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ORIGINAL RESEARCH

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Long-arm clip for Transcatheter Edge-to-Edge Treatment of Mitral and Tricuspid Regurgitation – Ex-Vivo Beating Heart Study

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ABSTRACT

Background: A longer-arm clip design for transcatheter edge-to-edge repair of mitral and tricuspid valves could be beneficial in treating complex valve pathologies. Its hemodynamic effects and usability are unknown. This study aims to assess its new design in an ex-vivo beating heart model.

Methods: The long-arm clip was implanted in porcine left (n = 14) and right (n = 6) hearts with induced degenerative mitral regurgitation and functional tricuspid regurgitation, respectively. Hemodynamic conditions were assessed at baseline, pathology and post-treatment. Usability and grasping quality were evaluated during simulated treatment.

Results: Mitral valve treatment significantly increased cardiac output ($p < 0.001$) and decreased mean left atrial pressure during ventricular systole ($p = 0.001$) with respect to pathological conditions. Tricuspid treatment with grasping involving septal leaflet significantly increased cardiac output (posterior-septal grasping: $p = 0.006$; anterior-septal grasping: $p = 0.04$). There was no significant increase of transvalvular gradient pressure nor tissue damage.

Conclusion: Long-arm clip treatment was feasible in porcine hearts, it effectively reduced regurgitation and did not significantly increase the transvalvular pressure gradient.

Abbreviations: MV, mitral valve; DMR, degenerative mitral regurgitation; FTR, functional tricuspid regurgitation; TV, tricuspid valve; XTR Clip, long-arm clip; P2, posterior middle scallop of mitral valve; MRF, mitral regurgitation fraction; A-P, medial grasping of anterior and posterior leaflets; A-S, medial grasping of anterior and septal leaflets; P-S, medial grasping of posterior and septal leaflets; CO_s, systemic cardiac output; CO_p, pulmonary cardiac output; AoP, mean aortic pressure; PAP, mean pulmonary artery pressure; LAP, mean left atrial pressure; LAP_{syst}, mean left atrial pressure during ventricular systole; Δp_m, mean diastolic pressure gradient across mitral valve; Δp_t, mean diastolic pressure gradient across tricuspid valve; APd, mid-systole mitral antero-posterior distance; CI, confidence interval

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KEYWORDS Mitral; tricuspid; regurgitation; valve repair; edge-to-edge; transcatheter; MitraClip; ex-vivo model

Introduction

Mitral (MV) and tricuspid valve (TV) pathologies are age-related and their burden is predicted to increase as the life expectancy rises.[1] MV regurgitation is the most common valvular pathology with an overall prevalence of 2%, with 70% of surgical cases being degenerative aetiology (degenerative mitral regurgitation; DMR).[2,3] Functional tricuspid regurgitation (FTR) is typically observed secondary to left heart diseases, and severe FTR has been specifically associated with high mortality when untreated.[4]

Since these valvular diseases occur with increased frequency in elderly populations having high surgical risk, MV and TV treatment with a transcatheter approach is being increasingly used. Edge-to-edge MV treatment with MitraClip device (Abbott Structural Heart, Santa Clara, CA, USA) is the most commonly used catheter-based technique for MV repair with over 75,000 implants to date. Over 10 years clinical experience has demonstrated high procedural success (up to 97% patients with mitral regurgitation reduction to grade ≤2) and low adverse events rate (0.1% procedural mortality).[5,6] These results have also encouraged translation of the technique to FTR treatment with promising initial clinical outcomes.[7,8]

Non-standard approaches have been applied to enable the use of the device in scenarios with extreme coaptation defects (e.g. zipping procedure, drugs, intra-aortic balloon pump support).[9,10] In such situations, a long-arm clip device could be beneficial not only in terms of further improving ease of the grasping, but may also broaden the population of patients that could be treated with clip-based therapy. However, effects of longer clip arms on valvular pressure gradients is unknown,

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Supplemental data for this article can be accessed here.

which could relate to long-term outcomes.[11] Moreover, device positioning and implantation through MV and TV with a longer arm clip have not yet been systematically assessed.

The aim of this experimental study was to evaluate, in an ex-vivo beating heart platform, the effects of DMR and FTR treatment with a novel clip featuring extended arms by means of (1) the immediate post-operative hemodynamic changes, and (2) device usability.

Materials and methods

Device description

A new clip has been developed as an additional implant size option to the current MitraClip NT device. The novel design, referred to in this publication as "XTR Clip" (Figure 1), has arms that were extended from 9 mm (existing commercially available clip) to 12 mm. The new clip's gripper component, which contacts the atrial side of the leaflets, has also been extended and the number of frictional element rows along its length was increased from four to six.

