

The Effect of a Novel Transcatheter Edge-to-Edge Mitral Valve Repair Device in a Porcine Model of Mitral Regurgitation

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Background: A new technique has been developed for treating mitral regurgitation (MR) via a transapical approach, which encompasses an easy-to-use leaflet clamp and a smaller-sized delivery system (14F-16F).

Objectives: We aimed to evaluate the effectiveness of this device in a porcine model of acute MR.

Methods: Acute MR was induced in 36 anesthetized porcine subjects by severing the chordae supporting the corresponding segment of the leaflet. The ValveClamp system was then transapically implanted on the prolapsing segment under epicardial echocardiographic guidance. Echocardiographic assessments were performed before and after the transapical interventions. All of the animals were killed 30 days after the procedure to verify the proper location of the implanted devices.

Results: Epicardial echocardiography revealed severe MR (n = 26) or moderate to severe MR (n = 10) in the pig model of acute MR. Overt MR reduction was observed following the procedure through echocardiography; residual MR was absent in 10 cases, mild in 17 cases, and moderate in 9 cases. There was no evidence of mitral stenosis at the end of the procedure in terms of mitral valve area and mitral valve pressure gradient. Autopsy demonstrated that all ValveClamp devices were precisely placed to clamp the prolapsing segment of the mitral valve.

Conclusions: Transapical implantation of the ValveClamp device under epicardial echocardiographic guidance was effective and safe in reducing acutely induced MR in this pig model. It is potentially applicable as a novel user-friendly transcatheter edge-to-edge mitral valve repair device for the treatment of MR in humans.

Key Words: Animal model • Degenerative mitral regurgitation • Transcatheter mitral valve repair • 3D transoesophageal echocardiography

INTRODUCTION

Moderate-to-severe mitral regurgitation (MR) is a common valvular heart disease that is associated with a significant increase in overall morbidity and mortality if

left untreated.¹ About one-half of patients who present with severe symptomatic MR are unsuitable for classic surgical valve replacement or repair approaches due to the increased risk of surgery.²

In the last few years, transcatheter mitral valve repair has become a fertile field of innovative treatment strategies. The MitraClip system represents the most widely used technology to address edge-to-edge transcatheter mitral valve repair,³⁻⁶ and it is recommended in the current guidelines for treating patients with symptomatic, functional or degenerative, grade $\geq 3+$ MR and a prohibitive surgical risk.^{7,8}

The ValveClamp system (Shanghai Hanyu Medical Technology, Shanghai, China) is a novel edge-to-edge re-

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pair device designed as a transapical means for ease of operation. The feasibility and safety of the ValveClamp system has been verified in pigs with native valves.⁹ The present study reports the initial application of this device in clamping a prolapsed valve in an animal model of acute MR.

MATERIALS AND METHODS

The ValveClamp system

Basically, this device encompasses an easy-to-use leaflet clamp, a valve-crossing device, a delivery system, and an introducer sheath (Figure 1). The clamp device is comprised of a front clamp, rear clamp, and closed ring. The front clamp and rear clamp include two clamping arms. The arm lengths of the front and rear clamps are 9 mm and 10 mm, respectively (Figure 2). Each front clamping arm and each corresponding rear clamping arm hold an object through the interaction force generated by closing and pushing against each other. The front clamp has a clamping bar, and the rear front clamp has a clamping ring. The clamping bar can pass through the center hole of the clamping ring so that the clamping arms of the two clamps can close onto each other. The clamping ring of the rear clamp can be completely screwed into the closed ring. The closed ring has an outer diameter of 3.5 mm, and it is sleeved outside the periphery of the clamping arms so that the clamping arms can close towards the central line as needed and the clamping is tighter. The surfaces of the ends of the clamping arms and the external wall of the closed ring are covered with polyester film to promote rapid endothelialization. The valve-crossing device is comprised of a cylin-

