Direct access transcatheter mitral annuloplasty with a sutureless and adjustable device: preclinical experience

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Abstract: OBJECTIVES: The aim of the study was to evaluate the technical feasibility and performance of a transcatheter mitral annuloplasty system. METHODS: Adult swines (n = 15) underwent left thoracotomy through the 4th-5th intercostal space. A transcatheter device (CardioBand, Valtech-Cardio Ltd) was introduced through an 18F sheath through the left atrium and attached to the annulus between the posterior and anterior commissures using echocardiographic and fluoroscopic guidance, on the beating heart. The sutureless device was implanted using a steerable delivery system to deploy sequential fixation elements. Following implantation, the device length was adjusted on the beating heart to reduce the intercommissural and septolateral dimension, under echocardiographic guidance. Finally, the flexible adjustment tool was withdrawn from the working sheath and the atrial purse-string closed. All but five animals were sacrificed acutely by intent, while the others were sacrificed at 90 days. RESULTS: All animals survived the acute implant. One animal died at the third post-operative day due to bleeding. The annuloplasty system was successfully implanted in all animals. A mean of 12 ± 3 fixation elements were deployed. The band length was reduced up to 20% after implantation in each animal. At necropsy, the location of the implant was within a few millimetres of the annulus (3.5 ± 4 mm). In three animals, fixation elements were implanted inadvertently in the leaflets, but no coronary lesions were observed. All animals survived the acute implant. One animal died on the third post-operative day due to bleeding. In the four long-term survivors, the implanted annuloplasty device showed satisfactory healing and no ring dehiscence. CONCLUSIONS: Transcatheter minimally invasive, beating-heart implantation of an adjustable annuloplasty band is feasible in the animal model. This approach may be an alternative to open surgical procedures in high-risk patients.

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ORIGINAL ARTICLE

Direct access transcatheter mitral annuloplasty with a sutureless and adjustable device: preclinical experience†

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Abstract

OBJECTIVES: The aim of the study was to evaluate the technical feasibility and performance of a transcatheter mitral annuloplasty system.

METHODS: Adult swines ($n = 15$) underwent left thoracotomy through the 4th–5th intercostal space. A transcatheter device (CardioBand, Valtech-Cardio Ltd) was introduced through an 18F sheath through the left atrium and attached to the annulus between the posterior and anterior commissures using echocardiographic and fluoroscopic guidance, on the beating heart. The sutureless device was implanted using a steerable delivery system to deploy sequential fixation elements. Following implantation, the device length was adjusted on the beating heart to reduce the intercommissural and septolateral dimension, under echocardiographic guidance. Finally, the flexible adjustment tool was withdrawn from the working sheath and the atrial purse-string closed. All but five animals were sacrificed acutely by intent, while the others were sacrificed at 90 days.

RESULTS: All animals survived the acute implant. One animal died at the third post-operative day due to bleeding. The annuloplasty system was successfully implanted in all animals. A mean of 12 ± 3 fixation elements were deployed. The band length was reduced up to 20% after implantation in each animal. At necropsy, the location of the implant was within a few millimetres of the annulus (3.5 ± 4 mm). In three animals, fixation elements were implanted inadvertently in the leaflets, but no coronary lesions were observed. All animals survived the acute implant. One animal died on the third post-operative day due to bleeding. In the four long-term survivors, the implanted annuloplasty device showed satisfactory healing and no ring dehiscence.

CONCLUSIONS: Transcatheter minimally invasive, beating-heart implantation of an adjustable annuloplasty band is feasible in the animal model. This approach may be an alternative to open surgical procedures in high-risk patients.

Keywords: Mitral regurgitation • Transcatheter mitral repair • Mitral annuloplasty

INTRODUCTION

Mitral valve annuloplasty (MVA) is a routine procedure during open heart valve repair surgery. Ring annuloplasty increases the durability of the repair due to increase in coaptation and reduction in structural stress on valve tissue [1–3].