Ex-vivo beating heart model

Percutaneous treatments of MV and TV regurgitation using the XTR Clip device design were assessed in an ex-vivo beating heart model that was specifically designed for MV[12] and TV[13] treatment assessment. Porcine left or right hearts were actuated by a positive displacement pump causing dynamic opening and closing of the heart valves. The aorta or pulmonary artery were connected to a flow loop simulating systemic or pulmonary circulation impedance with adjustable peripheral resistance, respectively. In both left and right heart testing protocols, the systems were set to reproduce physiological resting conditions (heart rate 60 beats/min; stroke volume 70 mL). Peripheral resistance was adjusted to yield mean baseline aortic and pulmonary artery pressures at approximately 100 mmHg and 15 mmHg, respectively. With this setup, pressure changes could be observed depending on flow conditions at pathological and post-treatment conditions. Echocardiography was used to measure valve morphology and to help guide device implantation (iE33 equipped with X7-2t probe, Philips, Eindhoven, The Netherlands). Direct visualization of the valves in the atrial view was enabled by fiberscope imaging (ENF-GP, Olympus Corp., Tokyo, Japan).

DMR treatment protocol

DMR model

The DMR pathological condition was induced by adopting the well-established experimental approach[14–16] based on direct cutting of the primary chordae tendineae attached to the free edge of the posterior middle scallop (P2). This resulted in a P2 flail which coincided with the most common DMR lesion.[17] Representative fiberscopic and echocardiographic snapshots of the baseline and pathological MV are presented in Figure 2A.

Protocol

A total of 14 heart samples were evaluated in the following conditions: baseline, DMR and post-treatment. Following DMR creation the obtained pathological model was classified as moderate or severe DMR based on mitral regurgitation fraction (MRF) which was estimated from the aortic flow measurement as explained in the Appendix. The samples with MRF>50% were considered as severe.[18]

Implantation technique

The XTR Clip was implanted by an expert operator, possessing clinical and experimental experience, under direct fiberscopic guidance (for procedure control and repeatability) and echocardiographic guidance support. To ensure clinically representative maneuvers, the steerable guide catheter was inserted into a silicon model of the inferior vena cava which in turn was attached to the left atrium via a surgically-made access through the fossa ovalis. The clip delivery system was then inserted into the guide catheter and the clip was

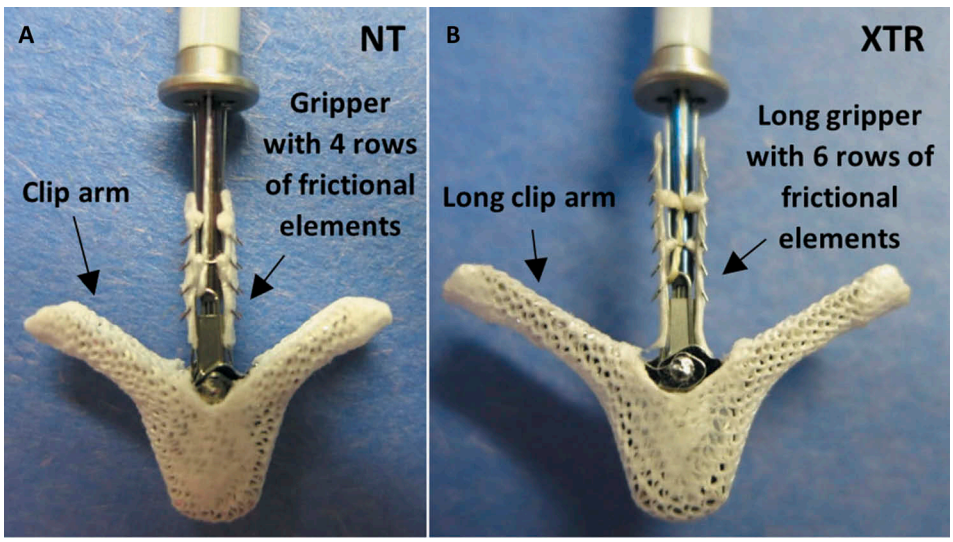

Figure 1. Images of commercially available NT clip device: (A) and design of XTR clip (B).

