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Transcatheter Edge-to-Edge Treatment of Functional Tricuspid Regurgitation in an Ex Vivo Pulsatile Heart Model

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ABSTRACT

BACKGROUND Although associated with left heart pathologies, functional tricuspid regurgitation (FTR) is often left untreated during left heart surgery. Hence, owing to its degenerative character, reoperation is often needed, encompassing an impressive (25% to 35%) mortality rate. Thus transcatheter approaches to FTR are raising great interest.

OBJECTIVES The authors evaluated the post-treatment effectiveness of the edge-to-edge technique using the percutaneous mitral valve repair device in an ex vivo pulsatile model of FTR.

METHODS The devices were implanted in 11 porcine hearts simulating FTR. In each heart, single-clip treatments involved grasping leaflet pairs in the medial or commissural position (6 combinations). Two-clip treatments were then performed considering all possible 15 combinations of leaflet pairs and medial/commissural grasping. Cardiac output, mean pulmonary pressure, and mean diastolic valve pressure gradient were evaluated in physiological and simulated pathological conditions (FTR), and post-treatments.

RESULTS Grasping the septal and anterior leaflets allowed for the best post-procedural outcome, ensuring a complete re-establishment of physiological-like hemodynamics. Septal and posterior grasping induced a significant recovery from FTR, although less marked. Conversely, grasping the anterior and posterior leaflets did not reduce FTR, and was detrimental in some specific cases.

CONCLUSIONS This experimental work demonstrated that the transcatheter edge-to-edge repair technique is a feasible approach for FTR. The study investigated this approach to develop a selective, specific structural intervention methodology for treating FTR, considering the several biomechanical factors that alter proper functionality of valvular substructures. These results can be used to guide the development of edge-to-edge repair techniques in treatment of FTR. (J Am Coll Cardiol 2016;68:1024–33) © 2016 by the American College of Cardiology Foundation. Published by Elsevier. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Mild to severe tricuspid valve (TV) regurgitation affects 1.6 million patients in the United States (1). It is associated with comorbidities such as peripheral edema, reduced cardiac output (CO), and heart failure, and can lead to premature death (2–4). This pathology can be secondary to damage of the TV structures (degenerative tricuspid regurgitation) or to structural changes in the

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right heart (annular dilation and ventricular enlargement) that lead to improper TV leaflet coaptation, such as functional tricuspid regurgitation (FTR). Approximately 90% of all severe TV regurgitation is related to FTR (5,6).

FTR is often secondary to left heart pathologies, such as mitral valve regurgitation and stenosis (1,4). These pathologies can induce pressure and volume overload in the right ventricle (RV), which in turn can induce ventricle enlargement and tricuspid annular dilation. In this phase, TV regurgitation is typically mild. However, annular dilation is progressive and asymmetric, mostly involving the anterior and posterior leaflets that pull away from the coaptation lines with the septal leaflet (**Central Illustration**, panel A). FTR becomes more severe with increased RV dilation, which induces papillary muscle displacement and leaflet tethering, further worsening the FTR (1,4,7,8).

FTR is seldom treated during left heart surgery. Despite being well accepted that FTR is a deteriorating pathology, tricuspid treatment is usually only performed concomitantly to left heart surgery in cases of severe regurgitation. Consequently, the rate of FTR recurrence or worsening after surgical treatment of the left heart remains high, especially given the aging population (1,2,7,9). This leads to a potentially high frequency of reoperations, with in-hospital mortality as high as 25% to 35% (1,2). Thus, transcatheter approaches to FTR are considered an attractive strategy (1,2,7,10).

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Among the few transcatheter devices exploitable for FTR treatment, a percutaneous mitral valve repair system (MitraClip System, Abbott Vascular, Santa Clara, California), developed for mitral valve regurgitation, is a promising option (1,2,10). It allows replicating, in a less invasive manner, the edge-to-edge surgical approach that has provided good results in addressing FTR when combined with other therapies (11).

Several published clinical applications (12–15) of the percutaneous mitral valve repair system for treating TV regurgitation suggest the potential of this approach, particularly when septal and anterior leaflets are grasped (12,14). Open issues in this approach include the 3-leaflet anatomy, gaps between the leaflets, and the high density of tricuspid chordae, particularly in the commissural (Com) position.

This paper presents a systematic experimental study of the transcatheter edge-to-edge repair technique applied to an ex vivo model of FTR. Our aim was to evaluate the feasibility and efficacy of this technique in the 3-leaflet TV, focusing on assessing immediate post-operative outcomes in relation to: 1) which pair of leaflets is grasped; 2) where the pair of leaflets are grasped; and 3) if a 2-clip implantation improves results.