Recently, transcatheter mitral repair is emerging as an alternative therapy in high-risk patients who are not referred for surgery [4]. Leaflet repair with the MitraClip (Abbott Vascular, Menlo Park, CA, USA) is currently available in Europe for clinical use [5]. Miscellaneous solutions are under development for annular repair.

CardioBand™ (ValtechCardio, OrYehuda, Israel) is a transcatheter MVA system designed to implant a Dacron posterior annuloplasty band with a sutureless technique, on the beating heart, under echocardiographic and fluoroscopic guidance.

We describe the initial preclinical experience with the transatrial version of the device, which is designed to implant the annuloplasty band via a minimally invasive, direct access approach to the left atrium.

METHODS

Fifteen animals, weighing 70–90 kg, underwent the CardioBand procedure. Under general anaesthesia, a muscle sparing left

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thoracotomy in the 4th or 5th intercostal space was performed, avoiding damage to the latissimus dorsi muscle, and the pericardial sac was incised in T-fashion, exposing the left atrium. Prophylactic Lidocaine 100 mg intravenously was administered prior to any manipulation of the heart. Pre-operative measurements of the mitral valve with epicardial echocardiography (HP sonos 1000, Philips Andover, MA, USA) were performed. A purse string was then placed in the middle of the left appendage to insert the CardioBand delivery system. Heparin was administered at 100 units/kg and repeated if the activated clotting time was shorter than 300 s until the delivery system was in the left atrium.

The CardioBand™ system

The CardioBand delivery system (Fig. 1b) is a steerable device carrying the implant (Dacron band) and the anchors (metallic helices). The implanted band is then contracted using an adjustment tool (Fig. 1a). Access to the mitral valve was gained by inserting a specifically designed 18F introducer sheath (Fig. 1c) with sealing valve through the wall of the left atrium, within a purse string. A protection cover envelops the implant during insertion of the delivery system through the introducer. A knob at the end of the device controls the distal steerable tip for manoeuvring the implant towards the annulus. The first anchor was positioned at the posteromedial commissure (Fig. 2a). This target was located by epicardial echocardiography using both short- and long-axis views. Great care was taken to exclude the leaflet contact with the tip of the delivery system, and to maintain a perpendicular aim of the delivery system related to the annular plane, to allow penetration of the anchors in the base of the left ventricle. The anchor implant is reversible until the anchor is completely delivered and released from the delivery system. Once the anchor is fully implanted, an advance button releases the implant at constant lengths. An anchor magazine, which contains up to 15 helical anchors, is used to sequentially deliver the anchors to fixate the ring to the tissue. The following anchor implants continued in counter clock-wise fashion (Fig. 2b) from the posteromedial commissure, towards the antero-lateral commissure, along the annular perimeter under echocardiographic guidance, and tactile feedback (necessary from the mid-portion of the posterior leaflet to the antero-lateral commissure due to poor imaging). Once deployment of the implant was completed, another button disconnected the implant from the delivery system and connected it to the adjustment tool (Fig. 2c). Rotating the adjustment roller contracts or expands the band on the beating heart under echocardiographic guidance (Fig. 2d). Since healthy animals without mitral regurgitation (MR) were in use in this study, maximal contraction was performed by a constant length (up to 20%), as opposed to contraction for the purpose of MR fixation. Once the desired contraction was obtained, the implant was released from the adjustment tool

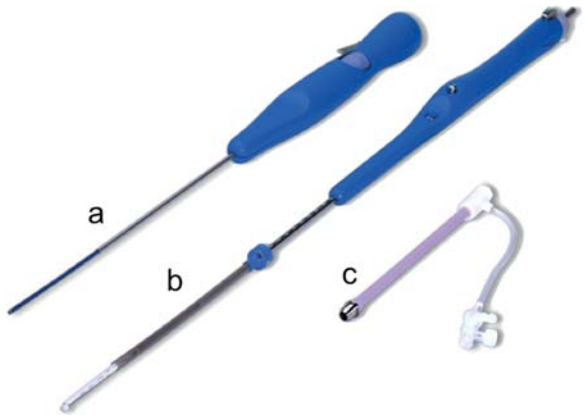

Figure 1: The CardioBand delivery system (**b**). The implanted band is then contracted using an adjustment tool (**a**). The specifically designed 18F introducer sheath to approach the mitral valve (**c**).

