Percutaneous reduction of septal-to-lateral mitral annular distance to increase mitral leaflet coaptation length: Preclinical study results

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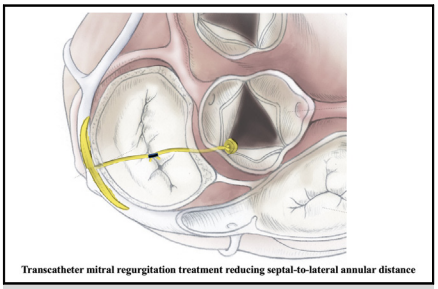
ABSTRACT

Objectives: Percutaneous indirect annuloplasty has emerged as a treatment strategy for functional/ischemic mitral regurgitation. This study sought to evaluate the feasibility of percutaneous indirect annuloplasty technique using a new device.

Methods: The device has 3 components: the "saddle" inserted into the great cardiac vein, the "plug" positioned in the left ventricular outflow tract, and the "bridge," a transatrial suture connecting the 2 holding elements. The aim was to shorten the septal-to-lateral distance of the mitral annulus by pulling on the saddle element. The procedure was performed through venous access in healthy adult sheep. A dedicated catheter holding a needle was used to deploy the saddle into the great cardiac vein and pierce its wall toward the left atrium to deploy the expanded polytetrafluoroethylene suture that is part of the bridge. A catheter for transseptal puncture was inserted for crossing the interatrial septum and piercing the aortic-mitral curtain, thereby allowing the plug to be deployed. The plug was held in place by the second part of the expanded polytetrafluoroethylene bridge. The 2 parts of the bridge were then joined to reduce the septal-to-lateral mitral annular distance. The septal-to-lateral distance and the coaptation length at P2 level were measured before and after the procedure using echocardiography.

Results: Overall, 10 animals were treated, 7 successfully. The mean procedure duration was 110 ± 81 minutes. Septal-to-lateral distance decreased from 3.8 mm to 2.6 mm (30%), and maximum increase of mitral leaflet coaptation was 4 mm.

Conclusions: This new approach seems promising for percutaneous treatment of functional mitral regurgitation. (JTCVS Techniques 2023;17:65-72)



Transcatheter MR treatment reducing SL annular distance.

CENTRAL MESSAGE

Original device and technique for indirect mitral annuloplasty. A promising approach for transvenous echocardiography-guided treatment of functional MR.

PERSPECTIVE

This indirect mitral annuloplasty procedure using a novel device and a fully venous approach is technically feasible. It could represent a new treatment for MR in patients with high surgical risk, particularly because posterior leaflet dynamics are not adversely affected. Concerns specific to indirect annuloplasty devices include device thrombosis, erosion, chronic inflammation, and device failure.

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Functional or ischemic mitral regurgitation (MR) occurs when normal or nearly normal mitral leaflets are prevented from proper coaptation by underlying left ventricular dysfunction or mitral annular dilatation. When the annulus is dilated, the septal-to-lateral (SL) mitral annular distance is increased and the mitral annulus loses its typical D shape assuming a circular geometry.

The surgical correction of dilated mitral annulus consists in placing an undersized, rigid annuloplasty ring, which is secured by many sutures directly to the mitral annulus. The physical durability of this technique, called "direct

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Abbreviations and Acronyms

CL = coaptation length
ePTFE = expanded polytetrafluoroethylene
GCV = great cardiac vein
LVOT = left ventricular outflow tract
MR = mitral regurgitation
SL = septal-to-lateral
TEE = transesophageal echocardiography

annuloplasty," has been demonstrated. Although MR recurrence is possible after annuloplasty mainly due to progressive ventricular dilatation, direct mechanical failure of the ring is rare.[1]

In recent years, at least 2 percutaneous treatments for MR have gained interest and have been granted market approval, one approaching mitral leaflets (MitraClip, Abbott Vascular) and one performing a direct annuloplasty that reduces the length of the posterior mitral annulus (Cardioband, Edwards Lifescience), both of which have been associated with significant improvement of heart failure symptoms.[2] These positive clinical results boost researchers, and additional transcatheter strategies addressing MR are being developed. An example is the Kalios ring (Affluent Medical) that allows percutaneous adjustment of SL distance after surgery, thereby avoiding the need for a reoperation in case of MR recurrence.[3]