ABBREVIATIONS AND ACRONYMS

ANOVA = analysis of variance

A-P = anterior-posterior

CO = cardiac output

Com = commissural

Δp = diastolic pressure gradient across the tricuspid valve

FTR = functional tricuspid regurgitation

Med = medial

P_{pul} = pulmonary pressure

RV = right ventricle/ventricular

S-A = septal-anterior

S-P = septal-posterior

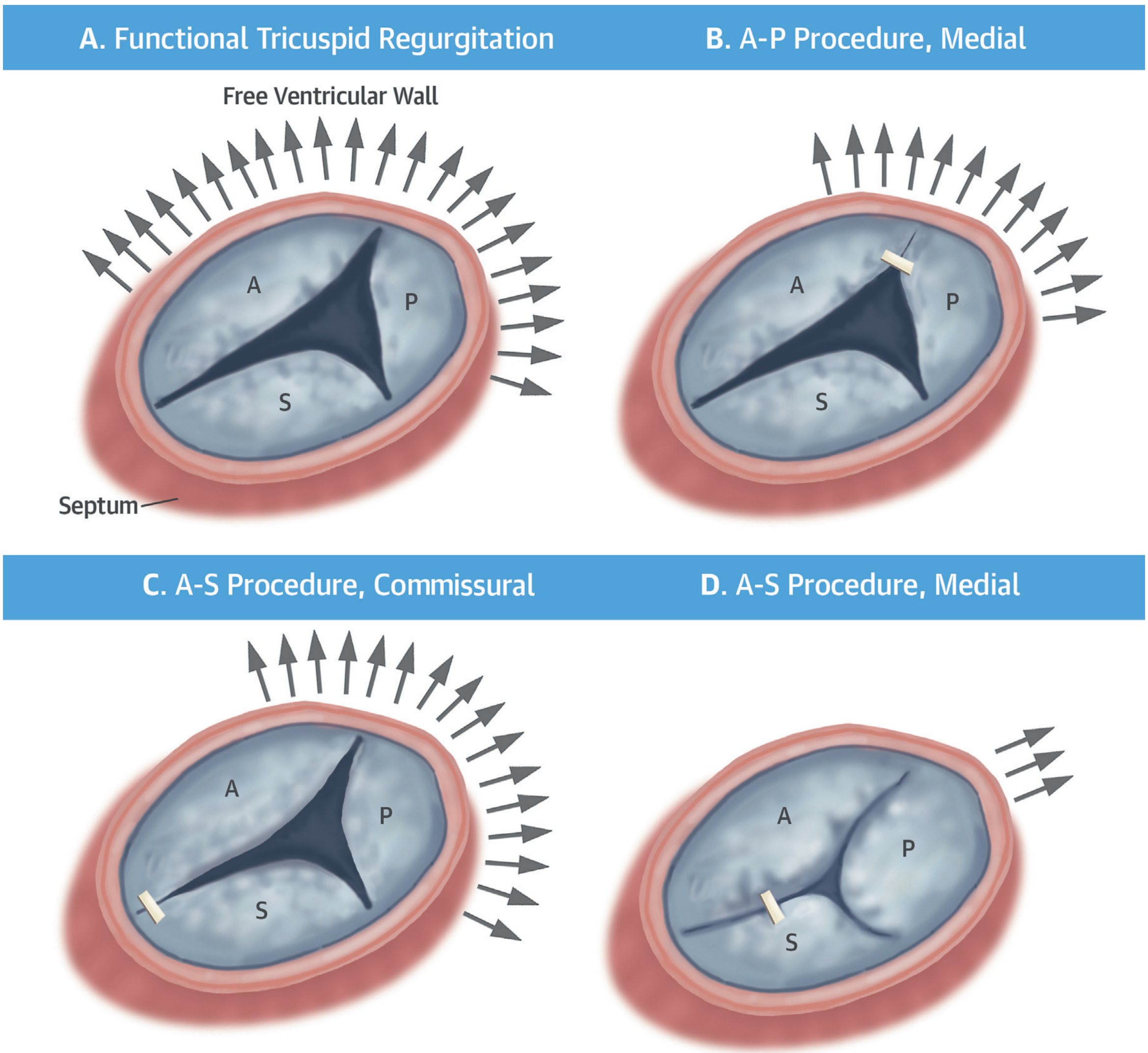
TV = tricuspid valve

METHODS

Derived from a mock loop extensively used to simulate human circulation, the experimental system consisted of a pulsatile pump connected to a porcine heart obtained from the abattoir. The system accurately replicated the pulse flow and heart valve function in a beating heart (16–19). (More details are in the Online Appendix.) The right heart CO, mean pulmonary pressure (P_{pul}), and mean diastolic pressure gradient across the TV (Δp) were obtained from acquired data. Direct visualization of the valvular apparatus was recorded with a fiberscope (Olympus Europe, Hamburg, Germany) inserted in the right atrium. Echocardiographic views of the TV were acquired using an Epiq7 equipped with an X7-2t probe (Philips, Eindhoven, the Netherlands). The mock loop was set to simulate physiological rest conditions (heart rate 60 beats/min; stroke volume 70 ml; P_{pul} 10 to 15 mm Hg). Saline solution was used as working fluid.

