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Mastering Mitral Leaflets Coaptation After Valve Repair with Adjustable Mitral Annuloplasty Ring: Proof of Concept in Mock Loop Study

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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. Mitral valve (MV) functioning was evaluated in terms of leaflets coaptation height at P2 level using epicardial echocardiography. The test has been completed on eight swine hearts. Ring size was 30 mm. The balloons were inserted in the connecting line. Each segment of the posterior annulus was independently activated over three 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 ± 0.3 mm Hg after 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. *ASAIO Journal* 2017; 63:168–173.

Key Words: mitral valve repair annuloplasty, mitral regurgitation, surgical mitral repair, heart failure, mitral repair ring, minimally invasive mitral repair

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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 anesthesia. If the residual MR is more than moderate, the surgeon tends to replace the valve even if the replacement harms left ventricular remodeling 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 MRs associated with poor left ventricular function, the complete correction of the MR with an undersized ring is historically associated with postoperative 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 postoperative phase which dramatically increases the mortality and morbidity risks.[4] Both the surgeon and the patient are 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 postoperative complications in patients with poor left ventricle function.[3] A device that could perform both these functions with a transcatheter approach would avoid reoperation.

In this article, we present a device for MV annuloplasty conceived for reshaping the mitral annulus after surgical implantation using transcatheter technique.

The primary end-point 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 end-points are to assess the technical feasibility of the procedure and the functional assessment of the MV.

Materials and Methods

Device Description

The MitralMaster (MiMa) (Kephalios SA, Aix-en-Provence, France) is an original ring for MV annuloplasty adding to the

functional features of the classic Carpentier-Edwards mitral ring, the possibility of reshaping 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 transcatheter technique, under echocardiographic or fluoroscopic guidance. The balloon is inflated with saline solution, deflated after 15 seconds, 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 is 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 1–5 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] 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) placed in the systemic impedance simulator (P_{sis}, **Figure 4**), in left atrium and in the ventricle (P_{atr} and P_{ven}, respectively). Mitral valve and atrio-ventricular (AV) flow rates (Q_{mv} and Q_{av}, respectively) were acquired with time-transient flow meters equipped with 1" probes (HT110R, Transonic Systems Inc., Ithaca, NY). One probe was placed upstream from the MV, and the other downstream to the AV. Data were sampled at 200 Hz and recorded with an A/D board (USB6210, National Instruments, Austin, TX).

Experimental Procedure and Data Collection

In adult swine's heart, the MV was exposed through left atrium incision. The valve was assessed for integrity, and the distance between the trigons was 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 three samples, mitral leaflets received ink spot markers to provide a qualitative visual evaluation of coaptation area changes. The connecting line exits the left atrium at the level of the left atriotomy. The heart was housed into the mock loop as elsewhere detailed, and the circulation started simulating physiologic rest conditions (60 bpm of heart rate, 65 ml 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 after 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 before and after 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 MV and the mitral ring during the simulated cardiac cycle.