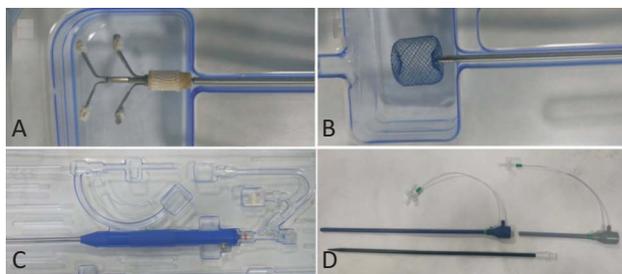


Figure 1. The ValveClamp system (A) The clamp device, which includes a front clamp, a rear clamp, and a closed ring. (B) The valve-crossing device. (C) The delivery system. (D) The 16 Fr introducer sheath, provided with an associated dilator and a loading sheath.

der mesh made of a Ni-Ti alloy and a stainless-steel rod. The introducer sheath has an inner diameter of 16 Fr, and it has an associated dilator and a loading sheath.⁹

Animal preparation and device implantation

From October 2017 to February 2018, 40 young adult porcine subjects (Yorkshire pigs) (body weight, 80-95 kg) were enrolled into the study. All of the experimental protocols were approved by the institutional committee on animal research, and the study was performed in accordance with the Guide for the Care and Use of Laboratory Animals (NIH Publication No. 85-23, Revised 1996).

Anesthesia was induced by intramuscular injection of ketamine (2.2 mg/kg), telazol (4.4 mg/kg), and xylazine (2.2 mg/kg), and it was maintained with isoflurane (1-2%). Electrocardiogram monitoring was performed.

After localizing the ventricular apex by transthoracic echocardiography, an anterolateral mini-thoracotomy was performed in the fifth or sixth intercostal space by making a small incision. Then, under the guidance of intraoperative epicardial echocardiography (IEE), the puncture site was confirmed. The lower segment of the sternum was split, and the apex was exposed where a double pledget-supported purse-string suture was placed. Heparin (300 units/kg) was then administered intravenously.

Acute MR was induced in anesthetized porcine subjects by severing the chordae supporting the corresponding segment of the leaflet with a custom-made device. Thinner marginal chordae were preferred, because cutting a primary chorda might induce excessively severe MR. The operator identified thin marginal chordae that were near to the leaflet margin and could be cut by a small tension force. In contrast, the primary chordae

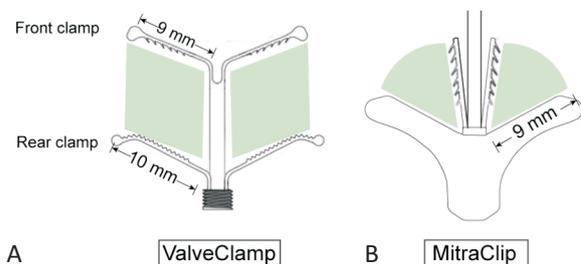


Figure 2. Schema of the capture range with ValveClamp (A) and MitraClip (B). Owing to a novel arrangement of grasping clamps, the capture range (green areas) of ValveClamp is considerably larger than that of MitraClip despite of the similar dimension of arms.

were near to papillary muscles and could only be cut by a large force. Then it was severed using the custom-made device with a small tension force. If the MR was not significant (grade $\geq 3+$) after cutting one chorda, more chordae were severed. Assessments of MR were finally performed by IEE. The biplane mode was then used to obtain apical 2-chamber and long axis views to guide the procedure.

ValveClamp implantation was then performed as described previously.⁹ Briefly, a 16 Fr introducer sheath was introduced into the left atrium (LA) with the help of a valve-crossing device. The valve-crossing device was then retrieved, and the clamp device was loaded into the introducer sheath and advanced to the tip level inside the introducer sheath. The clamp device proceeded slowly until the front clamp was fully opened. To open the rear clamps, the introducer sheath was carefully pulled back under echo guidance. A combination of three-dimensional and X-plane IEE imaging was used to position the clamp arms at the middle of the regurgitant jet and perpendicular to the valve coaptation line.

After checking its position and orientation, the clamp device was retrieved back gently during the diastolic phase so that the rear clamp was placed just under the leaflets, while the front clamp remained in the left atrium. Leaflet engagement was achieved by finely advancing the catheter until the leaflets rested on the arms. The front clamp was pulled back to capture the leaflets, and then the closed ring was moved forward to cover the ventricular end of the clamp arms, making them close to each other. If the residual MR was deemed satisfactory (grade $\leq 2+$), the device was then released; otherwise the device was re-opened, gently pushed back to the left atrium and relocated before the next clamping, until the intended effect was obtained. Adequate reduction of MR to a grade of 2+ or less was assessed using echocardiography.

