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**Mastering Mitral Leaflets Coaptation after Valve Repair with Adjustable Mitral Annuloplasty Ring: prove of concept in mock loop study**

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Running title: Trans-catheter adjustable annuloplasty ring

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## Abstract

This investigation sought to determine the feasibility of a novel mitral ring designed to reshape mitral annulus on beating heart, after surgery. The mitral ring is intended to improve mitral leaflets coaptation to correct residual and recurrent mitral regurgitations. It could also provide progressive correction of mitral regurgitation. The device was tested in ex vivo beating heart model.

The novel mitral ring is selectively deformable in P1, P2 and P3 segments using a dedicated angioplasty-type balloon. The deformation should increase leaflets' coaptation reducing distance between the two leaflets. It was implanted using standard surgical techniques. The mock-loop is based on passive beating heart. MV functioning was evaluated in terms of leaflet coaptation height at P2 level using epicardial echocardiography.

The test has been completed on 8 swine hearts. Ring size was 30mm. The balloons were inserted in the connecting line. Each segment of the posterior annulus was independently activated over 3 progressive positions. Balloon inflation pressures were between 15 and 21 bar. Maximum coaptation height increase was 7 mm. Mean pressure gradient across the MV was  $1.7 \pm 0.3$  mmHg post complete activation of the device.

The device allowed significant increase in coaptation height at P2 level after adjustments at P1, P2 and P3. Results were consistent and reproducible. This feasibility study demonstrates the possibility to reshape the mitral annulus on beating heart to precisely increase MV leaflets' coaptation height.

Keywords: mitral repair annuloplasty, mitral regurgitation, surgical mitral repair, heart failure, mitral repair ring, minimally invasive mitral repair.

## **Introduction**

The surgical repair of mitral regurgitation (MR), in some patients, could become a real challenge even for experienced cardiac surgeons. In some degenerative MR, the complex reconstruction could culminate in residual MR that is typically underestimated under general anaesthesia. If the residual MR is more than moderate, the surgeon tends to replace the valve even if the replacement harms left ventricular remodelling and has negative impact on long term survival (1). In case of less than moderate residual MR, the surgeon tends to accept the compromise of incomplete repair of the regurgitation. Both solutions are frustrating for the surgeon and have negative impact on patient's long term outcome (1,2). In some functional MR associated to poor left ventricular function, the complete correction of the MR with an undersized ring is historically associated to post operative left heart failure due to the sudden increase in the left ventricle afterload (3,4). Therefore, the surgeon has to choose between leaving the MR untreated and let the disease take its fatal course or being ready to use inotropic and circulatory support in the post operative phase which dramatically increases the mortality and morbidity risks (4). The surgeon and the patient are both uncomfortable with these solutions.

Independently from the pathophysiology, regurgitation is always a lack of leaflets coaptation. A device able to increase the coaptation length of mitral leaflets only in the area where residual or recurrent MR is present would definitely improve the quality of the surgical repair and probably the clinical outcome, potentially reducing the need for mitral valve (MV) replacement. Also a device able to progressively increase mitral leaflets coaptation would allow the progressive increase in the afterload of the left ventricle possibly reducing post-operative complications in patients with poor left ventricle function (3). A device that could perform both these functions with a trans-catheter approach would avoid reoperation.

In this paper we present a device for MV annuloplasty conceived for reshaping the mitral annulus after surgical implantation using trans-catheter technique.

The primary endpoint of the study is to validate the hypothesis that a novel mitral ring can increase the coaptation height of MV leaflets on ex vivo beating heart in a mock circulatory loop. Secondary endpoints are to assess the technical feasibility of the procedure and the functional assessment of the MV.