EXPERIMENTAL MODEL OF FTR. We used porcine hearts from pigs weighing 170 ± 8 kg. Similar to published literature (20,21), the model exploited the tendency of the TV annulus and RV to dilate in order to achieve an experimental model of FTR. In the experimental apparatus, these extremely compliant structures started to dilate at physiological pulmonary pressure values. More specifically, the anterior and posterior portions of the TV annulus dilated, thus pulling the anterior and posterior leaflets away from the septal leaflet. Moreover, due to RV dilation, the papillary muscles anchored to the free ventricular wall were displaced, thus inducing leaflet tethering and in turn further TV incontinence. In the ex vivo model, both of these biomechanical determinants were controlled by means of 2 adjustable bands placed around the heart: 1 around the valvular plane, the other at the level of the papillary muscles. The first band was used to regulate annular diameter; the second to confine and control the RV dilation, thus adjusting papillary muscle displacement and associated leaflet tethering. To obtain physiological TV behavior, the 2 bands were adjusted until experienced surgeons visually verified proper coaptation of the leaflets. CO evaluation, direct fiberscope views, and echocardiographic images were used to support this decision. When the bands were released,

CENTRAL ILLUSTRATION FTR and Edge-to-Edge Treatment Outcomes



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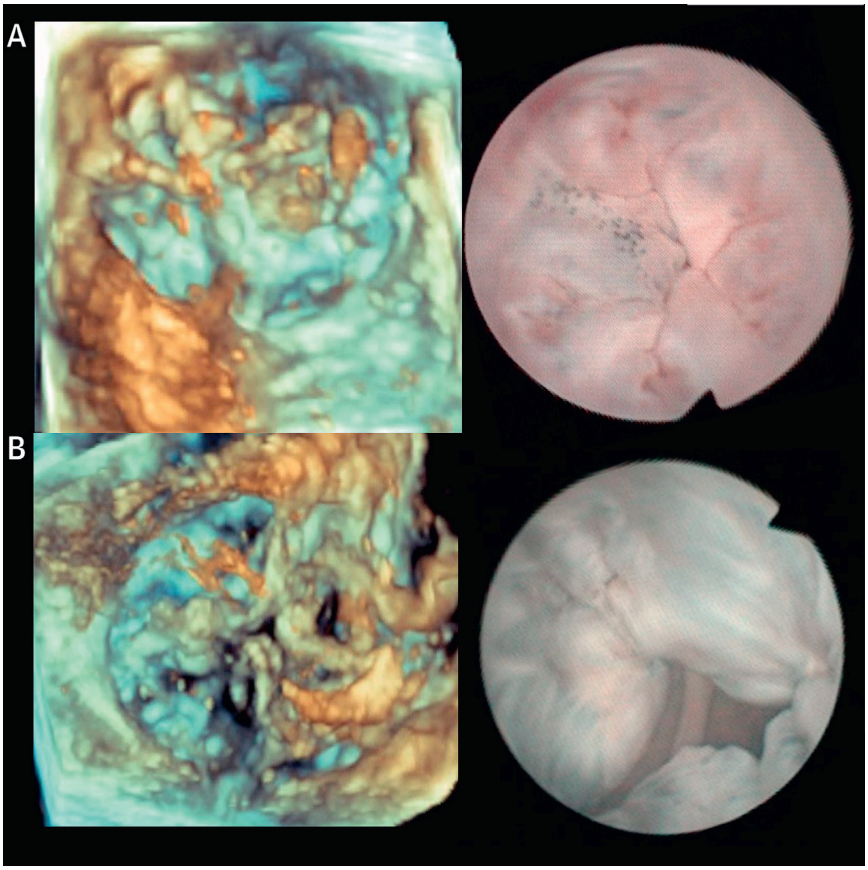
(A) In functional tricuspid regurgitation (FTR), the anterior (A) and posterior (P) leaflets of the valve are pulled away **(arrows)** from the septal (S) leaflet. **(B)** The edge-to-edge technique is performed by the transcatheter clip between the A and P leaflets, in medial position. Whereas the treatment enhanced coaptation between A and P leaflets, the gap between A-P and S leaflets remain unaltered **(arrows)**, if it is not worsened by A-P tethering induced by the treatment. Cardiac output (CO) did not change following the treatment. **(C)** With the edge-to-edge technique performed in the commissural position between A and S leaflets, there were no relevant changes in leaflet coaptation, thus no variation in the CO pre- and post-treatment. **(D)** The edge-to-edge technique between S and A in the medial position allowed for a recovery of the coaptation lines between all the 3 couples of leaflet, with relevant increment in valve competence. Also see Online Video 1.

coaptation was lost, mean CO consequently decreased, and surgeons qualitatively evaluated the leaflet configuration by intracardiac fiberscope video inspection and echocardiographic imaging. Figure 1 shows representative snapshots of the physiological (top row) and pathological (bottom row) model of TV obtained from echocardiographic and fiberscope video recordings.

IMPLANTATION TECHNIQUE. An expert operator implanted devices under fiberscope guidance, using echography as a support imaging technique, allowing for accurate and repeatable clip positioning.

FIGURE 1 **Coapting and Regurgitant TV**



Three-dimensional echocardiography and fiberscope images display **(A)** the physiological model and **(B)** the simulated functional tricuspid regurgitation obtained by means of right ventricular and tricuspid valve annular dilation. TV = tricuspid valve.