Evaluation protocol

Echocardiography was performed using a commercially available ultrasound machine (IE33, Philips Medical Systems, N.A.) equipped with a fully sampled matrix array transducer (X5-1). A detailed 2-dimensional Doppler echocardiographic examination was performed after inducing MR as well as immediately after ValveClamp implantation. MR was characterized by echocardiogra-

phy using the guidelines of the American Society of Echocardiography.¹⁰ Images were stored digitally for offline analysis using QLAB 10.8 commercially available software (Philips Medical Systems). Three-dimensional imaging mode was used to evaluate the site and stability of the device, as well as the motion of the mitral valve. All of the animals were killed 30 days after the procedure to verify the proper location of the implanted devices and to identify any tissue damage or thrombosis. Procedural success was defined as a reduction of MR by ≥ 1 grade with a residual MR of \leq grade 2+.

Statistical analysis

Hemodynamic and structural data obtained from continuous variables were summarized and reported as mean and standard deviation. The paired t test was used to compare the preimplant and postimplant data, and a p value < 0.05 was considered to be significant. SPSS version 21.0 software (SPSS Inc, Chicago, Ill) was used.

RESULTS

At baseline, echocardiography demonstrated no significant (grade $\geq 2+$) MR or mitral valve pathology. When one or two thin chordae of the mitral leaflet were cut, mitral valve prolapse with MR (grade $\geq 3+$) could be detected in each of the cases by color Doppler echocardiography. A total of 40 pigs were initially enrolled into the study. Before the ValveClamp implantation, 3 pigs died of uncontrollable acute lung edema because the MR was too severe, and one pig died due to an anesthesia accident. Of the other 36 pigs, prolapse of the A2 scallop was seen in 23, prolapse of the P2 scallop was present in 11, and prolapse of the A3 or P3 scallop was seen in 1 each.

All of the ValveClamp devices were deployed successfully under the guidance of IEE. After ValveClamp deployment, echo assessments revealed that the ValveClamp attenuated MR to $\leq 2+$ in 100% of the pigs. In detail, residual MR was absent in 10 cases (27.8%), mild in 17 cases (47.2%), and moderate in 9 cases (25%). Accordingly, the vena contracta width (VCW) was substantially decreased (7.60 ± 2.87 versus 2.35 ± 1.06 mm, $p < 0.001$).

Every pig was implanted with one ValveClamp de-

vice without causing damage to the valvular or subvalvular apparatus. IEE also showed that all of the devices were implanted on the prolapsing segments and that a double-orifice mitral valve anatomy had been created (Figure 3). Accordingly, the mitral valve area (MVA) decreased from $4.72 \pm 1.16 \text{ cm}^2$ to $3.25 \pm 0.87 \text{ cm}^2$ ($p < 0.001$). In addition, the pigs showed significantly elevated maximum mitral valve pressure gradient (MVPG_{max}) and mean mitral valve pressure gradient (MVPG_{mean}) (1.95 ± 0.47 versus $3.66 \pm 0.62 \text{ mmHg}$ and 0.87 ± 0.31 versus $1.7 \pm 0.28 \text{ mmHg}$, $p < 0.001$ for both). All of the absolute values of the mean gradient were less than 4 mmHg. Differences in parameters including left ventricular ejection fraction (LVEF) and cardiac dimensions were statistically insignificant ($p > 0.05$). The changes in hemodynamic parameters, cardiac size, and functional parameters after the procedure are presented in Table 1.

It took 72-105 minutes from the chest incision to the suture, including cutting the chordae. The duration of catheterization ranged from 21-45 min.

Autopsy further demonstrated that all devices were precisely implanted on the prolapsing segments. No procedure-related complications (for example, detachment of the device, thromboembolism, and damage to the valve structure) were observed within 30 days following repair.