## **Methods**

Device description. The MitralMaster (MiMa), (Kephalios SA, Aix-en-Provence, FR) is an original ring for mitral valve annuloplasty adding to the functional features of the classic Carpentier-Edwards mitral ring, the possibility of reshape the mitral annulus any time after the surgical implant. The reshaping process could be done in several steps and over the time. The device consists of rigid ring sutured to the mitral annulus using interrupted suture technique and a connecting line that links the ring to the subcutaneous tissue where it would be easy to access any time after the operation. The connecting line allows a dedicate balloon to reach mitral annulus from skin incision using trans-catheter technique, under echocardiographic and/or fluoroscopic guidance. The balloon is inflated with saline solution, deflated after 15sec and then retrieved. The balloon catheter is not permanently implanted. Balloon inflation results in permanent ring deformation and the ring itself guarantees the durability of the deformation (figures 1 and 2). It's the ring itself that guarantees the durability of the deformation. Deformation segments of the ring correspond to the anatomical regions of the posterior mitral annulus P1, P2 and P3. Each segment can be deformed independently from other segments (figure 3). Each segment has a deformation range of 1 to 5 mm (figure 2). The balloon is retrieved at the end of the procedure. The connecting line stays in place. The deformation of the ring is intended to increase mitral leaflets coaptation reducing the distance between anterior and posterior leaflets.

### Mock circulatory loop with passive beating heart.

The mock loop was described in detail elsewhere (5,6). Briefly, it consisted of a pulsatile volumetric pump, a hydraulic afterload mimicking the input impedance of the human systemic circulation, and an atrial preload that closed the hydraulic loop. The mock loop was instrumented to allow for experimental hydrodynamic investigation on the implanted device in simulated rest conditions. Pressures were acquired with piezoelectric transducers (140PC series, Honeywell Inc, Morristown, NJ, USA) placed in the systemic impedance simulator ( $P_{\text{sis}}$ , Figure 4), in left atrium and in the ventricle ( $P_{\text{atr}}$  and  $P_{\text{ven}}$  respectively). MV and AV flow rates ( $Q_{\text{mv}}$  and  $Q_{\text{av}}$  respectively) were acquired with time-transient flow meters equipped with 1" probes (HT110R, Transonic Systems Inc, Ithaca, NY, USA). One probe was placed upstream from the MV, and the other downstream to the AV. Data were sampled at 200Hz and recorded with an A/D board (USB6210, National Instruments, Austin, TX, USA).

### Experimental procedure and data collection

In adult swine's heart the mitral valve was exposed through left atrium incision. The valve was assessed for integrity and the distance between the trigons measured to select valves having this distance between 30 and 32 mm. The ring (size 30) was then sutured using interrupted suture technique with 2/0 Tycron (figure 5). Sutures' needles are inserted into dedicated "button holes" on the inner surface of the ring to simplify the surgical procedure and avoid accidental damage of fragile components of the device. In 3 samples, mitral leaflets received ink spots markers to provide a qualitative visual evaluation of coaptation area changes. The connecting line exit the left atrium trough the surgical incision. The heart was housed into the mock loop as elsewhere detailed, and the circulation started simulating physiological rest conditions (60 bpm of heart rate, 65mL of stroke volume imposed by the pump). Saline solution at 37° C was used as working fluid. To assess proper working

conditions in the mock loop, the following quantities were acquired in all the tested samples following ring implantation:

- CO: cardiac output evaluated from the AV flow curves ( $Q_{av}$ ).
- $P_{art}$ : mean simulated arterial pressure, evaluated from  $P_{sis}$

Moreover, in three heart samples the following hydrodynamic quantities were evaluated and compared ante and post ring activation in P1, P2 and P3:

- $Q_{mv, sys}$ : mean MV systolic leakage evaluated from the MV flow curve  $Q_{mv}$ .
- $\Delta P_{mv, dia}$ : mean diastolic pressure drop across the MV (mean value of  $P_{atr}-P_{ven}$  evaluated over the diastole).

A 5 mm diameter fiberscope (ENF-GP, Olympus Corp, Tokyo, Japan) was then inserted in the left atrium to acquire images of the mitral valve and the mitral ring during the simulated cardiac cycle. A cardiac ultrasound (HDI5000, Philips, Eindhoven, The Netherlands) was used to acquire images of the mitral valve from epicardium (figure 6). Specifically, the height of the mitral leaflets coaptation (HMC) at P2 level was acquired in baseline conditions. Then, the balloon was inflated in P2 position at increasing pressures in order to achieve small, medium and large displacement of the P2 part of the ring. The procedure was repeated for P1 and P3. For each sample a total of 13 echo measurements were taken. The changes in HMC were recorded.