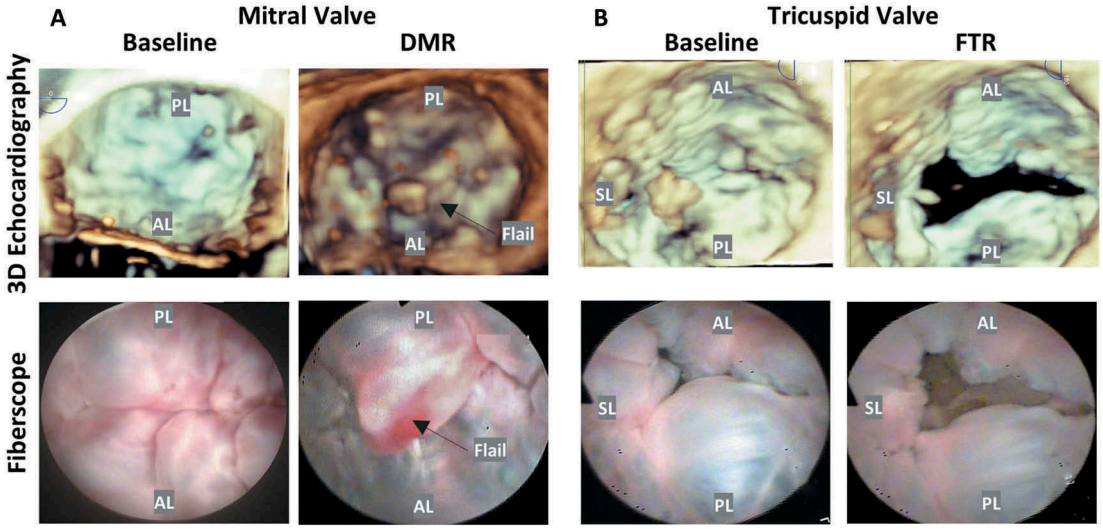

Figure 2. Ex-vivo pathological models: Representative 3D echocardiographic (upper row) and fiberscopic (lower row) images in the atrial view of baseline and pathological models of mitral (A) and tricuspid (B) valve. PL, posterior leaflet; AL, anterior leaflet; SL, septal leaflet.

advanced into the left atrium above the MV. After confirming clip perpendicularity to the valvular plane, its arms were opened and the clip was advanced below the valvular plane. Finally, the P2 flail was grasped along with the corresponding anterior middle scallop and the clip was closed.

FTR treatment protocol

FTR model

As described elsewhere[13,19] the FTR pathological model exploited the tendency of the right porcine ventricle to dilate under physiological pressure in an ex-vivo setup. TV annulus dilation and right ventricular papillary muscle displacement were observed, leading to TV regurgitation. This experimental model is characterized by regurgitation orifice area of 1.3 ± 0.9 cm^2. Valve competency could be restored if desired by tensioning two adjustable bands placed externally to the right ventricle at TV annulus and papillary muscle level. Representative fiberscopic and echocardiographic snapshots of the baseline and pathological TV are presented in Figure 2B.

Protocol

Six right heart samples were evaluated at baseline, FTR and post-treatment conditions including medial grasping of the following leaflet pairs: anterior-posterior (A-P), posterior-septal (P-S) and anterior-septal (A-S).

Implantation technique

The XTR Clip implantation in the TV was performed in a similar manner to the DMR treatment previously described. However, in this case, access to the right atrium was made directly via inferior vena cava. Grasping at A-P, P-S and A-S positions was performed in randomized order. After completing the grasping at the first position, the clip was re-opened, retracted back into the right atrium and the procedure was repeated with grasping performed at the second and the third position.

Hemodynamics assessment

The MV and TV regurgitation and overall hemodynamics were quantified at baseline, pathological and post-treatment conditions by direct hemodynamic measurements including: systemic/pulmonary cardiac output (CO_s/CO_p), mean aortic/pulmonary pressure (AoP/PAP), mean left atrial pressure (LAP), mean left atrial pressure during ventricular systole (LAP_{syst}) and mean diastolic pressure gradient across MV/TV ($\Delta p_m/\Delta p_t$). Mid-systole mitral antero-posterior distance (APd) was obtained from echocardiographic images.

Usability and grasping quality assessment

Ease of grasp was assessed by counting the number of grasping attempts required to successfully capture both leaflets within the XTR Clip. Grasping quality was assessed by quantifying the amount of leaflet tissue captured between the clip arms and grippers. The clip arm length was divided into 12 sections corresponding to the 12 frictional element rows distributed along the two grippers (six rows on each, see Figure 1) and leaflet insertion percentage was calculated as the ratio between the number of frictional element rows engaged with tissue after capture and the total number of frictional element rows.