For this study, superior vein access was chosen as direct access to the TV. After inserting the fiberscope in the atrium for direct visual inspection, a J-shaped wire was placed under direct visualization. The steerable guide with its dilator was placed a few centimeters outside the outflow of the superior vena cava to exploit the guide's steerable properties. After removing the dilator, the clip delivery system was introduced and oriented in the atrium to obtain a straight and perpendicular trajectory of the clip over the TV plane as required by the experimental protocol. The clip arms were opened at 180° and the TV crossed. Once the leaflets were grasped, the clip was closed and the tension on the system released as instructed by the device manufacturer. After the hemodynamics parameters were recorded, the clip was opened, reverted, and gently pulled back in the right atrium, for a new grasping in a different position. In each heart sample, the clip was deployed only in the position recommended by the protocol (**Table 1**).

EXPERIMENTAL PROTOCOL. Twelve hearts obtained from the local abattoir were selected for study. Gross anatomic determinants of the TVs were measured and compared with the published reports, to confirm that the porcine TV is an acceptable anatomical model of the human TV. Data are reported in the Online Appendix. After checking for the absence of anatomic anomalies, the selected hearts were surgically prepared by experienced surgeons to be housed in the mock loop. Three configurations were tested with each heart. First, a physiological, continent TV was obtained, and data were acquired. Second, FTR was simulated via methods discussed earlier. Once data in the pathological configuration were acquired, the treatment of the FTR was performed using the percutaneous mitral valve repair device. In a

TABLE 1 Matrix of Tested Configurations

	Treatment Position					
Heart*	S-A Med	S-A Com	S-P Med	S-P Com	A-P Med	A-P Com
1	x	Deployed	x	x	x	x
2	x	x	Deployed	x	x	x
3	x	x	x	Deployed	x	x
4	x	x	x	x	Deployed	x
5	x	x	x	x	x	Deployed
6	Deployed	x	x	x	x	x
7	x	x	Deployed	x	x	x
8	x	x	x	x	Deployed	x
9	Deployed	x	x	x	x	x
10	x	Deployed	x	x	x	x
11	x	x	x	Deployed	x	x

*Heart 12 was discharged following initial grasp attempts due to heart structural failure related to the experimental mock loop.

A = anterior leaflet; Com = commissural position; Med = medial position; P = posterior leaflet; S = septal leaflet; X = grasping only.

randomized sequence, the clip was placed between septal and anterior leaflets (S-A), septal and posterior leaflets (S-P), and anterior and posterior leaflets (A-P). For each pair of leaflets, grasping was performed in both the Com and medial (Med) positions. Thus, 6 total grasping configurations were included for each heart. No clip was deployed in this first sequence of grasping. However, after completing this sequence of grasp and release at the 6 positions, the clip was finally deployed in 1 of the 6 positions. The test matrix in Table 1 details each grasping and deployment condition. As an example, in Heart #1, after the first clip was used to grasp and release at the 6 positions, it was finally deployed in the S-A Com position.

Next, the effectiveness of a 2-clip implantation was evaluated. After the first clip was delivered and deployed in 1 of the 6 positions, the second clip was delivered to grasp the remaining 5 positions in each heart.

Endoscopic intracardiac images were acquired before and after each clip grasp procedure to qualitatively assess the pathological model and the percutaneous mitral valve repair treatment effectiveness. Echocardiographic images were used to support these evaluations. Hemodynamic raw data before and after each grasp were sampled and recorded. From the raw data, CO, P_{pul}, and mean systolic Δp were averaged over 10 consecutive heart cycles.

TABLE 2 Single-Clip Treatments

			Post-Treatment	
	Physiological	Pathological	Medial	Commissural
CO, l/min	2.9 ± 0.4*	2.0 ± 0.4	2.6 ± 0.7*	2.1 ± 0.6
P_{pul}, mm Hg	11.0 ± 2.0*	6.6 ± 2.4	9.2 ± 3.8*	6.9 ± 2.9
Δp, mm Hg	0.1 ± 0.15	0.3 ± 0.06	0.4 ± 0.5	0.4 ± 0.6

Values are mean ± SD. *$p < 0.05$ (vs. pathological condition).

CO = mean cardiac output; Δp = mean diastolic pressure gradient across the tricuspid valve; P_{pul} = mean pulmonary pressure.

STATISTICAL ANALYSIS. Data are presented as mean ± SD. To clarify whether the differences among the treatments (A-P, S-P, and S-A in the Med and Com positions) were significant, analysis of variance (ANOVA) for repeated measures was performed. Comparison of the overall data from physiological samples, from Med treatments and from Com treatments compared with the pathological condition, were performed with ANOVA, using Bonferroni correction as a post hoc test.

Differences pre- and post-treatment in the 2-clip implantation treatments were evaluated with the Student *t* test, with no adjustment for multiple treatments. p Values <0.05 were considered significant. Statistics were evaluated using MiniTab 17 (Minitab, Coventry, United Kingdom).