#### Statistical analysis

Raw data were analysed calculating mean and standard deviation. Pre and post-activation hydrodynamic data were compared with Mann Whitney test. Pearson's chi-squared test ( $\chi^2$ ) was applied to sets of categorical data (HMC) to evaluate how likely it is that any observed difference between the sets arose by chance. A  $p < 0.05$  was considered significant.

## Results

The working conditions imposed by the mock loop did not change significantly following device activation ( $p=0.112$ ). All hearts had normal MV regurgitation ( $Q_{mv,sys}$  changed from  $0.2\pm 0.2$  L/min pre-activation to  $0.15\pm 0.1$  post-activation of the device). Ring size was 30mm, without significant under sizing. The measured cardiac output was  $3.0\pm 0.6$  L/min, with a mean simulated systemic pressure of  $86\pm 5.0$  mmHg. The working conditions imposed by the mock loop did not change significantly following device activation ( $p=0.112$ ). Mean pressure gradient across the MV ( $\Delta P_{mv,dia}$ ) was  $1\pm 1.1$  mmHg pre-activation, and  $1.7\pm 0.3$  post complete device activation ( $p=0.453$ ). The balloons were inserted without resistance and positioned in blind, limit switch mode. Each segment of the posterior annulus (P1, P2, P3) was independently activated over 3 progressive steps (small, medium, large deformation) without technical failure. Balloon inflation pressures were between 15 and 21 bar. After activation of P2 segment, HMC increase was  $3.2\pm 0.1$  mm; activation of both P2 and P1 led to  $5.5\pm 0.2$  mm of increase. The maximum HMC increase in P2 was 7.0 mm, and was recorded following complete activation of the device at maximum balloon pressurization. Figure 7 illustrates detailed results. The on-line movie recorded from the left atrium qualitatively shows the effect on coaptation of device activation. The  $\chi^2$  between baseline values and maximal HMC increase was  $< 0.01$ .

## Discussion

The future of MV regurgitation treatment is towards first surgical correction followed by late, iterative percutaneous adjustments of leaflets coaptation, if needed. Although mitral repair is still considered the gold standard for the surgical treatment of functional and degenerative MR, clinicians started to question the durability of the surgical repair, particularly in functional MR (2,3). A recent study analysed the outcomes of surgical treatment of severe ischemic MR comparing repair vs replacement and outlined that the recurrence of MR, which

was mostly moderate in degree, remained a progressive and excess hazard for patients undergoing mitral-valve repair. During the 2-year follow-up period, 58.8% of patients in the repair group had moderate or severe regurgitation, as compared with 3.8% in the replacement group (7). This deficiency in the durability of correction of MR confers a predisposition to heart failure, atrial fibrillation, and repeat interventions and hospitalizations (7,8).

Improve the durability of a surgical procedure that has been established almost 40 years ago and is still widely accepted, is a real challenge. Starting from the assumption that “coaptation is durability” (2), we focused our efforts to improve the height of the mitral leaflets coaptation during the surgical repair or whenever needed and without upsetting the standard surgical technique. The key feature of the device evaluated in this study is its capability to improve the coaptation height pushing the posterior leaflet towards the anterior, therefore, reducing the antero-posterior distance of the native mitral annulus. The MiMa should allow to control the amount of posterior leaflet displacement (from 1 to 5 mm) as well as to define the area of displacement (P1, P2, P3 according to surgical classification of posterior leaflet areas) as clearly seen from the camera placed in the left atrium. All the adjustments should be feasible any time after implant and using trans-catheter technique. In a clinical setting, the access port will be placed in the right subclavian region, under the skin, as a standard pacemaker. If a residual or recurrent regurgitation is detected, the guiding catheter is surgically exposed and used to introduce the dedicate balloon in the area of the posterior mitral leaflet at the regurgitation level. Balloon inflation should then displace the given area of the posterior leaflet towards the anterior, clearing or reducing the regurgitation. This is the first device offering the possibility of precisely adjust mitral leaflets coaptation with trans-catheter approach at any time and for several times after the implant.