Statistical assessment

All values were presented as mean ± standard deviation following the normal distribution assessed by the Kolmogorov–Smirnov test. ANOVA analysis for repeated measures was used to assess the statistical differences between baseline, pathological and post-treatment conditions. Bonferroni's post-hoc test was applied to compare pathological conditions with baseline and post-treatment conditions, whereas Tukey's

Multiple Comparison test was used to evaluate differences among FTR post-treatment conditions. Moderate and severe DMR subpopulations were compared by unpaired t-test. A p-value <0.05 was assumed as statistically significant. For post-treatment Δp_m and Δp_t expressed as 95% confidence intervals (CIs) range were compared with the value of clinical threshold for mitral stenosis after edge-to-edge repair equal to 5 mmHg.[11] The same value was used for TV stenosis threshold due to the lack of clinical reference. Lack of stenosis risk could be claimed if the upper limit of CI was not greater than the defined threshold.

Results

Mitral regurgitation treatment in DMR model

Table 1 summarizes all measured parameters related to XTR Clip use in DMR model. DMR condition induced significant hemodynamic changes of CO_s, AoP, LAP and LAP_{syst} (−59%, −44%, +22%, +34%, respectively, all $p \leq 0.001$) when comparing to the baseline. The estimated mean MRF in DMR conditions was 48 ± 24%, which represents a mix of moderate and severe samples. APd value was unchanged ($p = 0.4$) with respect to the baseline, as expected.

The treatment significantly improved the hemodynamic condition as evidenced by consistent increase of CO_s and AoP by 119% and 55% (both with $p < 0.001$), respectively and drop of LAP, LAP_{syst} and APd by −11% ($p = 0.007$), −18% ($p = 0.001$) and −7% ($p = 0.01$), respectively. The pathological and post-treatment Δp_m did not differ significantly while the 95% CI of post-treatment Δp_m ranged between 0.8 and 2.8 mmHg and the upper limit was below the defined stenosis-risk threshold (5 mmHg).

Table 2 summarizes the change in hemodynamic conditions when the data pool was subdivided into moderate and severe case groups. These two groups had mean MRF of 28 ± 15% and 67 ± 12%, respectively. In both subgroups, inducing DMR resulted in a significant drop of CO_s ($p < 0.001$ for both) and AoP ($p = 0.002$ for moderate cases, $p < 0.001$ for severe cases) and an increase of LAP_{syst} ($p = 0.001$ for moderate cases, $p = 0.01$ for severe cases). The treatment resulted in significant increases in CO_s ($p = 0.01$ in moderate cases, $p < 0.001$ in severe cases) and AoP ($p = 0.04$ in moderate cases, $p = 0.002$ in severe cases) and resulted in a significant decrease in LAP_{syst} ($p = 0.005$ in moderate cases).

When comparing the severe with moderate subpopulation, there was no significant difference in CO_s between the two groups at baseline ($p = 0.9$) and post-treatment ($p = 0.3$). However, in DMR conditions the severe subpopulation had a significantly lower CO_s when compared to the moderate subpopulation ($p = 0.01$).

Tricuspid regurgitation treatment in FTR model

In all six heart samples FTR conditions were successfully simulated. Table 3 summarizes hemodynamic results. Inducing pathological conditions resulted in a significant drop of CO_p (−28%, $p = 0.02$). Grasping in the A-S and P-S locations resulted in a significant increase of CO_p (47%, $p = 0.006$ and 38%, $p = 0.04$, respectively). Specifically, no statistical difference between the A-S and P-S treatments was found. PAP and Δp_t did not significantly change after clip implantation at any grasping locations. Upper limits of 95% CI of post-treatment Δp_t were as follows: 2.5 mmHg for A-P grasping, 2.3 mmHg for A-S grasping and 2.7 mmHg for P-S grasping and they all were below the defined stenosis threshold (5 mmHg).

Usability

The XTR Clip was successfully maneuvered and implanted in all cases using positioning and grasping techniques per the instructions for use. Two representative fiberscopic videos of

Table 1. XTR clip treatment in DMR model (14 samples): Overall comparison of the hemodynamic and echocardiographic parameters.