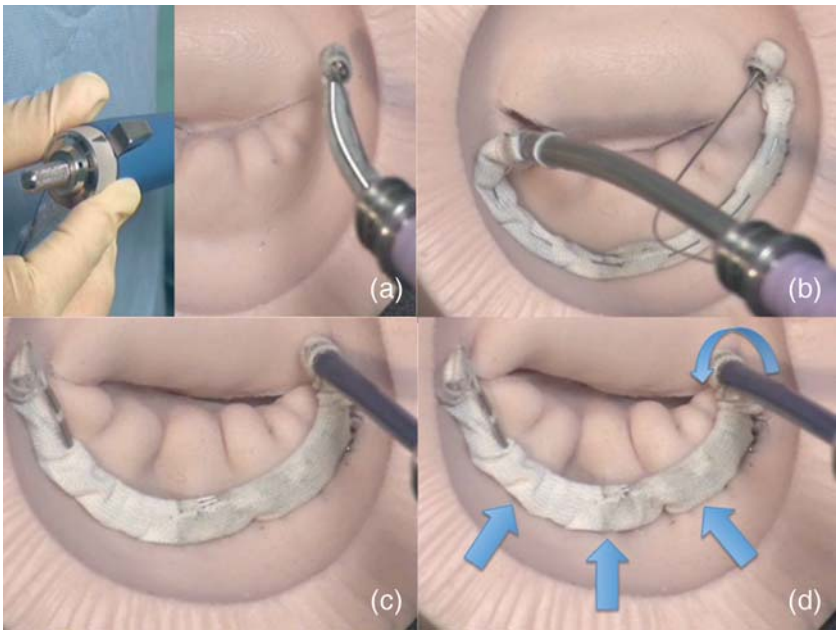

Figure 2: The first anchor is positioned at the posteromedial commissure (**a**). The following anchor implants continued in counter clock-wise fashion (**b**). Disconnection of the implant from the delivery system and connection to the adjustment tool (**c**). Adjustment of the band on the beating heart under echocardiographic guidance (**d**).

and the delivery system was removed from the 18F sheath. Finally, the sheath was removed and the purse string tied. The chest wall was then closed as usual. Post-operative antibiotic and analgesia therapy was continued during follow-up for up to 5 days.

Follow-up

Ten animals were sacrificed at the end of the acute implant, while five animals were kept alive and followed-up for a period up to 90 days post index procedure. Assessment of general clinical signs accompanied by haematological evaluation was performed pre-procedurally and during the course of the follow-up period. In addition, ultrasound echocardiography was performed for dynamic mechanical function, blood flow and heart anatomical measures (axis), at baseline, immediately after implantation, at 15 and 30 days post-implantation and before sacrifice (at 60–90 days). At the end of the follow-up period, all surviving animals were euthanized and the hearts were explanted for assessment.