The adequate functioning of the MV requires a beating left ventricle therefore we have chosen a platform with passive beating heart that has already been validated for trans-catheter MV



repair evaluation (5). It combines a reliable simulation of physiologic MV leaflets movements with the possibility of direct vision of the MV and the mitral ring from the left atrium. The possibility to modify the preload and the afterload of the left ventricle helped us to recreate almost physiologic conditions for a better evaluation of the device tested.

Balloon inflation was constantly associate to MiMa deformation in the targeted area with high reproducible results. The deformation length was clearly correlated to pressure inflation in such a way to establish a pressure / deformation curve that is used for the pre-clinical tests. Basically, we identified 3 degrees of displacement (small, medium, large) for each of the 3 areas in which the posterior leaflet is divided as illustrated in figure 7. This unique feature of the device tested, makes the control of the coaptation surface much more precise than other active annuloplasty devices in terms of parts of the posterior leaflet (P1, P3, P3) and degree of coaptation (small, medium, large). Existing reshaping mitral rings (enCore SQ , Micardia Co. Irvine CA) act to reduce the circumference of the mitral annulus, similarly to a sphincter and independently from the position of the regurgitation. Their action is, therefore, less specific and probably less efficient.

Results showed that the increase in HMC was reproducible and progressive (see Supplement Video, Supplemental Digital Content 1, <http://links.lww.com/ASAIO/A119>). The coaptation in P1 and P3 segments was difficult to measure due to the echocardiographic window available from the epicardium. Interestingly, in all hearts, the displacement of P1 and P3 segments resulted in increase in HMC at P2 level endorsing the hypothesis that the entire posterior part of the mitral annulus is displaced towards the anterior. The increase in HMC is achieved without shrinking the mitral annulus circumference as it occurs when the surgeon downsizes the mitral ring to achieve better leaflets coaptation (3). This unique feature of the MiMa explains why MV gradients were still in the physiologic range even after the complete activation of the device.

A potential detrimental effect of moving the posterior annulus towards the anterior could be the displacement of the leaflets coaptation plane towards the left ventricle outflow tract inducing Systolic Anterior Motion (SAM) effect (9). Any of the heart treated showed SAM effect, however we can not exclude that, in patients with small LV chamber, hypertrophy of the interventricular septum and acute mitro-aortic junction, SAM could appear after complete activation of the device.

The possibility of progressively correct the mitral regurgitation without iterative surgical interventions opens new therapeutic opportunity for functional MR in patients with low Left Ventricle Ejection Fraction (LVEF). These patients are at high mortality and morbidity risks when undergo mitral repair or replacement (10) mainly due to the sudden increase in the left ventricle afterload after complete correction of the MR. If the afterload increases over weeks or months, the left ventricle should have more time to adapt to it and this possibly reduces the risk of heart failure. The technique for increasing HMC after the surgical implant of the MiMa is trans-catheter and the procedure could be repeated any time after implant and as many times as necessary till the complete activation of the device making it the ideal tool to treat functional MR in patients with poor LVEF.

Moreover, the device addresses recurrent MR due to progressive LV dilatation possibly associate with HF progression. Each device's activation produces an anterior displacement of the corresponding part of the posterior leaflet, therefore reducing posterior leaflet excursion. This mechanism compensates the relative shortening of the chordae due to LV dilatation, avoiding the risks of a second intervention.

### **Conclusions**

There is a clear need for less invasive procedures to treat heart diseases in high risk patients. This study showed it is possible to increase the height of mitral leaflets coaptation on beating heart, with trans-catheter approach after implanting an original mitral ring. The procedure was

consistent with reproducible effects. This device could represent the new therapeutic option for the treatment of persistent and recurrent mitral regurgitation after surgical repair. It could also allow to surgically treat MR in low LVEF patients possibly reducing the complication rate associate to standard repair. Only the ongoing clinical studies will possibly demonstrate that MiMa improves long term results of mitral repair, avoids reoperation and rehospitalisation due to MR and allows to treat MR in patients with poor ventricular function.