The isolated percutaneous SL mitral annular distance reduction obtained without stitching the mitral annulus, known as "indirect annuloplasty," has emerged as a potential treatment strategy for acute and chronic MR in patients with high surgical risk, particularly because dynamics and posterior leaflet motion are not adversely influenced.[4] Some devices achieving an indirect annuloplasty are under clinical investigation and have all shown promising results in animal models.[5] As with any new technology, the overall safety and durability of these devices in the longer term are still unknown.

We report on the first preclinical study aimed at assessing the in vivo feasibility of a novel device for indirect percutaneous mitral annuloplasty.

MATERIALS AND METHODS

Device Description

As illustrated in Figure 1, the device has an anchor shape and consists of 3 elements: the "saddle" that is inserted into the coronary sinus; the "plug" that is positioned in the left ventricular outflow tract (LVOT), just below the commissure between the noncoronary and left coronary leaflets of the aortic valve, called the "aortic-mitral curtain"; and the "bridge" that connects the saddle and the plug. The length of the bridge can be adjusted to reduce the SL mitral annular distance. The saddle and plug are made of stainless steel, and the bridge is made of expanded polytetrafluoroethylene (ePTFE).

Deployment Technique

The procedure aims at improving leaflet coaptation by shortening the SL diameter of the mitral annulus. Delivery and deployment of the system are achieved through venous access to the right atrium, where 2 common procedures are performed: (1) catheterization of the coronary sinus, also known as the "great cardiac vein" (GCV), to deploy the saddle element; and (2) transseptal puncture to access the aortic-mitral curtain and deploy the plug element. Specifically, the coronary sinus is reached from the right jugular vein under fluoroscopy and a dedicated catheter holding a needle for transseptal puncture is advanced into it. The needle serves to pierce the coronary sinus toward the left atrium, above the mitral annulus, at the middle of the posterior leaflet of the mitral valve (P2), allowing a guidewire to reach the left atrium. By using over-the-wire technique, the saddle element is positioned into the coronary sinus with the ePTFE bridge floating in the left atrium. A second catheter for transseptal puncture is inserted into the left femoral vein to reach the left atrium. This catheter allows the puncture of the aortic-mitral curtain under echocardiographic control so that a guidewire can pass into the LVOT. The plug is deployed over the wire and held by the ePTFE bridge, which is still in the catheter. Then, a snare catheter is passed in the second catheter to grab the ePTFE bridge part coming from the coronary sinus. Next, the 2 parts of the ePTFE bridge are pulled and joined together using a stainless steel clip under echocardiographic control to reduce the SL distance and possibly increase leaflet coaptation. Figure 2 illustrates the procedure steps.

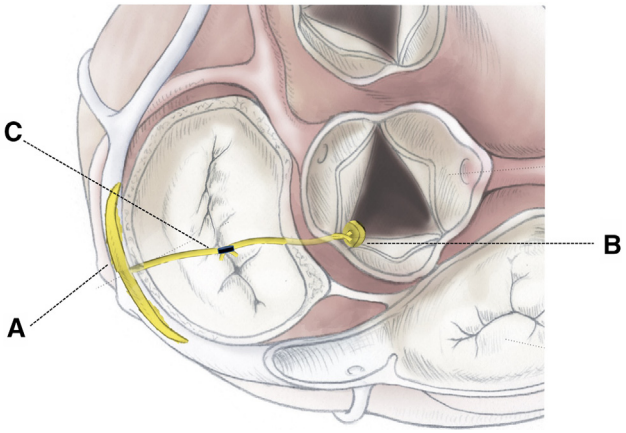

FIGURE 1. Schematic illustration of the device. A T-shaped metallic element (the saddle) (A) is placed in the GCV; a retaining metallic element (the plug) (B) is positioned into the LVOT, just below the aortic valve, in the aortic-mitral curtain; a connecting element made of ePTFE (the bridge) (C) joins the 2 elements by pulling the saddle toward the plug.

