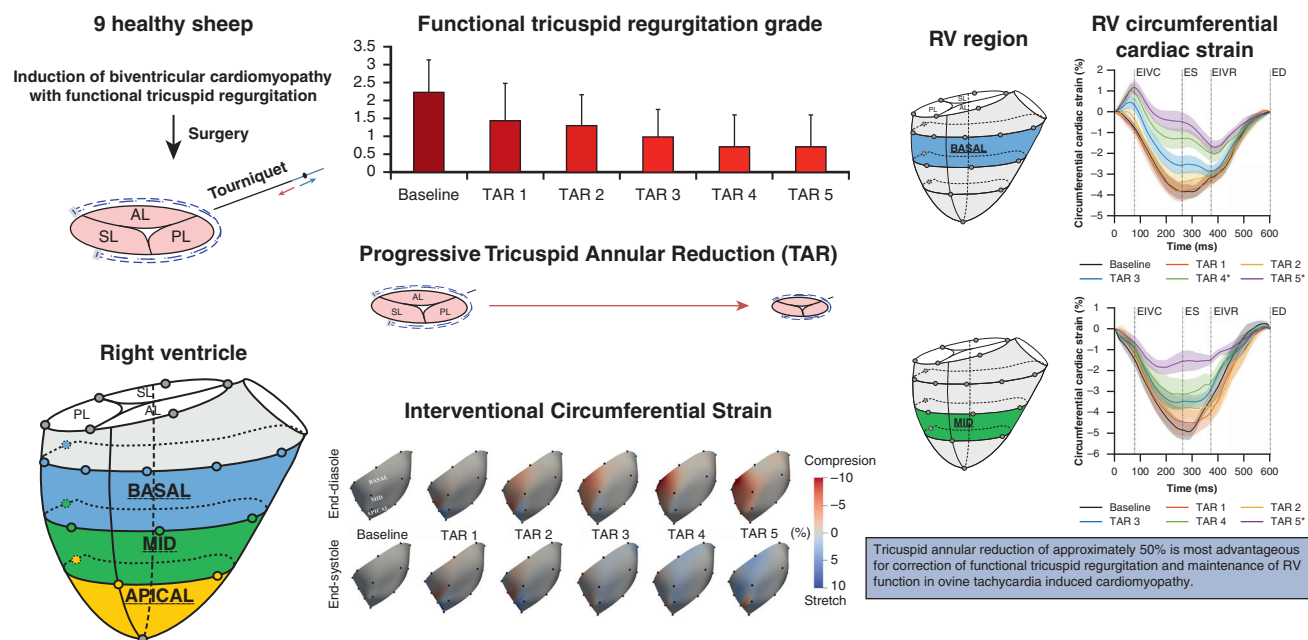


FIGURE 5. Graphical presentation of the methods, results, and implications of the present study. Interventional circumferential strains with progressive tricuspid annular reductions (TAR 1-5) are demonstrated as color maps of right ventricular (RV) free wall epicardium and are presented at end-diastole (ED) and end-systole (ES) for each intervention and referenced to baseline. Color tone bars indicate the range of RV deformation. The circumferential cardiac strains were calculated referenced to ED and are presented as mean \pm standard error of the mean during the averaged cardiac cycle ($n = 9$). * $P < .05$, repeated-measures analysis of variance with Bonferroni correction vs baseline at ES. AL, Anterior leaflet; PL, posterior leaflet; SL, septal leaflet; EIVC, end of isovolumic contraction; EIVR, end of isovolumic relaxation.

without valvular insufficiency revealed similar changes.¹² Longitudinal cardiac strain decreased with a progressive annular reduction in these cardiomyopathic hearts but was unaffected in our previous study on healthy sheep hearts without FTR.¹² These findings possibly may be due to the altered myocardial fiber orientation associated with functional TR and RV chamber remodeling.²⁹ We did not detect a direct effect of annular reduction on the regional RV geometry, in contrast to our previous acute experiments in healthy sheep.^{12,14} Nevertheless, RV volume decreased significantly after aggressive annular cinching, but whether this was due to a direct effect on RV geometry or reduction of volume overload through correction of FTR remains unclear.

Limitations

Our study has several important limitations that warrant caution in clinical extrapolation of these results. The number of animals used in this study was small, and our results should be used to generate hypotheses for further studies rather than to serve as a rigid guideline for TR repair. The data were collected in open-chest animals under general anesthesia, which can have a significant impact on RV function and TV dynamics, yet our previous studies in awake and anesthetized sheep did not show large

differences between experimental conditions.³⁰ Out of 20 study animals, 9 developed at least moderate FTR and successfully completed all steps of the protocol. This rate of failure was anticipated based on our inclusion criteria and the complexity of the study protocol. The effect of annular reduction on FTR and regional RV function was studied during acute conditions without permitting animal recovery or subsequent follow-up. However, our animal model encompassed annular dilatation, RV dysfunction, and RV chamber enlargement, reflecting known pathophysiological predictors of FTR,^{1,19} thus adding clinical pertinence to the study. We did not place sonomicrometry crystals on the interventricular septum or the papillary muscles, and thus the direct effect of annular cinching on subvalvular geometry could not be determined but could only be inferred. We used an adjustable polypropylene suture annuloplasty as a tool to progressively reduce annular size, but this differs from clinical implantation of annular prostheses of varying shapes and material properties. Only epicardial strains were taken into consideration in our study, and no information regarding mid and endocardial layer strains was obtained. We did not operate on functional MR, which potentially could alter the results of TR treatment. We feared that adding another procedure and cardioplegic arrest would further adversely affect the animals' cardio-pulmonary function.