ACCEPTED

## References

1. Suri RM, Clavel MA, Schaff HV, et al. Effect of Recurrent Mitral Regurgitation Following Degenerative Mitral Valve Repair: Long-Term Analysis of Competing Outcomes. *J Am Coll Cardiol*. 2016;67(5):488-98
2. Anyanwu AC, Adams DH. Why do mitral valve repairs fail? *J Am Soc Echocardiogr*. 2009;22(11):1265-8
3. Mihos CG, Santana O. Mitral valve repair for ischemic mitral regurgitation: lessons from the Cardiothoracic Surgical Trials Network randomized study. *J Thorac Dis*. 2016;8(1):E94-9
4. Salmasi MY, Acharya M, Humayun N, et al. Is valve repair preferable to valve replacement in ischaemic mitral regurgitation? A systematic review and meta-analysis. *Eur J Cardiothorac Surg*. 2016;50(1):17-28
5. Vismara R, Leopaldi AM, Piola M, et al. In vitro assessment of mitral valve function in cyclically pressurized porcine hearts. *Med. Eng. Phys*. 2016;38:346–353.
6. Gelpi G, Romagnoni C, Vismara R, et al. Intracardiac Visualization of Transcatheter Mitral Valve Repair in an In Vitro Passive Beating Heart. *Circulation*. 2015;1:131-132.
7. Goldstein D, Moskowitz AJ, Gelijs AC et al. Two-Year Outcomes of Surgical Treatment of Severe Ischemic Mitral Regurgitation. *N Engl J Med* 2016; 28(4):344-53
8. Di Salvo TG, Acker MA, Dec GW, et al. Mitral valve surgery in advanced heart failure. *J Am Coll Cardiol* 2010;55:271-282
9. Alfieri O, Lapenna E. Systolic anterior motion after mitral valve repair: where do we stand in 2015? *Eur J Cardiothorac Surg*. 2015 Sep;48(3):344-6.
10. Kainuma S, Taniguchi K, Daimon T, et al. Mitral valve repair for medically refractory functional mitral regurgitation in patients with end-stage renal disease and advanced heart failure. *Circulation*. 2012 11;126(11-1):S205-13.

## Legends

Figure 1. Schematic representation of the MiMa working principle. The balloon is inserted in the connecting line (d) and advanced till the P2 segment (a and b). The balloon is then inflated causing permanent deformation of the ring in the P2 area (c). After the procedure, the balloon is retrieved.

Figure 2. Schematic representation of progressive deformation of the ring. The P2 segment is displaced towards the anterior leaflet of 2mm (a), 3mm (b) or 5mm (c) depending on balloon inflation. Maximum displacement is achieved in one or more steps over time, according to patient's need.

Figure 3. The 3 anatomical segments of the posterior leaflet are displaced independently from each other. Maximum expansion of the 3 segments corresponds to the maximum displacement of the posterior leaflet towards the anterior leaflet that MiMa can achieve.

Figure 4. Right, a photography, and left, a schematic of the pulsatile mock loop. PD: pulse duplicator; LV: left ventricle; SIS: systemic impedance simulator; PR: preload reservoir;  $P_{ven}$ : ventricular pressure;  $P_{atr}$ : left atrium pressure;  $P_{sis}$ : arterial pressure.  $Q_{mv}$ : mitral valve flow;  $Q_{ao}$ : aortic valve flow.

Figure 5. Integrity of the mitral valve has been assessed. Inter trigon distance is 32. The ring (size 30) is sutured on the mitral annulus using interrupted 2/0 Tycron sutures. The connecting line exit the left atrium at the level of the right end of the atrial incision (a). A plastic flange (b) is sutured to the aorta to facilitate the connection to the mock circuit. A similar flange is inserted into the left ventricle trough the apex to connecting the heart to the mock circuit.