Parameter	Baseline	DMR	Post-treatment
CO_s, L/min	2.7 ± 0.8*	1.1 ± 0.6	2.0 ± 0.6*
AoP, mmHg	92.1 ± 17.3*	50.6 ± 21.3	72.2 ± 20.9*
Δp_m, mmHg	1.1 ± 1.3	1.1 ± 1.0	1.9 ± 1.5
LAP, mmHg	19.5 ± 1.6*	23.8 ± 2.1	21.3 ± 2.3*
LAP_{syst}, mmHg	20.2 ± 1.7*	27.4 ± 4.0	22.5 ± 3.6*
APd, mm	33.0 ± 2.2	32.3 ± 2.0	29.9 ± 2.6*

Note. *Statistical significance vs. DMR ($p < 0.05$).
CO_s, cardiac output; AoP, mean aortic pressure, Δp_m, mean diastolic pressure gradient across mitral valve; LAP, mean left atrial pressure; LAP_{syst}, mean left atrial pressure during ventricular systole; APd, anteroposterior distance; DMR, degenerative mitral regurgitation.

Table 2. Severe (seven samples) and moderate (seven samples) DMR treatment with XTR clip: Hemodynamic conditions assessment.

	CO_s, L/min		AoP, mmHg		Δp_m, mmHg		LAP_{syst}, mmHg	
	Moderate	Severe	Moderate	Severe	Moderate	Severe	Moderate	Severe
Baseline	2.7 ± 0.9*	2.8 ± 0.7*	90.9 ± 11.3*	93.8 ± 21.7*	1.0 ± 1.3	1.3 ± 1.3	19.5 ± 1.3*	21.3 ± 1.0*
DMR	1.5 ± 0.5†	0.7 ± 0.4†	61.3 ± 22.6	39.8 ± 14.0	1.1 ± 0.8	1.2 ± 1.3	25.7 ± 2.7	29.0 ± 4.7
Post-treatment	2.1 ± 0.6*	1.8 ± 0.7*	80.1 ± 18.7*	64.4 ± 21.4*	1.7 ± 1.5	1.9 ± 1.7	20.9 ± 1.3*	24.9 ± 4.2

Note. *Statistical significance vs. DMR ($p < 0.05$); †Statistical significance between moderate and severe cases ($p < 0.05$).
CO_s, cardiac output; AoP; mean aortic pressure; Δp_m, mean diastolic pressure gradient across mitral valve; LAP_{syst}, mean systolic left atrial pressure; DMR, degenerative mitral regurgitation.

Table 3. XTR clip treatment in FTR model (six samples): Overall hemodynamic condition assessment.

			Post-treatment		
Parameters	Baseline	FTR	A-P	A-S	P-S
CO_p, L/min	2.3 ± 0.3*	1.6 ± 0.2	1.9 ± 0.3	2.4 ± 0.5*	2.2 ± 0.5*
PAP, mmHg	24.9 ± 1.6	20.8 ± 1.4	21.5 ± 2.6	23.1 ± 2.7	22.3 ± 4.1
Δp_t, mmHg	1.4 ± 0.6	2.0 ± 0.8	1.8 ± 0.6	1.3 ± 1.0	1.6 ± 1.1

Note. *Statistical significance vs. FTR ($p < 0.05$).
CO_p, cardiac output; PAP, mean pulmonary artery pressure; Δp_t, mean diastolic pressure gradient across tricuspid valve; FTR, functional tricuspid regurgitation; A-P, medial grasping between anterior and posterior leaflet; A-S, medial grasping between anterior and septal leaflet; P-S, medial grasping between posterior and septal leaflet.