DISCUSSION

The present study demonstrated that transapical mitral valve repair with the ValveClamp resulted in an expected reduction in MR without obvious evidence of

significant mitral stenosis immediately after the procedure. Moreover, the design of the ValveClamp conferred a shorter implantation time compared to the MitraClip and other MR treatment devices.¹¹⁻¹⁴

The edge-to-edge mitral valve repair technique, also known as the Alfieri stitch surgical technique, significantly decreases MR by suturing the leaflet edges at the site of regurgitation and produces a double-orifice valve. It has been shown to have durable results to correct degenerative and functional MR when employed in conjunction with an annuloplasty ring.¹⁵⁻¹⁷

The ValveClamp system is a novel edge-to-edge mitral valve repair system that was designed for ease of operation. There are several theoretical advantages of

Table 1. Changes in hemodynamic parameters, cardiac size, and functional parameters after the ValveClamp procedure

	Preoperation	Postoperation	p value
VCW-max (mm)	7.60 ± 2.87	2.35 ± 1.06	0.000
MVA (cm^2)	4.72 ± 1.16	3.25 ± 0.87	0.000
MVPG-max (mmHg)	1.95 ± 0.47	3.66 ± 0.62	0.000
MVPG-mean (mmHg)	0.87 ± 0.31	1.7 ± 0.28	0.000
LVEDD (mm)	46.08 ± 2.85	46.44 ± 3.53	0.239
LVESD (mm)	29.11 ± 3.44	29.08 ± 3.62	0.940
LVEF (%)	66.53 ± 6.47	67.14 ± 4.93	0.256
LAD (mm)	35.75 ± 2.24	36.42 ± 1.99	0.057
LAA (mm^2)	12.95 ± 2.22	12.64 ± 1.55	0.301

LAA, left atrial area in the apical 4 chambers; LAD, left atrial anterior-posterior diameter; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; MVA, mitral valve area; MVPG-max, maximum mitral valve pressure gradient; MVPG-mean, mean mitral valve pressure gradient; VCW-max, max vena contracta width.

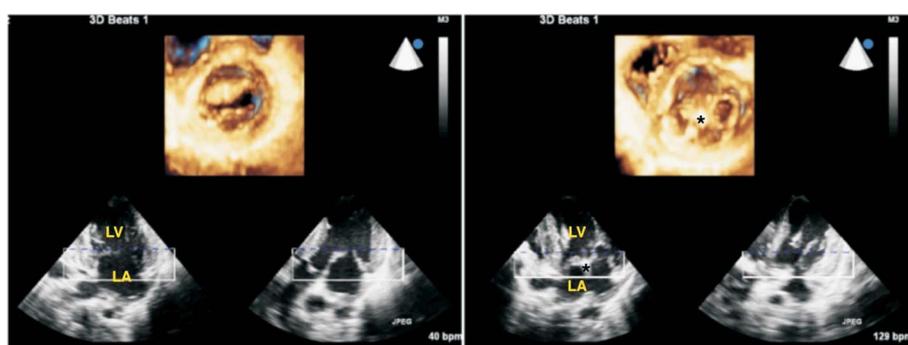


Figure 3. Real-time 3D mode showing the “en face” view of mitral valve orifice and the implanted device. The device was located in the A2/P2 segment, which created two symmetrical orifices. LA, left atrium; LV, left ventricle.

ValveClamp. First, the configuration of the clamp arms expands the capture range for grasping leaflets, and it is considerably larger than that of the MitraClip despite the similar dimensions of grasping arms (Figure 2). This characteristic may make it easier to grasp leaflets with ValveClamp and potentially affords a greater chance of success than MitraClip, especially in patients with flail or prolapse gaps larger than 10 mm. Second, the ValveClamp system does not require transseptal puncture and is delivered through the cardiac apex where the intervention route is short and straightforward, so that the clamp position can be easily adjusted by just moving the related external handle of the delivery system. The ValveClamp can be used solely under echocardiographic guidance (Figure 4) where favorable imaging of the heart and the device can be achieved to potentially facilitate the clamping operation. The full device can undergo endothelialization after the procedure.⁹

Our results indicated that the ValveClamp system could significantly reduce the severity of MR in a porcine model of mitral valve prolapse. We demonstrated that residual MR was absent or mild in 75% of the subjects and moderate in 25%. Furthermore, the left ventricular systolic function was well balanced, and there

was no evidence of mitral stenosis at the end of the procedure in terms of MVA and pressure gradient.