CONCLUSIONS

In an ovine model of tachycardia-induced cardiomyopathy and FTR, we found that normalization of TA size with suture annuloplasty was insufficient to abolish FTR, whereas aggressive TA reduction effectively treated FTR but significantly decreased regional RV function and strain. We postulate that a moderate TAR of approximately 50% may be most advantageous for correcting tricuspid insufficiency while maintaining RV function, but additional subvalvular interventions should be considered to achieve complete valvular competence. We believe that caution in a “one size fits all” approach needs to be exercised owing to the heterogeneity of RV function and size in the clinical presentation of functional TR.

Conflict of Interest Statement

Jazwiec and Malinowski are Peter C. and Pat Cook Endowed Research Fellows in Cardiothoracic Surgery. Rausch has a speaking agreement with Edwards Lifesciences. All other authors have nothing to disclose with regard to commercial support.

References

- Dreyfus GD, Martin RP, Chan KM, Dulguerov F, Alexandrescu C. Functional tricuspid regurgitation: a need to revise our understanding. *J Am Coll Cardiol*. 2015;65:2331-6.
- Chikwe J, Itagaki S, Anyanwu A, Adams DH. Impact of concomitant tricuspid annuloplasty on tricuspid regurgitation, right ventricular function, and pulmonary artery hypertension after repair of mitral valve prolapse. *J Am Coll Cardiol*. 2015;65:1931-8.
- Sakata T, Mogi K, Sakurai M, Nomura A, Fujii M, Kaneyuki D, et al. Effect of tricuspid annuloplasty concomitant with left heart surgery on right heart geometry and function. *J Thorac Cardiovasc Surg*. 2018;156:1050-61.
- Fukuda S, Gillinov AM, McCarthy PM, Matsumura Y, Thomas JD, Shiota T. Echocardiographic follow-up of tricuspid annuloplasty with a new three-dimensional ring in patients with functional tricuspid regurgitation. *J Am Soc Echocardiogr*. 2007;20:1236-42.
- McCarthy PM, Bhudia SK, Rajeswaran J, Hoercher KJ, Lytle BW, Cosgrove DM, et al. Tricuspid valve repair: durability and risk factors for failure. *J Thorac Cardiovasc Surg*. 2004;127:674-85.
- Navia JL, Nowicki ER, Blackstone EH, Brozzi NA, Nento DE, Atik FA, et al. Surgical management of secondary tricuspid valve regurgitation: annulus, commissure, or leaflet procedure? *J Thorac Cardiovasc Surg*. 2010;139:1473-82.e5.
- Fukuda S, Song JM, Gillinov AM, McCarthy PM, Daimon M, Kongsarepong V, et al. Tricuspid valve tethering predicts residual tricuspid regurgitation after tricuspid annuloplasty. *Circulation*. 2005;111:975-9.
- Ghoreishi M, Brown JM, Stauffer CE, Young CA, Byron MJ, Griffith BP, et al. Undersized tricuspid annuloplasty rings optimally treat functional tricuspid regurgitation. *Ann Thorac Surg*. 2011;92:89-95; discussion 96.
- Maghami S, Ghoreishi M, Foster N, Dawood MY, Hobbs GR, Stafford P, et al. Undersized rigid nonplanar annuloplasty: the key to effective and durable repair of functional tricuspid regurgitation. *Ann Thorac Surg*. 2016;102:735-42.
- Huffman LC, Nelson JS, Lehman AN, Krajacic MC, Bolling SF. Identical tricuspid ring sizing in simultaneous functional tricuspid and mitral valve repair: a simple and effective strategy. *J Thorac Cardiovasc Surg*. 2014;147:611-4.
- Cheng A, Nguyen TC, Malinowski M, Liang D, Daughters GT, Ingels NB Jr, et al. Undersized mitral annuloplasty inhibits left ventricular basal wall thickening but does not affect equatorial wall cardiac strains. *J Heart Valve Dis*. 2007;16:349-58.
- Malinowski M, Jazwiec T, Goehler M, Bush J, Quay N, Ferguson H, et al. Impact of tricuspid annular size reduction on right ventricular function, geometry and strain. *Eur J Cardiothorac Surg*. January 29, 2019 [Epub ahead of print].
- Malinowski M, Proudfoot AG, Langholz D, Eberhart L, Brown M, Schubert H, et al. Large animal model of functional tricuspid regurgitation in pacing induced end-stage heart failure. *Interact Cardiovasc Thorac Surg*. 2017;24:905-10.
- Jazwiec T, Malinowski M, Bush J, Goehler M, Quay N, Parker J, et al. Right ventricular free wall stress after tricuspid valve annuloplasty in acute ovine right heart failure. *J Thorac Cardiovasc Surg*. 2019;158:759-68.