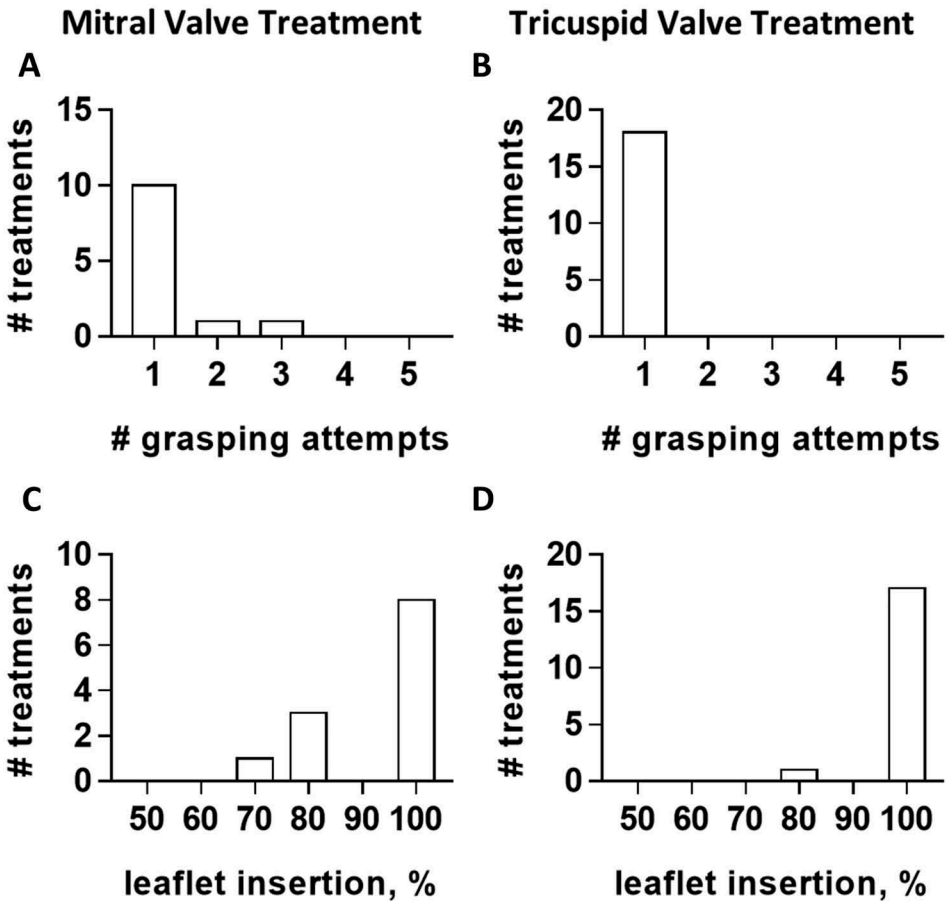

Figure 3. Usability (upper row: A,B) and grasping quality (lower row: C,D) assessment for DMR (left column) and FTR (right column) treatment with XTR Clip.

the implantation procedures in MV and TV are available as supplemental materials.

In the majority of DMR cases (12 out of 14) and in all 18 FTR treatments (six samples in three grasping positions) the first grasp resulted in successful capture of MV/TV leaflets, constituting procedural success (Figure 3A and B).

Grasping quality

Upon successful leaflet grasping, full and symmetrical tissue insertion was achieved in 10 out of 14 DMR cases and 17 out of 18 of FTR treatments (Figure 3C and D, respectively). Overall average leaflet insertion percentage during DMR and FTR treatments was 93% and 99%, respectively. The lowest obtained insertion covered 67% and 83% of leaflet tissue in the DMR and FTR cases, respectively.

Discussion

The transcatheter edge-to-edge treatment with a long-arm clip was recently approved for clinical use. Until now only one case was reported and suggested the feasibility and improved ease of grasping with the XTR Clip.[20] As extensive clinical data on this clip design are not yet available, this ex-vivo study provides quantitative insights on the XTR clip performance at a very early phase of its clinical application.

Specifically, in this study DMR and FTR ex-vivo models were used to quantify acute hemodynamic changes following the treatment with the XTR Clip and to assess the clip

usability and grasping quality. The comparison of the pathological and post-treatment conditions revealed that the treatment significantly reduced the regurgitation and did not cause any significant increase in mean pressure gradient across either MV or TV. The XTR Clip was applied with a similar user perception and performance in a wide range of the distances between the free leaflets' edge in both degenerative and functional etiologies of MV and TV, respectively.

Pathological models

The treatment was applied to ex-vivo pathological models mimicking the most common forms of MV and TV pathologies.[21] Creating these pathologies always resulted in significant changes in hemodynamic outputs when compared to the physiologic baseline. Under constant pumping setting (pump stroke volume and heart rate), the measured changes in CO_s/CO_p from physiological to pathological and then post-treatment conditions reflect purely the changes in MV and TV regurgitation.

The models were previously applied in other ex-vivo or in-vivo valvular treatments studies[14–16,19,22] and this form of testing allowed for quantification of the changes induced by the treatment in a repetitive and controllable manner.

Regurgitation reduction

The XTR Clip treatment in both DMR and FTR experimental models resulted in significantly increased CO_s and CO_p, respectively. It reflects the successful edge-to-edge treatment with a decrease of regurgitation through both MV and TV. The observed trends in DMR model were comparable with acute changes observed clinically in DMR patients treated with standard length clip.[23] The comparison of severe and moderate DMR treatment outcomes revealed that XTR Clip therapy allowed reaching a similar success rate in both groups and no statistically significant differences in post-treatment hemodynamics were observed.