RESULTS

All animals survived the acute implant. One animal died at the third post-operative day due to bleeding from the internal mammary artery during thoracotomy. The annuloplasty system was implanted in all animals. A mean of 13 ± 2 fixation elements were deployed. Implant device time (time from insertion of the device in the left atrium to the deployment of the last fixation element) was 23 ± 8 min (range 15–40 min). In one animal, ventricular fibrillation induced by heart manipulation necessitated electrical defibrillation, while extrasystolic beats were common during helix anchor deployment. No animal required post-implant inotropic support. In all animals, echocardiographic imaging was insufficient for guiding the procedure in the antero-lateral half of the posterior annulus; therefore, implantation was guided by a combination of epicardial echocardiography and manual palpation of the annulus. The band length was reduced up to 20% after implantation in each animal (Fig. 3a and b). As a result of band implantation, valve area, intercommissural and septolateral distance of the annulus were significantly reduced (Table 1). The quality of the image prevented a measurement of coaptation length. Prior to euthanasia, 90-day transthoracic echocardiography demonstrated no or trace MR in all four survivors, with no ventricular dysfunction. At necropsy, the location of the implant was within a few millimetres of the annulus (3.5 ± 4 mm). In three acute experimental animals, fixation elements were implanted inadvertently in the base of the leaflets, but no coronary lesions were observed. In all cases, the misplaced implants were located in the antero-lateral portion of the posterior annulus, in the area where imaging was poor. In the four long-term survivors, the implanted annuloplasty device showed satisfactory healing and no major ring dehiscence. Four animals survived the chronic follow-up time. At gross anatomy examination of the CardioBand, healing of the device was excellent, with tissue in-growth and endocardial covering of the devices. In addition, gross examination did not show migration of any of the anchors or damage to them or to the tissue as a result of contraction.

The implant did not cause any thrombus formation, toxicity or hyperplasia/hypertrophy.

Although minimal areas of implant dehiscence were observed, no device defects were observed and the implant seemed to be firmly attached to the annulus. No damage was caused to native mitral annulus or to adjacent structures except for some adhesions with the posterior leaflet, which did not seem to affect the function of the mitral valve. Gross anatomy findings of animals implanted with CardioBand system revealed that the implant was well healed and covered by fibrous tissue (Fig. 4a and b).

DISCUSSION

Our data demonstrate that it is feasible to implant a sutureless and adjustable MVA band with a transcatheter approach, under beating heart conditions, in the animal model.

Although the procedure has been successful in the animal model, several challenges have to be overcome before proceeding to clinical application.

Sutureless fixation

The CardioBand system is a sutureless ring for MVA. Particularly when considering minimally invasive surgery, suturing and knot-tying are time consuming. The CardioBand system includes a proprietary method to fixate the annuloplasty Dacron band to the annular tissue using multiple helix anchors. The device has been designed for transcatheter beating heart use, but has also been used in a minimally invasive open-heart approach

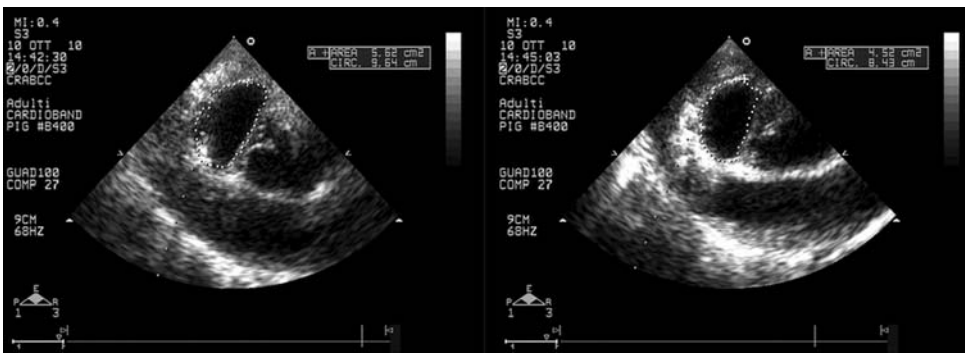

Figure 3: Band length before the adjustment (**a**); reduction in the band length up to 20% after the adjustment (**b**).

Table 1: Echocardiographic findings

	Pre-implant	vs	Post-implant	vs	Post adjustment
Area (diastolic), cm^2	9.8 ± 2.14	$P < 0.0001$	8.0 ± 2.0	$P < 0.0001$	6.7 ± 1.7
CC (systolic), mm	3.5 ± 0.4	$P < 0.0001$	3.2 ± 0.3	$P < 0.0001$	2.9 ± 0.3
SL (systolic), mm	2.5 ± 0.4	$P < 0.0001$	2.2 ± 0.4	$P = 0.0002$	2.1 ± 0.4

Area (diastolic): diastolic cross-sectional area measured at the short-axis epicardial view; CC (systolic): annular systolic intercommissural distance measured at the short-axis epicardial view; Annular SL (systolic): systolic septo-lateral distance measured at the short axis epicardial view.