Experimental Procedure

The research protocol was approved by the Lausanne University and Cantonal Ethics Committee of Vaud (Authorization Number VD3384 valid from September 13, 2018). Healthy adult sheep, 65 to 85 kg in weight, underwent full sternotomy under general anesthesia to access the epicardium and perform epicardial ultrasound. A cardiac ultrasound (HDI5000, Philips) was carried out to acquire images of the heart using a transesophageal echocardiography (TEE) probe or an epicardial probe. 18F introducers were positioned in both femoral veins to gain access to the right atrium under fluoroscopy. The right jugular vein was also cannulated with a 12F introducer to access the coronary sinus. Animals were administered 100 U/kg intravenous heparin to achieve an activated clotting time more than 200 seconds. Two specific echocardiographic parameters were measured at the beginning of the procedure and after device deployment: (1) the SL distance, defined as the projected distance from the trigone-to-trigone line to the posterior peak; (2) the coaptation length (CL), defined as CL = Ad-Ac, where Ad equals the whole length of the anterior leaflet during diastolic phase and Ac equals the length of the uncoapted-free portion

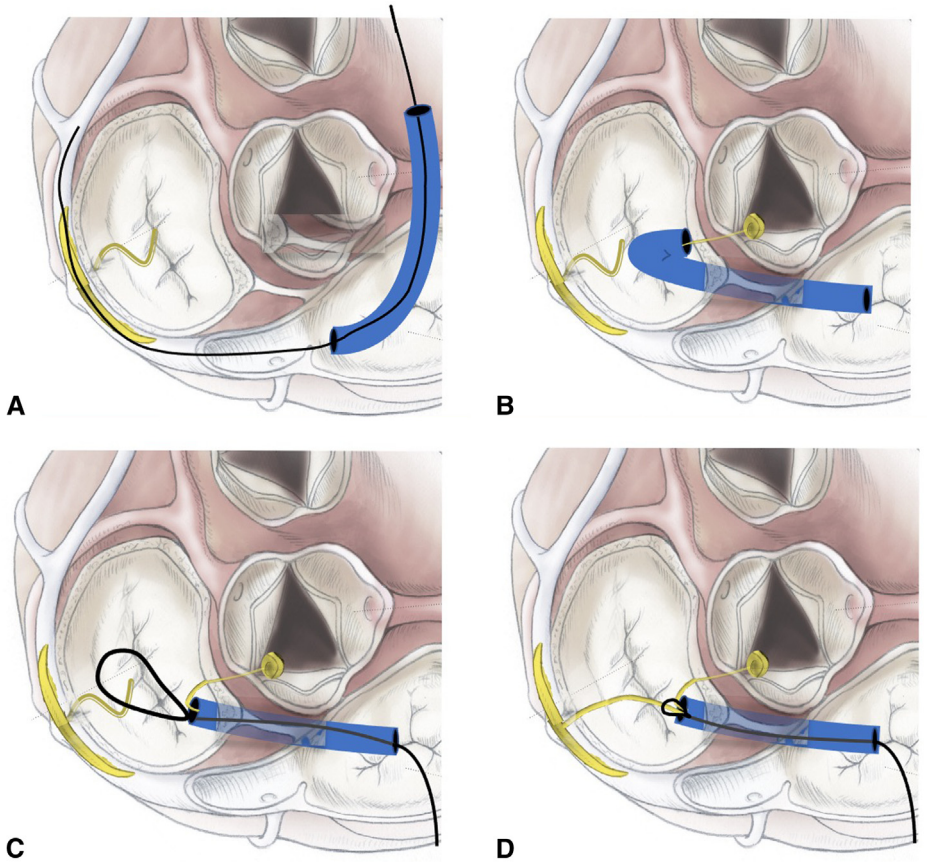

FIGURE 2. Step-by-step description of the procedure. Device elements are in *yellow*. A, Catheterization of the coronary sinus to deploy the saddle element into it and to pierce the coronary sinus toward the left atrium, above the mitral annulus, where the ePTFE wire is deployed. B, Transseptal puncture to access the aortic-mitral curtain to deploy the plug element over a guidewire. The plug is held in place by a second ePTFE wire that is still in the catheter. C, A snare catheter is passed in the second catheter to grab the ePTFE part coming from the coronary sinus. D, The 2 parts of the ePTFE bridge are then pulled and joined together using a stainless steel clip under echocardiographic control to reduce the SL distance.

of anterior leaflet at end systole.[6] The transmitral gradient was also measured before and after device deployment. At the end of the procedure, the animals were killed with an overdose of pentobarbital and their hearts were explanted for macroscopic analysis.