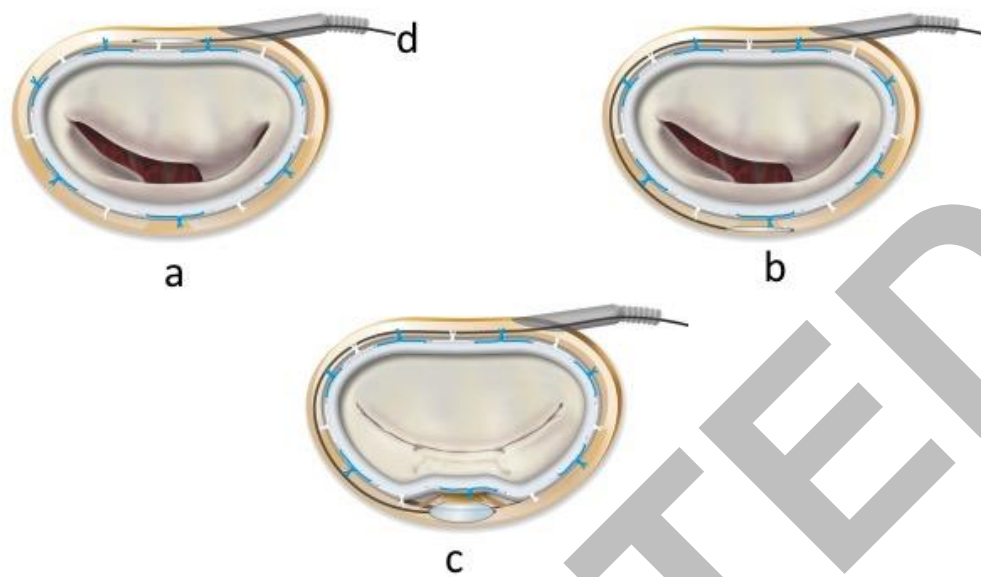
Figure 6. Echocardiogram with epicardic view of the 4 cavities. LA: left atrium; LV: left ventricle; a: height of mitral leaflets coaptation (HMC); b: ring at the level of A2.

Figure 7. Detailed results on average coaptation increase (HMC) associate to small, medium and large deformation of each P segments. The amount of deformation depends on inflation balloon pressure.

Video. Left atrial view of the MiMa during P2 segment activation. The ring has been sutured using 2/0 interrupted suture technique. Balloon in P2 position is progressively inflated causing the anterior displacement of P2 portion of the posterior leaflet.

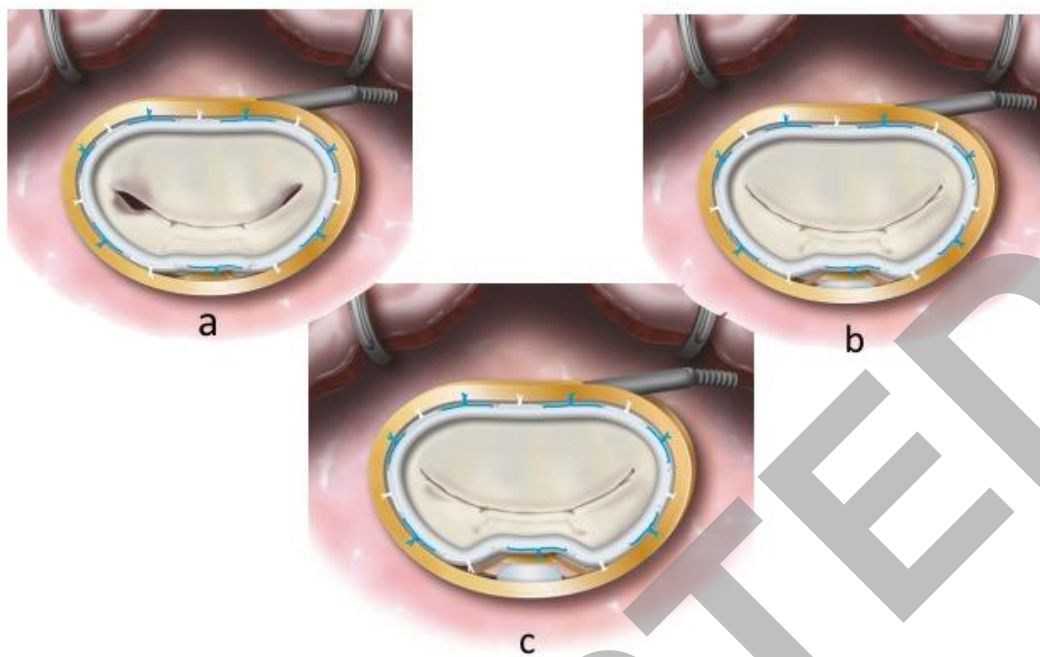
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Figure 1.