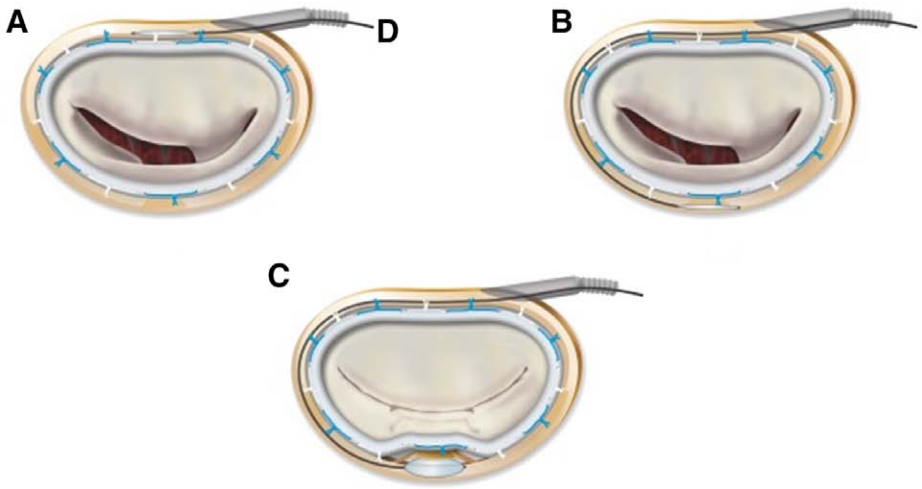

Figure 1. Schematic representation of the MiMa working principle. The balloon is inserted in the connecting line (**D**) and advanced till the P2 segment (**A** and **B**). The balloon is then inflated causing permanent deformation of the ring in the P2 area (**C**). After the procedure, the balloon is retrieved.

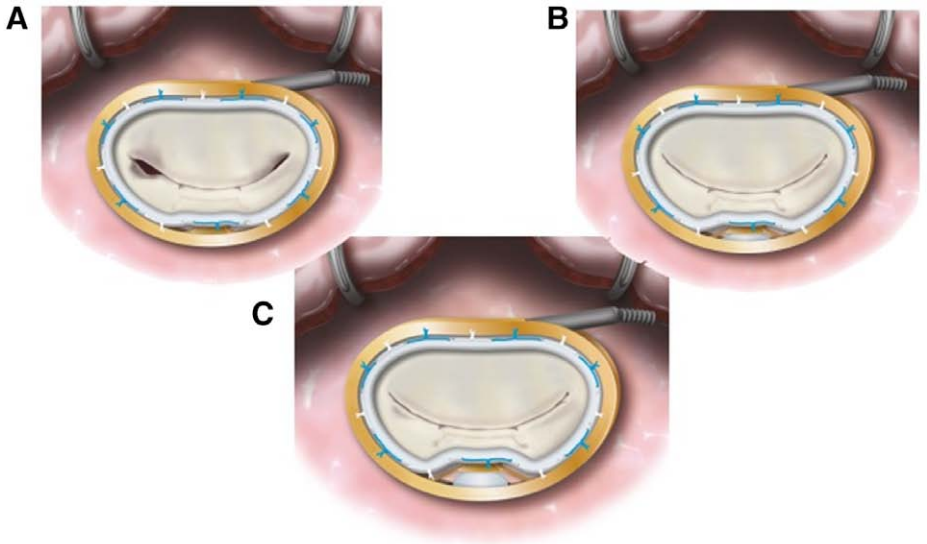

Figure 2. Schematic representation of progressive deformation of the ring. The P2 segment is displaced toward the anterior leaflet of (**A**) 2 mm, (**B**) 3 mm, or (**C**) 5 mm depending on balloon inflation. Maximum displacement is achieved in one or more steps over time, according to patient's need.

A cardiac ultrasound (HDI5000, Philips, Eindhoven, The Netherlands) was used to acquire images of the MV 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 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 analyzed calculating mean and standard deviation. Pre- and postactivation hydrodynamic data were compared with Mann–Whitney test. Pearson's χ^2 test 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 after device activation ($p = 0.112$). All hearts had normal MV regurgitation ($Q_{mv,\ sys}$ changed from 0.2 ± 0.2 L/min preactivation to 0.15 ± 0.1 L/min postactivation of the device). Ring size was 30 mm, without significant undersizing. The measured cardiac output was 3.0 ± 0.6 L/min, with a mean simulated systemic pressure of 86 ± 5.0 mm Hg. The working conditions imposed by the mock loop did not change significantly after device activation ($p = 0.112$). Mean pressure gradient across the MV ($\Delta P_{mv,\ dia}$) was 1 ± 1.1 mm Hg preactivation, and 1.7 ± 0.3 mm Hg after 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 three 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 ± 0.1 mm; activation of both P2 and P1 leads to 5.5 ± 0.2 mm of increase. The maximum HMC increase in P2 was 7.0 mm, and was recorded after complete activation of the device at maximum balloon pressurization. **Figure 7** illustrates detailed results. The on-line movie (Supplemental Digital Content 1, http://links.lww.com/ASAIO/A119) recorded from the left atrium qualitatively shows the effect on coaptation of device activation. The χ^2 between baseline values and maximal HMC increase was less than 0.01.