Study End Points

The primary end point was efficacy of the device in reducing the SL distance and increasing CL at the A2-P2 level. The secondary end points included induced iatrogenic aortic valve regurgitation and secondary fistula between the aortic root and the left atrium.

Statistical analyses were performed using GraphPad Prism V6.0d (GraphPad Software) and SPSS Statistics 22 (IBM Corp). Continuous data are presented as mean and standard deviation.

RESULTS

The procedure was conducted in 10 animals and successfully completed in 7. The reasons for noncompletion of the procedure included a lesion of the aortic valve in 2 animals and a perforation of the free wall of the coronary sinus causing pericardial tamponade in 1 animal. Echocardiography did not show any intracardiac shunt between the LVOT and the left atrium. The mean procedure duration was 110 ± 81 minutes. In the 7 animals in which the procedure was achieved, SL distance decreased from 3.8 ± 0.5 mm to 2.3 ± 0.5 mm, which corresponds to an average reduction of 35%. CL increase ranged from 2 to 4 mm (Figure 3). No changes in the transaortic gradient were measured after the deployment of the device. Detailed results are presented in Table 1. Macroscopic analysis of the hearts confirmed the correct positioning of the device.

DISCUSSION

Studies on cardiac physiology have shown that, in early systole, the mitral annulus undergoes sphincter-like contraction resulting in an area reduction of approximately 25%. This facilitates coaptation by drawing the free margins of the mitral leaflets into proximity, prepositioning them such that rising left ventricular pressure is able to press them together to form a competent overlapping coaptation zone approximately 1 cm in height.[7,8]

Historical experimental and clinical studies have established that, at the mitral annulus level, functional and