Adjustment of the ValveClamp during the procedure may lead to damage to the mitral valve apparatus and the left atrial wall. The ValveClamp itself acts as a foreign body, and endocardial injury may lead to thrombosis. However, there was no evidence of thrombosis or impairment of the cardiac structure or other related complications. In terms of the clamping site, there was a good correlation between echocardiography and autopsy results.

There are several limitations to this study. First, the model induced acute MR, which is different from a chronic MV myxomatous disease in a clinical scenario, while the follow-up was only performed within 30 days. Therefore, the long-term efficacy of this device for chronic MR should be tested in further studies. Second, IEE was employed to guide the implantation as favorable image quality had not been obtained with transesophageal echocardiography (TEE) in pigs. The maneuverability of the IEE probe placed at the apex was limited, and this may have hindered the transapical procedure. TEE is preferred in clinical trials as it guides the procedure more consistently and reliably than IEE.

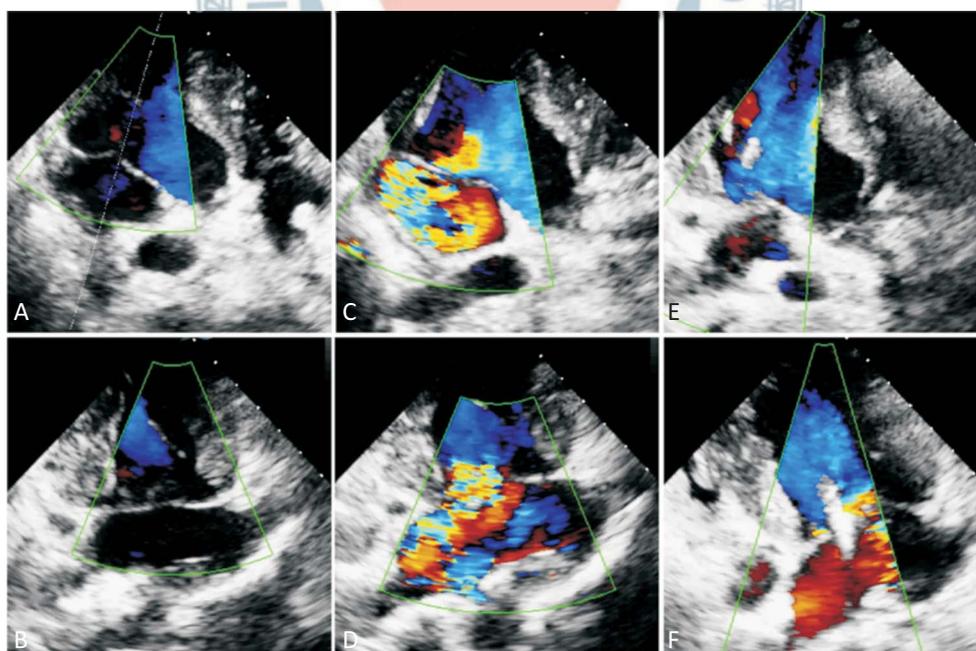


Figure 4. Image of X-plane mode showing the procedure of the ValveClamp implantation A and B: There was only slight MR before establishment of the acute model. C and D: Cutting the major chordae supporting the A2 segment instantly caused severe MR. E and F: The moment the clamp arms were clamped on the leaflet, MR attenuated substantially (A, C and E: apical long axis view; B, D and F: apical 2-chamber view). LA, left atrium; LV, left ventricle.

CONCLUSIONS

The ValveClamp system offers a technically easier procedure that can be transapically performed and monitored via epicardial ultrasound. The feasibility and safety of the ValveClamp system has been verified in pigs with native valves. In the present study, the ValveClamp system was successfully implanted in all of the cases under epicardial echocardiographic guidance, and it conferred a high procedural success rate and short operation time. It is potentially applicable as a novel user-friendly transcatheter edge-to-edge mitral valve repair device for the treatment of MR in humans.

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CONFLICT OF INTEREST

Dr. Zhou and Dr. Pan are consultants for Hanyu Medical Technology. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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