RESULTS

A total of 144 grasping/deployment procedures in TV were performed. Each grasp was successfully carried out, without issues concerning excessive gaps between leaflets nor clip entrapment in the valve chordal apparatus. One of the 12 hearts was discharged following initial grasp attempts due to heart structural failure related to the experimental mock loop. A video (Online Video 1) recorded from the left atrium exemplifies the clipping procedures in the A-P and A-S positions.

SINGLE-CLIP IMPLANTATION. An overall ANOVA for repeated measure of the treatments showed statistically significant differences. Table 2 summarizes our overall pooled data obtained with single-clip implantations. Comparing physiological and pretreatment pathological conditions, the mean CO and the P_{pul} decreased by 31% (from 2.9 ± 0.4 l/min to 2.0 ± 0.4 l/min; $p < 0.05$) and 40% (from 11.0 ± 2 mm Hg to 6.6 ± 2.4 mm Hg; $p < 0.05$), respectively, whereas the Δp did not vary significantly ($p = 0.363$).

Considering the Med treatments (MitraClip grasped at mid-leaflet location of both leaflets), TV functionality improved significantly with respect to pathological conditions. Mean CO increased to 2.6 ± 0.7 l/min, and P_{pul} increased to 9.2 ± 3.8 mm Hg ($p < 0.05$ compared with pathological data). Differences between these post-treatment data and physiological condition were not statistically significant, thus indicating a full recovery of initial valve continence. The Δp was 0.4 ± 0.5 mm Hg, with no statistical difference compared with untreated samples.

TABLE 3 Single-Clip Treatments: Specific-to-Treatment Data

Treatment		CO (l/min)			P_{pul} (mm Hg)			Δp, (mm Hg)	
Position	Leaflets	Pathological	Post-Treatment	Δ%	Pathological	Post-Treatment	Δ%	Pathological	Post-Treatment
Medial									
	S-P	2.0 ± 0.5	2.9 ± 0.7	+43%*	7.5 ± 2.6	11.3 ± 4.2	+51%*	0.3 ± 0.4	0.5 ± 0.5
	S-A	2.0 ± 0.4	2.9 ± 0.3	+41%*	6.7 ± 2.2	10.2 ± 2.2	+53%*	0.3 ± 0.5	0.3 ± 0.4
	A-P	1.9 ± 0.4	1.9 ± 0.4	−3%	6.8 ± 2.6	6.1 ± 2.5	−11%	0.4 ± 0.4	0.6 ± 0.5
Commissural									
	S-P	2.0 ± 0.4	2.1 ± 0.7	1%	6.3 ± 2.2	6.5 ± 2.4	+4%	0.4 ± 0.5	0.5 ± 0.5
	S-A	2.0 ± 0.4	2.4 ± 0.7	+18%	6.4 ± 2.1	8.7 ± 3.7	+37%	0.1 ± 0.8	0.2 ± 0.8
	A-P	2.1 ± 0.4	1.9 ± 0.3	−6%	5.7 ± 2.5	5.5 ± 1.6	−3%	0.2 ± 0.5	0.5 ± 0.4

Values are mean ± SD (evaluated over 11 samples). *$p < 0.05$ (vs. pathological condition).
Abbreviations as in Tables 1 and 2.

Conversely, the Com treatments (clip grasped at Com location) did not significantly improve valve continence. Following these treatments, CO was 2.1 ± 0.6 l/min and P_{pul} 6.9 ± 2.9 mm Hg. The Δp did not change significantly (0.4 ± 0.6 mm Hg) after Com treatment either.

Table 3 and Figure 2 report the experimental data grouped by pair of treated leaflets and by grasping position. Medial treatments involving the septal leaflet allowed the model to achieve a CO and P_{pul} of 2.9 ± 0.7 l/min and 11.3 ± 4.2 mm Hg (S-P Med), and 2.9 ± 0.3 l/min and 10.2 ± 2.2 mm Hg (S-A Med), respectively. Both increments were statistically significant with respect to the pathological conditions, demonstrating recovery of hemodynamics comparable to the physiological model. Regarding Com treatments, S-A Com grasping induced a nonstatistically significant increment in CO (+18%) and in P_{pul} (+37%), whereas S-P Com grasping had no relevant effect on flow rate and pressure.

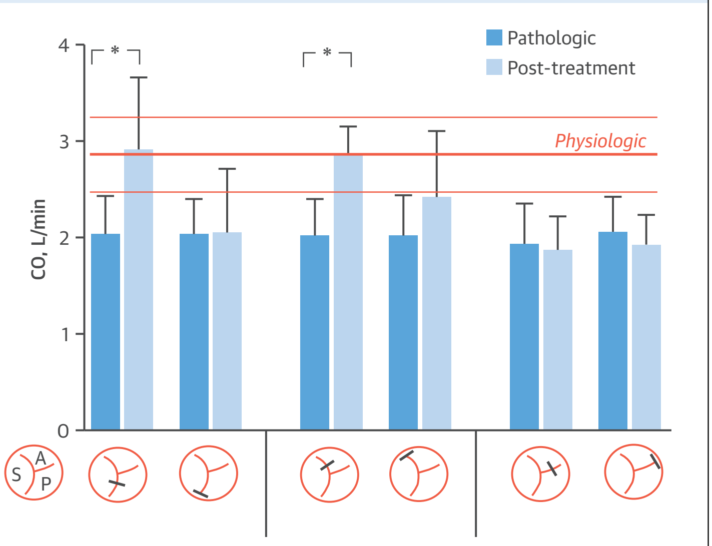
It is noteworthy that the A-P treatments, regardless of Med or Com grasp, induced a slight, even if not statistically significant, worsening of CO and P_{pul} with respect to the pathological conditions.