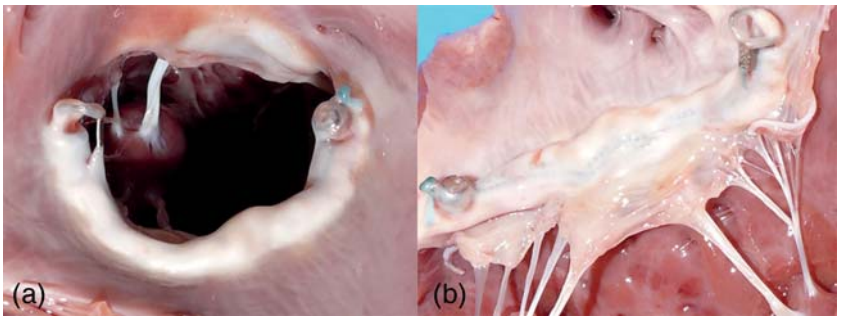

Figure 4: Gross anatomy findings of animals implanted with CardioBand system (**a**); healing of the CardioBand within the mitral annulus (**b**).

environment in the animal model. Although complete annuloplasty is probably more effective than posterior band annuloplasty, the latter solution was preferred for safety reasons, since the risk of aortic valve injury is a potential issue in a transcatheter approaches, especially given the problems with the imaging quality in the animal model. However, our acute data confirm that posterior annuloplasty alone is able to determine a significative reduction in annular areas and diameters.

The concept of using a helix screw anchors is commonly applied for pacemaker and defibrillator leads fixation [6, 7]. The helix anchor is designed to enable a safe and precise attachment of the annuloplasty ring to the soft tissue of the mitral annulus. In addition, the helix screw concept allows repositionability and retrievability of the anchors. Replacing the suturing technique with a minimally invasive off-pump mitral valve repair, using helix anchors, was introduced and tested a decade ago by Morales *et al.* [8]. Their tests included *in vitro* simulations of haemodynamic and mechanical consequences of screw implantation, in explanted human mitral valves. Next, the screw was tested *in vivo* in dogs. The authors reported no screw detachment or migration from the mitral valves less than 6.8 million cycles. Postoperative echocardiograms in two dogs demonstrated consistent coaptation, no screw migration, no clotting and no regurgitation or stenosis. In an animal sacrificed after 12 weeks, the screw was fully integrated in the mitral soft tissues.

Histological analysis of the implanted CardioBand devices showed that the fabric and metallic components were incorporated in a mild-to-moderate fibrous pannus of relatively homogeneous thickness.

No dehiscence was observed in the chronic animal hearts. The potential risk of dehiscence is related to sufficient penetration of the fixation elements into the tissue, to the accurate placement of anchors during the deployment and to the forces applied on the band to reduce annular dimensions. The CardioBand device has been designed to be applicable to both type I and IIIb mitral valve dysfunction, although in the latter case, it could be used in combination with other devices such as the MitraClip.

Examination of anterior and posterior mitral leaflets from all implanted animals in this study was unremarkable. Similarly, no device-related microscopic changes were observed in the left, right or septal heart sections from any animal in the study.

No circumflex artery injury was observed in the study, mainly because the helix anchors are implanted in the base of the left ventricle, with a direction perpendicular to the annular plane, towards the apex of the ventricle and far from the atrioventricular groove. None of the anchors was in the proximity of the circumflex coronary artery nor the coronary sinus.