The treatment of FTR in the experimental model showed that procedural success can be expected when grasping involved the septal leaflet along with either the anterior or posterior leaflet, while clipping in the A-P location did not significantly improve hemodynamic conditions. This finding agrees with initial clinical observations following transcatheter edge-to-edge FTR treatment[24,25] and confirms the results of our previous ex-vivo beating heart study[19] where a commercially available device was used to grasp TV leaflets. The same study yielded similar hemodynamic outcomes to the present one (recovery of post-treatment CO_p to the baseline level).

Pressure gradient assessment

The longer clip arms did not cause any statistically significant increase of either mitral or tricuspid pressure gradients in the bench model and post-treatment Δp_m and Δp_t did not reach the clinically defined threshold for valve stenosis.[11] In fact, they were at least 2 mmHg lower. Moreover, post-treatment pressure gradient changes in the present study for the XTR Clip were comparable to previous values measured for a commercially available device tested in similar conditions for MV and TV treatments.[19,26] Present findings suggest that the long-arm clip would not be associated with mitral and tricuspid stenosis. Clinically infrequent post-treatment increase of Δp_m with a higher occurrence after multiple clip placement was reported[11] and the preference between residual regurgitation or elevated pressure gradient is debated.[27] In our experiments one clip per valve was implanted always under the same loading conditions in similar anatomical scenarios. Therefore, the findings need to be further confirmed clinically (with a wide range of stroke volumes, the presence of annulus calcifications, baseline annulus size, and leaflet thickness and mobility).

Atrial pressure monitoring

A decreasing trend in left atrial pressure was noted in this experimental study after pathological MV grasping. The most significant change was observed during ventricular systole where, in clinical settings, the v-wave occurs. It agrees with atrial pressure changes which are occasionally collected during transcatheter edge-to-edge treatment.[23,28,29] This finding indicates that intraprocedural LAP monitoring during transcatheter MV treatment can provide a valuable insight to the treatment success and may assist with intraprocedural decision making, such as clip placement.

Usability and grasping quality

The increased clip arm length did not require any changes to the standard positioning and grasping techniques per the instruction for use and the majority of performed graspings were successful at the first attempt in the experimental model. Similarly, grasping quality featuring full and symmetric leaflets insertion was achieved in most of the performed treatments. According to an in-silico study this could favor a safer outcome due to improved mechanical stresses distribution among the leaflets.[26] Nonetheless, usability of the XTR clip should be confirmed in real clinical setting where intraprocedural echocardiographic imaging especially of TV is considered challenging.[30]

Increased contact surface area between the device and the leaflets in long-arm clip procedure did not cause gross tearing of the leaflets tissue in this study as assessed post-procedurally once the heart was removed from the system (see Figure 4). However long-term biomechanical interaction between the device and the soft tissue warrants further study.

Addition to implant size – potential benefits

The introduction of longer clips could open new opportunities to treat anatomically more challenging cases. This could be particularly important in FTR treatment where severe coaptation defects (>2 cm) are observed[24] and there is a need for effective percutaneous FTR treatment devices.[31,32] Moreover, one can speculate that the long-arm clip could ensure improved grasping quality thus reducing the number of clips that needed to be implanted.