Regarding TV pressure gradients, the maximum recorded value of 0.4 ± 0.5 mm Hg was observed in S-A Com tests, with no statistical significance compared with the pre-treatment value, nor clinical relevance.

TWO-CLIP IMPLANTATION. Table 4 reports numerical data for CO and pressures grouped by leaflet and grasping position. Figure 3 reports the CO recorded in all the possible positions/leaflets combinations. Medial treatment, regardless of the leaflet pair treated, induced an increment with respect to pathological conditions in both CO (+35%; $p < 0.05$) and P_{pul}, (P_{pul} +29%; $p = 0.13$). Commissural treatments induced negligible and nonsignificant increments in CO and P_{pul} (+10% and +16%, respectively; $p > 0.52$), whereas the pooled CO increment was slightly more relevant (+22%; $p = 0.9$) following a zipping procedure (i.e., the Med and Com grasping between the same couple of leaflets).

Data showed varying trends dependent on the location of the first clip. In heart samples in which the first clip deployment was in a Med position, CO increased from 2.1 ± 0.4 l/min (pathological) to 2.4 ± 0.4 l/min (post first procedure; $p < 0.05$), and remained stable post second procedure (2.4 ± 0.5 l/min; $p = 0.611$). In heart samples, in which the first clip deployment was performed in Com positions, CO

FIGURE 2 Mean CO



Mean cardiac output (CO) was evaluated in simulated pathological conditions as well as post-treatment with single-clip implantations in anterior (A), posterior (P), and septal (S) leaflets. *$p < 0.05$. Variations between physiological and pathological conditions were always statistically significant.

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TABLE 4 2-Clip Treatments

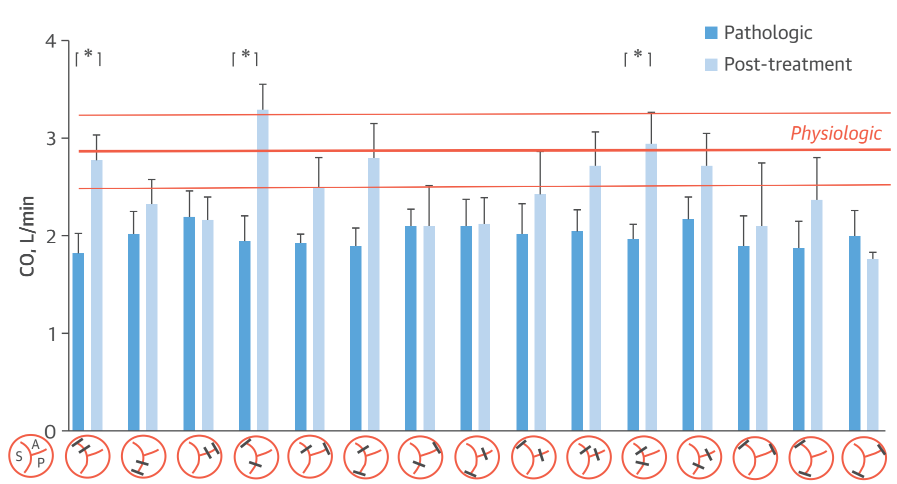
Treatment		CO (l/min)			P_{pul} (mm Hg)			Δp (mm Hg)	
Position	Leaflets	Pathological	Post-Treatment	Δ%	Pathological	Post-Treatment	Δ%	Pathological	Post-Treatment
Medial									
	S-P + S-A	2.0 ± 0.3	3.0 ± 0.6	+49%*	7.3 ± 1.3	12.1 ± 2.7	+66%	0.4 ± 0.3	0.8 ± 0.6
	A-P + S-A	2.1 ± 0.4	2.7 ± 0.7	+33%	8.1 ± 1.1	9.8 ± 6	+21%	0.1 ± 0.1	0.5 ± 0.2
	A-P + S-P	2.2 ± 0.4	2.7 ± 0.7	+25%	7.4 ± 1.0	7.4 ± 4.6	0%	0.3 ± 0.3	1.2 ± 0.8
Commissural									
	S-P + S-A	1.9 ± 0.6	2.4 ± 0.9	+27%	6.2 ± 2.4	7.0 ± 4.9	+12%	0.2 ± 0.2	0.3 ± 0.3
	A-P + S-A	1.9 ± 0.5	2.1 ± 1.1	+11%	4.7 ± 2.2	6.6 ± 5.0	+40%	0.2 ± 0.3	0.4 ± 0.1
	A-P + S-P	2.0 ± 0.5	1.8 ± 0.1	−12%	5.1 ± 3.7	5.1 ± 0.3	0%	0.4 ± 0.1	0.3 ± 0.1
Medial + Commissural†									
	S-P	2.0 ± 0.4	2.3 ± 0.5	+15%	6.6 ± 2.3	4.5 ± 3.9	−32%	0.7 ± 0.6	0.9 ± 0.7
	S-A	1.8 ± 0.5	2.8 ± 0.6	+52%*	6.9 ± 2.0	7.9 ± 1.4	+14%	0.1 ± 0.2	0.3 ± 0.2
	A-P	2.2 ± 0.5	2.2 ± 0.4	0%	6.3 ± 3.4	6.4 ± 0.3	+2%	0.3 ± 0.3	0.4 ± 0.2