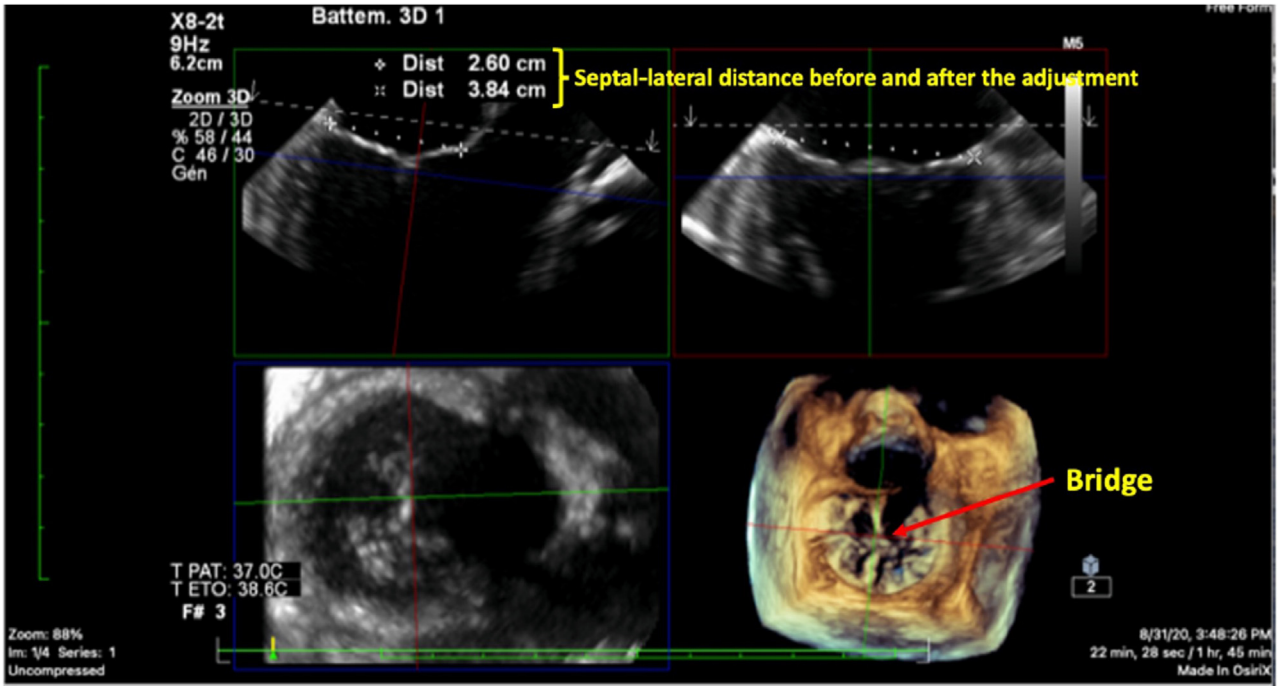

FIGURE 3. TEE with 3-dimensional reconstruction of the mitral valve showing the final result. *Upper left*: SL mitral annular distances before and after the procedure. *Lower right*: bridge overlying the mitral valve. *2D*, 2-dimensional; *3D*, 3-dimensional; *PAT*, patient temperature; *ETO*, trans-oesophageal probe temperature.

ischemic MR are characterized by a loss of the sphincter-like contraction activity and by an increase in the SL distance causing a lack of leaflet coaptation.[8,9] The surgical strategies that have been developed since the early 1970s to repair MR are mainly based on these observations and aim to restore leaflet coaptation by reducing the SL distance.[10] However, when the leaflets are severely diseased or the chordae are elongated or ruptured, further complex surgical repair procedures are needed, including leaflet resection and artificial chordae implantation.

Because of recent advances in medical device manufacturing and endovascular therapies, the mitral annulus can be reshaped without open procedures and transcatheter mitral valve repair approaches have gained recognition. The demand for transcatheter methods to correct MR notably in patients who are not eligible for edge-to-edge repair is dramatically increasing, and the device evaluated in this study has been developed to fulfill this demand.

The concept of using transcatheter techniques to reduce SL mitral annular diameter by pulling on a T-bar inserted into the GCV has been explored previously.[4,11] The PS3 system, also known as the "ARTO system," achieves SL distance shortening through direct traction between the interatrial septum at the fossa ovalis and the GCV at the level of the mid-P2 scallop by means of a transatrial suture that connects the 2 holding elements. Given that the PS3 system applies traction primarily at the P2 level, this force is only transmitted across a relatively short distance to effect a mitral annular shape change. This system has been assessed in an international, multicenter, prospective, single-arm study on 45 patients with symptomatic grade greater than 2 ischemic MR over a 1-year follow-up. The effective regurgitant orifice area decreased from 30.3 ± 11.1 mm^2 to 13.5 ± 7.1 mm^2 and regurgitant volumes from 45.4 ± 15.0 mL to 19.5 ± 10.2 mL. Mitral annular antero-posterior distance decreased from 45.0 ± 3.3 mm to

TABLE 1. Experimental findings after septal-to-lateral mitral annular distance reduction

Mitral valve	Baseline (healthy sheep)	After transcatheter annuloplasty	Indirect annuloplasty effects in %	*t* test
CL (mm)	4.2 ± 0.2	4.9 ± 0.2	+12%	$P < .001$
Mean transmitral gradient (mm Hg)	2 ± 0.5	2 ± 0.8	None	$P = NS$
SL distance (mm)	3.8 ± 0.6	2.6 ± 0.4	–35%	$P < .001$

CL, Coaptation length; *NS*, not significant; *SL*, septal-to-lateral.

38.7 ± 3.0 mm. At 30 days, there were 2 adverse events: one pericardial effusion requiring surgical drainage and one asymptomatic device dislodgement. Significant improvements in New York Heart Association functional class and the 6-minute walk test were observed at 30 days, which remained stable at 1 year.[5]

Although clinical results look extremely positive, one can question the durability of the repair achieved using the interatrial septum as an anchor point for pulling the posterior mitral annulus to increase leaflet coaptation. Because of its unique property of compliance, the atrial tissue can act as a volume reservoir of blood during ventricular systole. This property has been extensively studied[12,13] and is not questionable. Therefore, the interatrial septum tends to deform over time under the effects of physical constrains, including not only all causes of atrial pressure increase but also the pulling action of the transatrial horizontal suture connected to the T-bar positioned in the GCV.