Imaging guidance

As with other transcatheter techniques, image guidance in the animal model remains a great challenge. In animals, the most reliable imaging technology is epicardial and intracardiac echocardiography [9], since transoesophageal echocardiography is not feasible in most animals due to the interposition of a lung lobe between the heart and the oesophagus. In our model, imaging guidance by epicardial echocardiography has been excellent in the area between the posteromedial commissure and the mid portion of the posterior annulus, while images became insufficient for safe guidance in the remaining portions of the annulus. We attempted intracardiac echocardiography to guide some procedures, but without success. While echocardiography is necessary to identify the left heart structures, fluoroscopy remains mandatory to monitor device manipulation since three-dimensional (3D) echocardiography is not possible in the animal model. In the future, fluoroscopic guidance may integrate 3D reconstruction capabilities; however, differently from the aortic valve implantation, the mitral valve structures are more mobile,

and fusion imaging could not be sufficiently precise to guide interventions. Therefore, more sophisticated imaging technologies using tagging or 3D geonavigation may become necessary. Integrated CARTO system and intracardiac echocardiography are a promising technology to help complex structural heart interventions; however, this has only been tested in electrophysiology ablation therapies, and may not be appropriate for mitral valve interventions [10].

At present, live 3D echocardiography is the gold-standard imaging guidance for structural heart interventions including the MitraClip therapy [11, 12]. Three-dimensional echocardiography allows intuitive reconstructions of the anatomy, as well as multiplane and X-plane imaging to focus on specific anatomical targets. It is expected that the same imaging technology could be efficiently used to guide the CardioBand implantation in humans, although this requires a dedicated trial. We believe that the use of transoesophageal 3D echocardiography in the human will eliminate the limitations of the imaging observed in the animal model.

CardioBand vs other transcatheter annuloplasty solutions

CardioBand is the only transcatheter device reproducing the surgical implantation of an annuloplasty device. However, alternative transcatheter annuloplasty solutions are currently under investigation.

Kawata *et al.* developed a direct access transatrial mitral valve suture annuloplasty technique on the beating-heart under real-time 3D echocardiography guidance. The authors used a commercially available suturing device (Sutur Tek Endo 360-degree, Sutur Tek Inc., North Chelmsford, MA, USA) in an isolated porcine heart model. The suturing device was inserted through the left atrium. A De Vega-type [13] suture annuloplasty was performed under echo guidance. The number of tissue bites was 7.4 ± 0.8 and the total procedure time was 9.4 ± 2.4 min [14].

Coronary sinus devices have extensively been tested in preclinical as well as in clinical trials [15–21]. Although the concept of annular remodelling with a coronary sinus implant is attractive for the simplicity of the procedure, clinical results are still not convincing. The main limitations of coronary sinus devices are the anatomical variability of the coronary sinus (atrialization and distance from the mitral annulus) as well as the risk of compression of the circumflex artery [16].

Annular remodelling has been attempted also using therapeutic ultrasound. Jilaihawi *et al.* [22] reported the animal experience with the ReCor device (ReCor Medical, Inc., Ronkonkoma, NY, USA): a 12F balloon catheter was advanced into the left atrium with a transseptal approach and inflated with contrast-saline, positioned at the mitral annulus, and ultrasound energy was delivered circumferentially, to heat the annular tissue. Relative to baseline, the reduction in mitral valve annular diameter was 8.4% immediately post-procedure ($P < 0.001$), and 10.8% at 4 weeks ($P < 0.001$). Histology showed tissue thickening at the annular level. The risk of coronary artery lesions, as well as shrinking of native leaflets, is still unknown.

Goel *et al.* [23] reported similar results utilizing radiofrequency (RF) energy to heat and shrink the mitral valve annulus in an animal model with a proprietary device (QuantumCor, Lake Forest, CA, USA) that conforms to the annular shape to deliver RF energy via a standard generator to replicate a surgical mitral annular ring. The mean septolateral annular distance was reduced by a mean of 23.8%. Acute histopathology demonstrated no damage to the leaflets, coronary sinuses or coronary arteries.