Values are mean ± SD. *$p < 0.05$ (vs. pathological condition). †2 clips are grasped between the same pair of leaflets (zipping procedure). Abbreviations as in Tables 1 and 2.

was stable post first procedure (from 1.8 ± 0.5 l/min to 1.8 ± 0.3 l/min; $p = 0.635$), and increased to 2.5 ± 0.7 l/min post second Med procedure ($p < 0.05$ with respect to first).

Two-clip data confirmed that treatments involving the septal leaflet in Med positions induced an increase of both CO and P_{pul}. The most relevant increase in CO was recorded post 2-clip implantation in the S-A Com position and S-P Med position (+69% with respect to pathological data; $p < 0.05$). CO also increased when clips were implanted between S-A Med and S-P Med (+49%; $p < 0.05$) and with implantation of both clips along the S-A line of coaptation (+52%; $p < 0.05$). After each of these treatment conditions, physiological-like CO and P_{pul} were restored. It is noteworthy to add that when the 2 clips were implanted in Med and Com positions in S-P, the hemodynamics did not improve significantly. This could be due to a detrimental effect of Com implantation in S-P. The worst recorded TV function was recorded post-implantation of the clips in A-P Com and S-P Com positions (−12% of CO; p = NS with respect to pathological). Two-clip implantations did not induce a clinically relevant increase of the TV Δp

FIGURE 3 2-Clip Implantations



CO is compared pre- and post-implantation in the variations available using 2 clips. *$p < 0.05$. Abbreviations as in Figure 2.

in any of the treatment configurations (maximum Δp was 1.4 ± 0.7 mm Hg, recorded post A-P Com and S-P Med treatment).

DISCUSSION

This ex vivo study aimed at evaluating the feasibility and efficacy of the transcatheter edge-to-edge repair technique to treat FTR in the immediate post-operative scenario. Percutaneous mitral valve repair system implantation allowed for the improvement of the right heart CO without a significant increment of the valve pressure gradient. In the experimental model, the procedural outcomes were strongly dependent on the position where the clips were grasped (Med or Com) and the pair of leaflets grasped. In particular, the combination of treatments that included grasping the septal leaflet in the Med position were the most effective in recovering the physiological hemodynamic parameters.

Several transcatheter devices intended to treat TV regurgitation are currently under development or at early stages of clinical applications (22–24). The MitraClip system is not a specific device for the TV; on the contrary, it is approved and widely used to treat mitral regurgitation. Operator familiarity with the device, together with the feasibility of the edge-to-edge repair technique on the TV, has contributed to its off-label use in FTR. Although the first reported cases have been successful in reducing the degree of FTR (12–15), no study has assessed the immediate hemodynamic effects of TV clipping and the differences in results among various combinations of clipping strategies.

This study used an ex vivo porcine model of FTR that can replicate the 2 mechanisms responsible for TV incomplete leaflet coaptation: annular dilation and papillary muscle displacement. These 2 events were independently controlled by means of mechanically constraining right heart dilation. A first constraint was aligned to the valve annulus, thus confining and controlling annular dilation. A second constraint was placed at the level of the papillary muscles, to control their displacement, thus regulating leaflet tethering. By tuning both such constraints, the TV leaflets achieved a coapting configuration deemed satisfactory by the heart-surgeon team (**Figure 1A**). By releasing these constraints, a pathological condition, in terms of CO and pulmonary pressure decrease, were repeatedly achieved (**Figure 1B**).

SINGLE CLIP: WHICH LEAFLETS TO GRASP? The anterior and posterior segments of the TV annulus correspond to the free wall of the ventricle. When dilation occurs, the anterior and posterior segments of the annulus move away from the relatively fixed septal segment and elicit the loss of coaptation. Therefore, treatments involving the septal leaflet and 1 of the other 2 (anterior or posterior) leaflets are expected to reduce the gap between the free margin of the leaflets and improve leaflet coaptation. Study results confirmed these inferences. Grasping procedures that involved the septal leaflet achieved better post-procedural results in terms of cardiac output and pressure recovery.

Conversely, A-P 1-clip grasping consistently induced a decrease in CO, even if not statistically significant. The only potential effect of a clipping procedure in the A-P location: a reduction of the leaflet-gap area between A and P leaflets (**Central Illustration**, panel B), because the 2 leaflets are forced closer to each other by the clip. This procedure has no relevant effect on the shift of the A-P portion of the annulus with respect to the septal leaflet. There was no mechanical constraint to force the free and dilated A-P portion of the annulus to stay closer to the septal portion. Moreover, one can speculate that this procedure induced a reciprocal tethering of the A and P leaflets, causing their free margins to be pulled further away from the septal leaflet, thus worsening valve performance.