Rogers and colleagues[4] reported that the mean force required to achieve a 30% reduction in SL distance in an ovine model ranged from 1.16 N to 1.87 N, with a between-animal mean of 1.60 N (~0.36 lbf or 163 gram force). It can be speculated that compared with healthy hearts, the force necessary to achieve this displacement is higher in dilated hearts, whereas tissues, particularly atrial tissue, are weaker. This force applied over time on the interatrial septum could induce progressive displacement of the interatrial septum toward the GCV and eventually override the reduction in SL distance, thus compromising the durability of mitral annulus reshaping. In our view, a more solid point of attachment than the interatrial septum must be found to exert the pulling action needed to displace the posterior mitral annulus.

Anatomic studies of the heart have demonstrated that the fibrous skeleton of the heart is a high-density homogeneous structure of connective tissue that forms and anchors heart valves and influences the forces exerted by and through them.[14] It also provides a point of insertion for the bundles of the heart muscle and effectively separates the atria from the ventricles. It is made of the fibrous trigones, the aortomitral continuity, the subvalvular collar of the mitral valve, the membranous septum, the interleaflet triangles, and the tendon of Todaro. Most of the mitral annulus is fibrous, and at the aortic annulus level, the fibrous elements support only the noncoronary aortic sinus and parts of the right and left coronary sinuses: This area is called the aortic-mitral curtain and is the one we choose to anchor the plug element of the device assessed in this study (Figure 4). We hypothesized that the aortic-mitral curtain is strong enough to house the plug element without deforming over time and therefore contributes to annuloplasty durability. However, only long-term clinical results will confirm our assumption.

A crucial aspect of the endovascular procedure described in this study is to identify the area where the aortic-mitral curtain can be safely pierced while avoiding lesions of the surrounding valves. By using TEE 3-chamber view, it is possible to identify the proper location at the insertion of the middle part of A2 into the mitral annulus while also having a clear view on aortic valve leaflets (Figure E1). In our study, we observed 2 cases of aortic regurgitations: In 1 animal, perforation of the noncoronary leaflet of the aortic valve occurred because we misestimated the distance between the 2 aortic valve leaflets; in the second animal, the plug impinged the noncoronary leaflet preventing it from opening. The risk of damaging the aortic valve is real, but this should not discourage endovascular therapists to use this approach. Gaining experience with TEE 3-chamber view and defining new specific echocardiographic views of the aortic-mitral curtain would reduce the risk of such errors in the future.

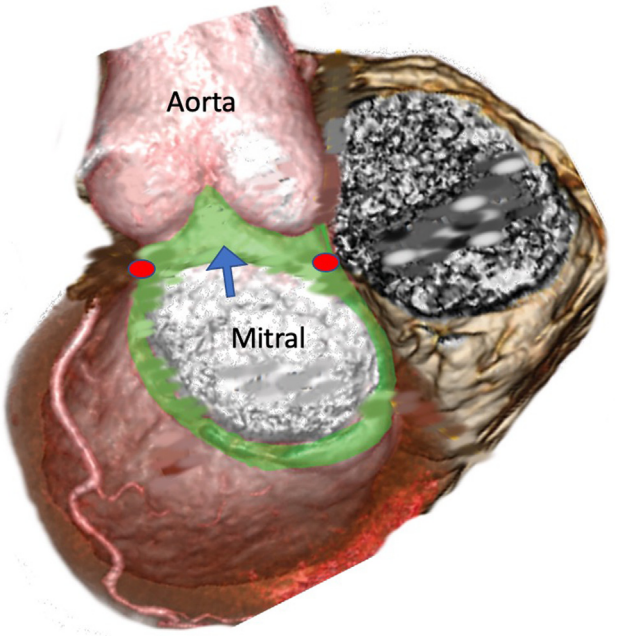

FIGURE 4. Three-dimensional computed tomography scan reconstruction of the healthy human heart. The *green area* corresponds to the fibrous skeleton of the heart. The *blue arrow* indicates the targeted area for piercing the fibrous skeleton of the heart: the aortic-mitral curtain, which is the fibrous area between the anterior leaflet of the mitral valve and the noncoronary and left coronary leaflets of the aortic valve. The *2 red spots* indicate the 2 trigones, anterior and posterior.