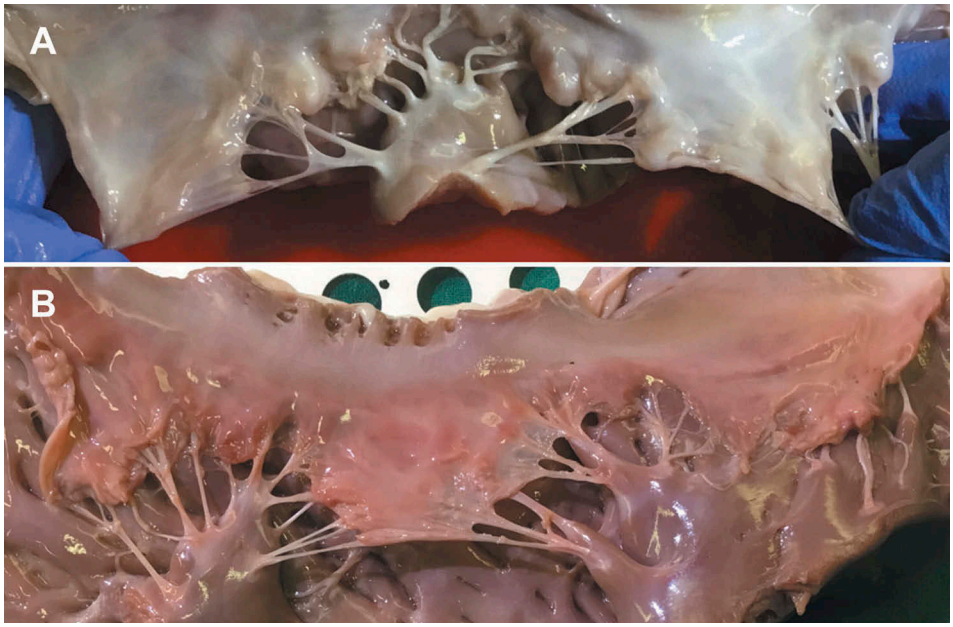

Figure 4. Gross macroscopic tissue damage assessment: No damage of the chordae nor tearing of the leaflets was observed in any of the mitral (A) or tricuspid (b) valve samples.

Limitations

The study carries intrinsic limitations of ex-vivo beating heart model. This modeling setup allows for quantification of immediate post-treatment hemodynamic alterations only and the mid/long-term results and device safety need to be further assessed clinically. The tests were performed with a single clip in resting loading conditions on porcine hearts which do not reproduce less frequently occurring anatomical features (calcified annulus, mixed aetiologies, leaflets degeneration). The results should be cautiously translated for specific cases not tackled in this study. Furthermore, the observed changes of left atrial pressure in our model were related to a simple hydraulic phenomenon which did not allow the direct evaluation of the v-wave value. The study focus was on reproduction of the graspings conditions in locations assigned by the study protocol, hence clip positioning was guided mainly by direct fiberscopic visualization with support of echocardiography instead of echocardiography with fluoroscopy support (as in the clinic).

Conclusions

In this study hemodynamics and usability features of DMR and FTR transcatheter edge-to-edge treatment with a long-arm clip design were evaluated in an ex-vivo beating heart model. It was shown that (1) the treatment of a large range of modeled pathologies (moderate and severe DMR as well as FTR) was successful as demonstrated by a gnificant increase of CO without procedural difficulty; (2) the XTR Clip did not induce any significant increase of pressure gradient either across MV or TV; (3) no leaflet damage was caused by use of the XTR Clip as assessed by post procedure necropsy; and (4) atrial pressure monitoring could serve as an additional indicator of procedural success. Further studies are needed to identify the group of patients that can specifically benefit from the XTR Clip therapy.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Appendix

Mitral regurgitation fraction (MFR) estimation was based on aortic flow measurement considering volume conservation principles in diastole and systole (Equations 1 and 2).

$$\overbrace{\phantom{AF_B + MB_B + cV_{B,S}}}^{\text{Systole}} \quad \overbrace{\phantom{MF_B + AB_B + cV_{B,D}}}^{\text{Diastole}}$$

$$Baseline: \; AF_B + MB_B + cV_{B,S} = MF_B + AB_B + cV_{B,D} \tag{1}$$

$$DMR: \; AF_{DMR} + MB_{DMR} + cV_{DMR,S} = MF_{DMR} + AB_{DMR} + cV_{DMR,D} \tag{2}$$

Where:
AF_X – aortic forward volume in condition X
AB_X – aortic backflow volume in condition X
MF_X – mitral forward volume in condition X
MB_X – mitral backflow volume in condition X
$cV_{X,Y}$ – accumulated intraventricular volume related to the ventricular compliance in condition X and phase Y
$X = B/DMR$ – baseline/degenerative mitral regurgitation
$Y = S/D$ – systole/diastole

The following assumptions were made:

- MB_B was negligible once the proper valve coaptation was confirmed via direct visualization: $MB_B = 0$
- The accumulated intraventricular volumes at baseline and DMR conditions during systole and diastole were assumed equal, the possible influence of pressure changes when going from baseline to DMR was neglected: $cV_{B,S} = cV_{DMR,S},\ cV_{B,D} = cV_{DMR,D}$
- Mitral forward volume in both conditions was assumed equal as the DMR pathological model introduced no changes to the diastolic phase: $MF_B = MF_{DMR}$

Combining Equations 1 and 2 using above-mentioned assumptions, MB_{DMR}, MF_{DMR} and MRF were derived as shown in Equations 3–5.

$$MB_{DMR} = AF_B - AF_{DMR} - AB_B + AB_{DMR} \tag{3}$$

$$MF_{DMR} = AF_{DMR} + MB_{DMR} - AB_{DMR} = AF_B - AB_B \tag{4}$$

$$MRF = \frac{MB_{DMR}}{MF_{DMR}} * 100\% = \frac{AF_B - AF_{DMR} - AB_B + AB_{DMR}}{AF_B - AB_B} \tag{5}$$