There are two devices designed to directly act at the annular level, similar to the CardioBand: the Mitralign (Mitralign, Tewksbury, MA, USA) and the Accucinch (Guided Delivery Systems, Santa Clara, CA, USA) [24].

Both devices are designed to implant anchors in the subvalvar area, near to the annulus, and to induce the annular size reduction by cinching the implanted anchors. While the Accucinch is designed to deliver multiple anchors along the full length of the posterior annulus, Mitralign is designed to implant anchors more selectively, similar to a Key procedure. Compared with the CardioBand approach, both systems require a retrograde approach to the mitral valve, which is likely to be less well tolerated, particularly in the case of depressed left ventricular function, due to the crossing of the aortic valve and to the potential for arrythmias. The antegrade approach, on the other hand, is known to be very well tolerated even in the setting of severely depressed ventricular function as demonstrated by Mitraclip implant in end stage failure [25].

In conclusion, the CardioBand system is the first device developed to strictly reproduce surgical annuloplasty. While the device functioned properly in the animal model, we experienced the lack of appropriate image guidance using epicardial echocardiography. Future studies are needed to experiment alternative imaging modalities, as well as to test the device in a diseased animal model to confirm safety and efficacy of transcatheter annuloplasty.

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Conflict of interest: Francesco Maisano, Hugo Vanermen, Michael Mack, Volkmar Falk and Ottavio Alfieri are consultants for Valtech Cardio.

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APPENDIX. CONFERENCE DISCUSSION

Dr G. Lutter *(Kiel, Germany)*: A new transcatheter mitral valve annuloplasty system was designed to implant a Dacron band to the posterior leaflet to perform annuloplasty on the beating heart with a sutureless technique, under echocardiographic and fluoroscopic guidance. So this is certainly a breakthrough towards minimally invasive mitral valve repair due to the fact that it strictly reproduces surgical annuloplasty. I have two questions and one remark. Can you elaborate a little bit about why you used a posterior band application solely? An anterior annuloplasty band might have had more effect in a diseased patient or model.

And secondly, can you give us more details on the repositionability and retrievability of your system so that we know how easy it is to act from the outside in the left atrium. Later on, I mean, you have shown here already a human case which is very good.

And third, the feasibility in an animal model has been demonstrated in your pigs. Although the initial minimally invasive procedure was successful, several challenges, as you have mentioned, such as imaging or a mitral regurgitation model, have to be overcome to proceed further in humans. You might have also some ideas on that.

Dr Maisano: This device has been designed from the beginning to be completely implantable in the beating heart in a closed heart fashion. The fixation elements are obviously different from sutures and they have to be implanted deep into the muscle to be effective. So obviously, we cannot use the same fixation elements in the aorto-mitral continuity. Therefore we decided, for simplicity and for safety, to develop the first-generation devices as posterior annuloplasty bands. Obviously, with similar technology, you can also achieve a complete annuloplasty ring. But you should consider different fixation methods for the anterior portion of the ring itself.

In terms of retrievability and repositionability, all fixation elements are fully repositionable until they are finally deployed. They can also be retrievable at the end of the procedure. If you decided in the middle of the procedure to bail out, there is a device to literally unscrew all the fixation elements. Obviously, it would be a complex procedure.

The third question was related to the animal model. We are working on healthy animals with no MR, because I don't think we need to demonstrate that annuloplasty works to fix MR, and the only real challenge we have found in this, as in many other projects, is image guidance. Image guidance is particularly critical in the animals. And we have pretty good imaging of the annulus from the posterior medial commissure to about P2, and very suboptimal imaging from P2 to the antero-lateral commissure with any different imaging modality. We have used epicardial echo TEE, as well as intracardiac echo, but with all kind of echo-based systems, we have some flaws.

However, the Leipzig group is actively working to incorporate image guidance using fluoroscopy, which will probably solve most of these issues. Additionally, we expect from the human trial to learn more about the use of 3-D echo for guidance of such procedures.