- Göktepe S, Bothe W, Kvitting JP, Swanson JC, Ingels NB, Miller DC, et al. Anterior mitral leaflet curvature in the beating ovine heart: a case study using video-fluoroscopic markers and subdivision surfaces. *Biomech Model Mechanobiol*. 2010;9:281-93.
- Meador WD, Malinowski M, Jazwiec T, Goehler M, Quay N, Timek TA, et al. A fiducial marker-based framework to assess heterogeneity and anisotropy of right ventricular epicardial strains in the beating ovine heart. *J Biomech*. 2018;80:179-85.
- Rausch MK, Bothe W, Kvitting JP, Göktepe S, Miller DC, Kuhl E. In vivo dynamic strains of the ovine anterior mitral valve leaflet. *J Biomech*. 2011;44:1149-57.
- Filsoufi F, Salzberg SP, Coutu M, Adams DH. A three-dimensional ring annuloplasty for the treatment of tricuspid regurgitation. *Ann Thorac Surg*. 2006;81:2273-7.
- Fukuda S, Gillinov AM, Song JM, Daimon M, Kongsarepong V, Thomas JD, et al. Echocardiographic insights into atrial and ventricular mechanisms of functional tricuspid regurgitation. *Am Heart J*. 2006;152:1208-14.
- Bolling SF, Deeb GM, Brunsting LA, Bach DS. Early outcome of mitral valve reconstruction in patients with end-stage cardiomyopathy. *J Thorac Cardiovasc Surg*. 1995;109:676-82; discussion 682-73.
- Rivera R, Duran E, Ajuria M, Carpentier's flexible ring versus De Vega's annuloplasty. A prospective randomized study. *J Thorac Cardiovasc Surg*. 1985;89:196-203.
- Tang GH, David TE, Singh SK, Maganti MD, Armstrong S, Borger MA. Tricuspid valve repair with an annuloplasty ring results in improved long-term outcomes. *Circulation*. 2006;114(1 Suppl):I577-81.
- Shinn SH, Dayan V, Schaff HV, Dearani JA, Joyce LD, Lahr B, et al. Outcomes of ring versus suture annuloplasty for tricuspid valve repair in patients undergoing mitral valve surgery. *J Thorac Cardiovasc Surg*. 2016;152:406-15.e3.
- Nappi F, Lusini M, Spadaccio C, Nenna A, Covino E, Acar C, et al. Papillary muscle approximation versus restrictive annuloplasty alone for severe ischemic mitral regurgitation. *J Am Coll Cardiol*. 2016;67:2334-46.
- Lohchab SS, Chahal AK, Agrawal N. Papillary muscle approximation to septum for functional tricuspid regurgitation. *Asian Cardiovasc Thorac Ann*. 2015;23:747-50.
- Matsumiya G, Kohno H, Matsuura K, Sakata T, Tamura Y, Watanabe M, et al. Right ventricular papillary muscle approximation for functional tricuspid regurgitation associated with severe leaflet tethering. *Interact Cardiovasc Thorac Surg*. 2018;26:700-2.
- Yamauchi H, Vasilyev NV, Marx GR, Loyola H, Padala M, Yoganathan AP, et al. Right ventricular papillary muscle approximation as a novel technique of valve repair for functional tricuspid regurgitation in an ex vivo porcine model. *J Thorac Cardiovasc Surg*. 2012;144:235-42.
- Kawada N, Naganuma H, Muramatsu K, Ishibashi-Ueda H, Bando K, Hashimoto K. Redefinition of tricuspid valve structures for successful ring annuloplasty. *J Thorac Cardiovasc Surg*. 2018;155:1511-9.e1.
- Gomez AD, Zou H, Bowen ME, Liu X, Hsu EW, McKellar SH. Right ventricular fiber structure as a compensatory mechanism in pressure overload: a computational study. *J Biomech Eng*. 2017;139.
- Jazwiec T, Malinowski M, Proudfoot AG, Eberhart L, Langholz D, Schubert H, et al. Tricuspid valvular dynamics and 3-dimensional geometry in awake and anesthetized sheep. *J Thorac Cardiovasc Surg*. 2018;156:1503-11.

Key Words: tricuspid valve, valve repair

000 Effect of variable annular reduction on functional tricuspid regurgitation and right ventricular dynamics in an ovine model of tachycardia-induced cardiomyopathy

Tomasz Jazwiec, MD, Marcin Malinowski, MD, Haley Ferguson, BS, Jeremy Wodarek, BS, Nathan Quay, BS, Jared Bush, BS, Matthew Goehler, BS, Jessica Parker, MS, Manuel Rausch, PhD, and Tomasz A. Timek, MD, PhD, Grand Rapids, Michigan; Zabrze and Katowice, Poland; and Austin, Texas

Tricuspid annular reduction of approximately 50% is most advantageous for correction of functional tricuspid regurgitation and maintenance of right ventricular function in ovine tachycardia-induced cardiomyopathy.