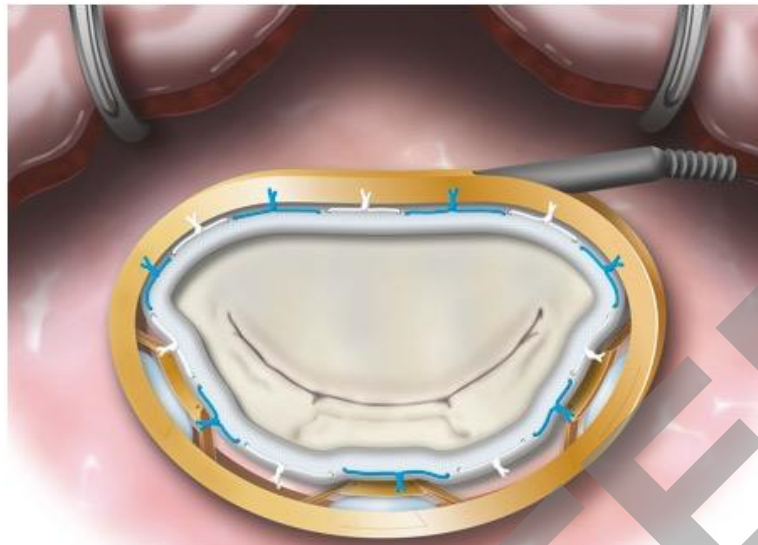
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Figure 2.



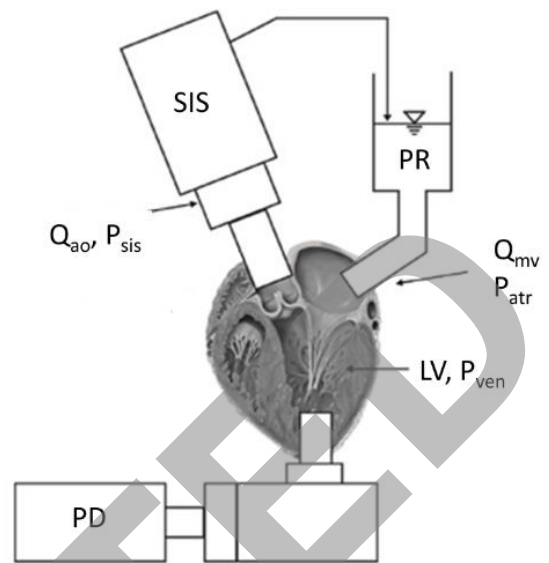
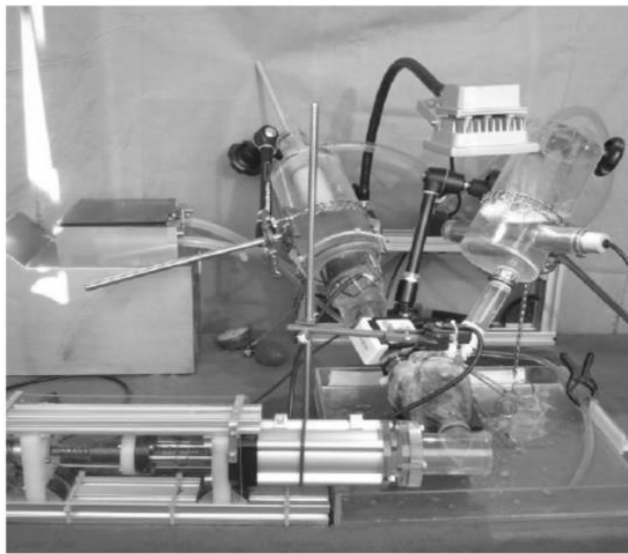


**Figure 3.**



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Figure 4.