TEE also guided the puncture of the coronary sinus toward the left atrium (Figure 5). The latter has to be performed at the P2 level, because previous anatomic series have shown that the mitral annular-GCV distance at the P2 level is short (<6 mm) when compared with the P3 level (10 mm).[15] Consequently, the force exerted by the system at the P2 location is transmitted across a relatively short distance to effect a mitral annular shape change.

As with all indirect annuloplasty systems involving placement of a metal element into the GCV, the T-bar

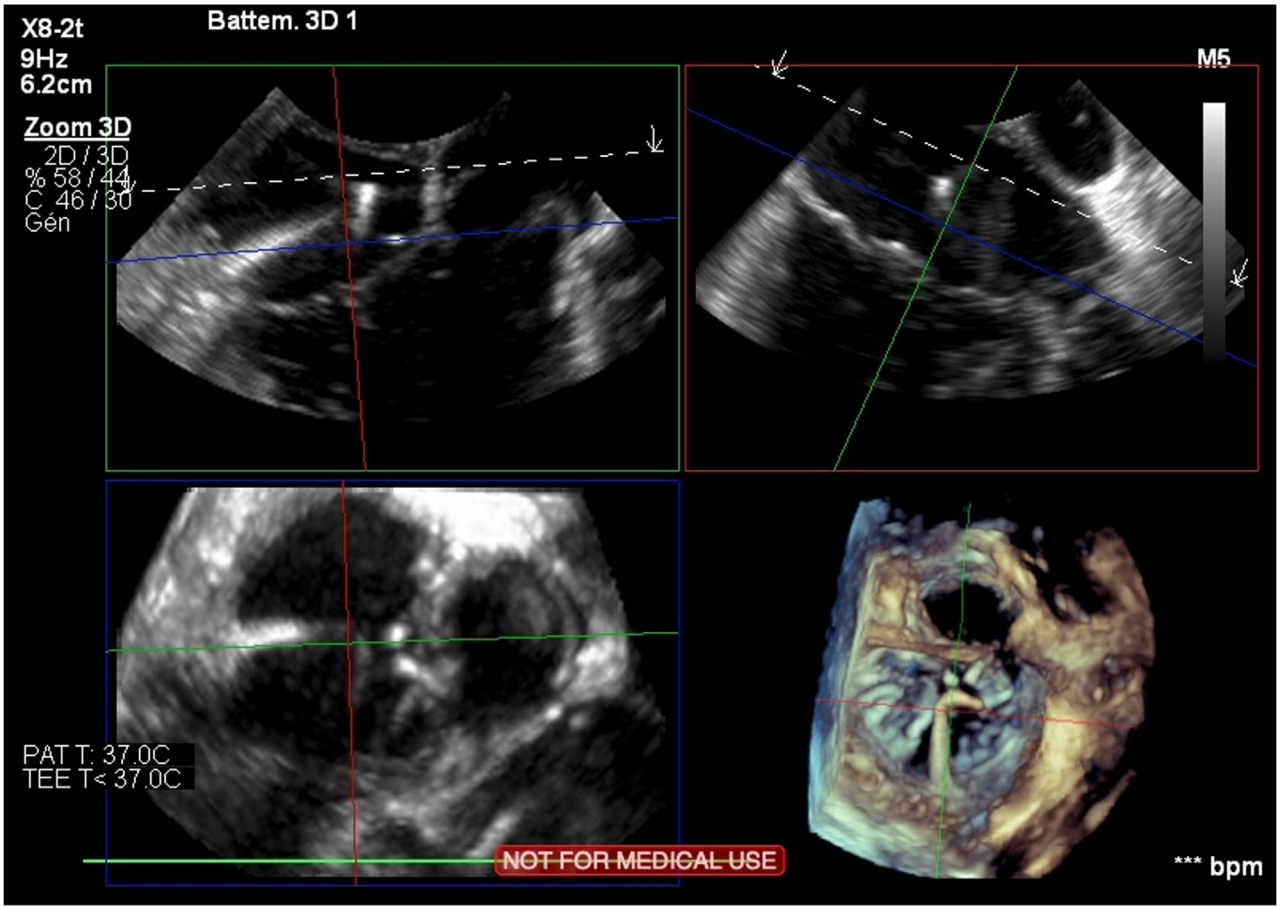

FIGURE 5. TEE with 3-dimensional reconstruction of the mitral valve showing the catheter coming from the coronary sinus, piercing the vein toward the atrium (*lower right*). *2D*, 2-dimensional; *3D*, 3-dimensional; *PAT*, patient temperature; *TEE*, transesophageal echocardiography.

(saddle) used in this study could potentially impinge the circumflex artery. Therefore, angiographic assessment of the circumflex artery crossing the GCV should be mandatory in a clinical setting.

A particular strength of the system evaluated in this study is its ability to achieve significant and predictable reduction in the septal lateral dimension: The maximum achievable degree of SL distance shortening was greater than the degree of shortening usually required to achieve correction of functional MR.

Study Limitations

This study carries some methodological limitations. Beside the fact that this is an acute study on a small number of animals, the experimental setup did not include a diseased mitral valve; therefore, we could only speculate that our results are reproductible and have to be validated in a clinical setting. Moreover, the ability of the anterior leaflet to move toward the annulus and to reach the posterior leaflet is essential to warrant a competent valve. If this movement is insufficient, the mitral valve will still leak, regardless of how much the posterior annulus is reduced.