SINGLE CLIP: WHERE TO GRASP? A statistically significant increment in TV continence was associated with Med grasping (**Table 2**). In particular, 1-clip Med grasps between S-A or S-P leaflets induced noteworthy and statistically significant increases in cardiac output and mean pulmonary pressure. Simulated physiological-like conditions were restored following these treatments (**Table 3**).

Conversely, the Com grasping was almost ineffective, if not detrimental (**Central Illustration**, panel C). The only exception was the Com grasping between septal and anterior leaflets, which led to an increment of 18% of the CO, though not statistically significant. A-P leaflet grasping at the commissure induced a worsening of the valve continence, and this was even more evident with respect to Med grasping.

1- VERSUS 2-CLIP PROCEDURE. The 2-clip treatment confirmed the 1-clip results, permitting speculation as to the effectiveness of the double-clip procedure. The procedures that involved at least 1 grasping of the septal leaflet in the Med position induced improvement of CO and pulmonary pressure in the experimental model. One important exception: when 1 clip was placed medially between septal and posterior leaflets and the other clip was placed in the commissure between anterior and posterior leaflets.

This confirmed that Com grasping, particularly between anterior and posterior, had only a small effect or was detrimental for TV functioning in the setup.

Although the 2-clip procedure did not induce relevant improvement in TV competence compared to a Med single-clip procedure, the so-called "zipping procedure" (i.e., the grasping of the Com and Med position of the same pair of leaflets) was particularly effective when applied between S-A leaflets, with a full recovery of physiological-like simulated hemodynamics, but ineffective between anterior and posterior. This confirmed the results of the 1-clip procedure: S-A procedures, regardless of clip positioning, were more effective in terms of functional recovery of the modeled FTR. Clinical data available to date suggested the same conclusion (12,14).

AN ANATOMICAL AND BIOMECHANICAL STANDPOINT. Results showed a relationship between procedural outcomes and the biomechanical determinants that underlie FTR. The best post-procedural results were obtained when grasping was performed between septal and anterior leaflets. The anterior leaflet functionality is known to be strongly affected by RV and TV annular dilation, in that its structural constraints (the anterior portion of the annulus and the anterior papillary muscle) are extremely free to move. This makes the anterior leaflet highly susceptible to be pulled away from the septal leaflet and subject to tethering. The overabundant coaptation zone of this leaflet, also reported in the published reports (25–27), was additionally suggested by anatomic analysis (see Online Appendix, where the anterior leaflet was found to be longer in length); this can be interpreted as a safe evolutionary mechanism aimed at hindering the loss of coaptation in the case of degenerative FTR. The grasping of the anterior and septal leaflets exploited this overabundant anatomy, with an effective recovery of the coaptation between the 2 leaflets (**Central Illustration**, panel D, Online Video 1).

STUDY LIMITATIONS. The ex vivo approach allowed the evaluation of hemodynamic data in the immediate post-procedural simulated scenario. The durability of the transcatheter edge-to-edge repair approach for the TV needs to be further investigated, as the few clinical cases reported to date are too recent. Nonetheless, the good results in terms of durability of the percutaneous mitral valve repair treatment in the mitral position are encouraging, keeping in mind that the pressures in the left heart are considerably higher than in the right heart.

In this study the implant procedures were performed pursuing high reproducibility of the grasping/delivery positions, rather than with an intent to replicate the clinical procedure. Implants were thus performed with direct inspection via the fiberscope and echography was used as a support technique. Visual inspection required fluid transparency, preventing the use of particles in the fluid, making color Doppler recording unfeasible. The catheterization laboratory scenarios differed in terms of clip delivery and post-procedural results control. Moreover, the standard implant procedure of the clip in the mitral valve is x-ray- and echo-guided. However, imaging of the TV is more challenging with respect to the mitral valve, due to anatomic complexity of the valve and of the RV (9). This could complicate the detection of the clip landing zone.

CONCLUSIONS

Severe symptomatic FTR remains a clinical dilemma and challenge for physicians. This study suggested that transcatheter edge-to-edge repair technique provides a feasible approach for the treatment of FTR. The possibility of using a minimally invasive, transcatheter edge-to-edge technique as a safe and effective alternative to surgery should be pursued and further investigated.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The pathogenesis of functional tricuspid regurgitation involves biomechanical alterations of valvular substructure. In an experimental model of transcatheter intervention, a clip placed at the medial position of the anterior and septal valve leaflets had the most favorable impact on the severity of on FTR compared with plication at other locations on the valve apparatus.

TRANSLATIONAL OUTLOOK: Clinical outcome studies are needed to extrapolate these findings to patient care.

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KEY WORDS anterior, leaflet, posterior, septal, transcatheter approach, tricuspid valve

APPENDIX For an expanded Methods section as well as a supplemental figure and video, please see the online version of this article.