**Figure 5.**

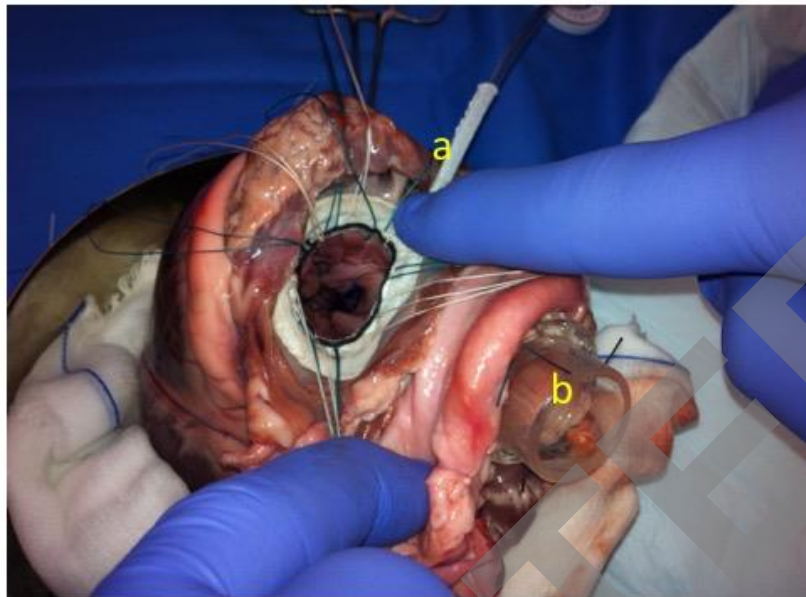


Figure 6.

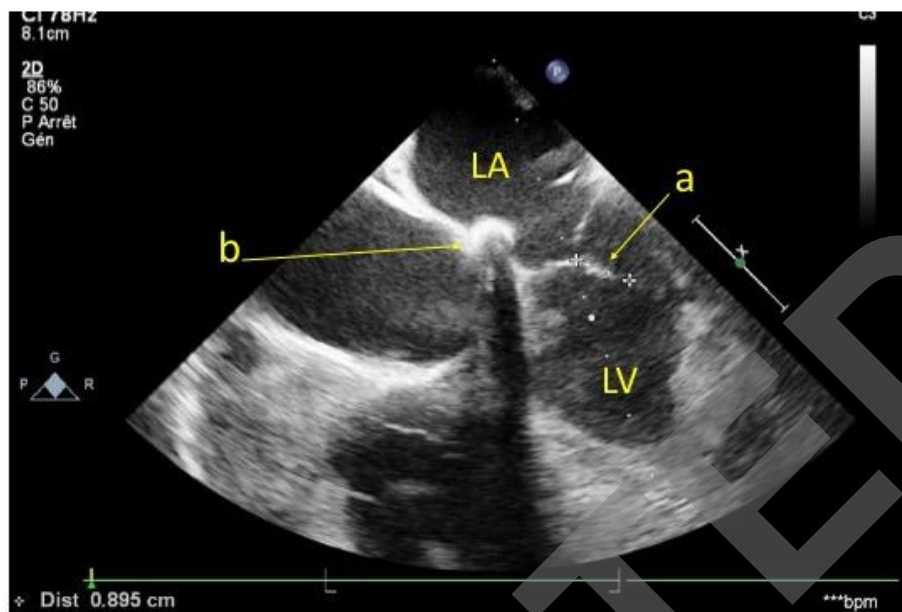


Figure 7.