[16] Another important limitation resides in the lack of chronic results, therefore in the durability of the mitral repair and in the evaluation of possible long-term complications on aortic valve and conduction system functions. There are also some technical concerns linked to the dexterity the therapists need to successfully complete the procedure: An expert in ultrasonographic cardiac imaging and an expert in structural cardiology have to join their expertise to achieve the safe and correct deployment of the device, particularly avoiding aortic valve and atrioventricular node lesions. We should also consider some possible discrepancy of the location of coronary sinus and the mitral annulus; therefore, precise guidance by TEE or direct echocardiography is crucially important. The operator also need to avoid the circumflex artery with the coronary sinus puncture.

CONCLUSIONS

Concerns specific to indirect annuloplasty devices include device thrombosis, erosion, biological incompatibility associated with chronic inflammation, and device failure due to fatigue or fracture.

Webcast

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Conflict of Interest Statement

P.T. and G.S. are shareholders of EYE Ltd. P.T. is a shareholder of MitralTechnologies SA. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: mitral regurgitation, mitral ring, mitral valve repair, percutaneous mitral valve surgery

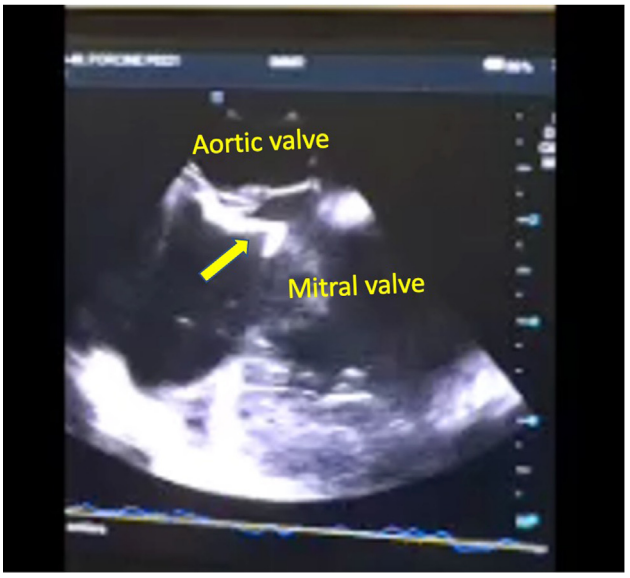

FIGURE E1. TEE images illustrating the technique of piercing the aortic-mitral curtain (*yellow arrow*) to safely deploy the retaining element (*the plug*) into the LVOT.