Discussion

The future of MV regurgitation treatment is toward first surgical correction followed by late, iterative percutaneous adjustments of leaflets coaptation, if needed. Although mitral repair

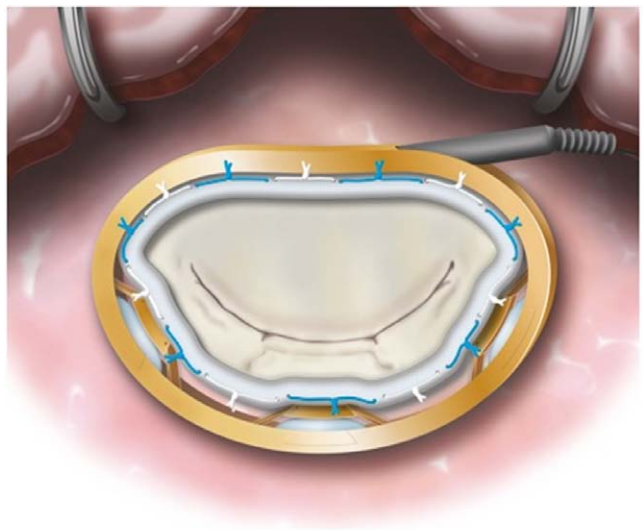

Figure 3. The three anatomical segments of the posterior leaflet are displaced independently from each other. Maximum expansion of the three segments corresponds to the maximum displacement of the posterior leaflet toward the anterior leaflet that MiMa can achieve.

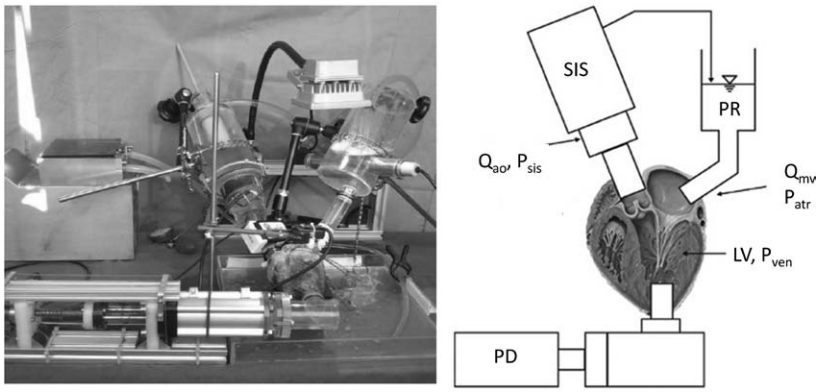

Figure 4. A photography (right) and a schematic of the pulsatile mock loop (left). LV, left ventricle; PD, pulse duplicator; PR, preload reservoir; P_{ven}, ventricular pressure; P_{atr}, left atrium pressure; P_{sis}, arterial pressure; SIS, systemic impedance simulator; Q_{mv}, mitral valve flow; Q_{ao},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

is still considered the gold standard for the surgical treatment of functional and degenerative MR, clinicians started to questioning the durability of the surgical repair, particularly in functional MR.[2,3] A recent study analyzed the outcomes of surgical treatment of severe ischemic MR comparing repair *versus* 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]

Improving the durability of a surgical procedure that has been established almost 40 years ago and is still wildly 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 toward the anterior, therefore, reducing the anteroposterior 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 transcatheter 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 toward the anterior, clearing or reducing the regurgitation. This is the first device offering the possibility of precisely adjusting mitral leaflets coaptation with transcatheter 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 transcatheter 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 associated with 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 preclinical tests. Basically, we identified three degrees of displacement (small, medium, large) for each of the three 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

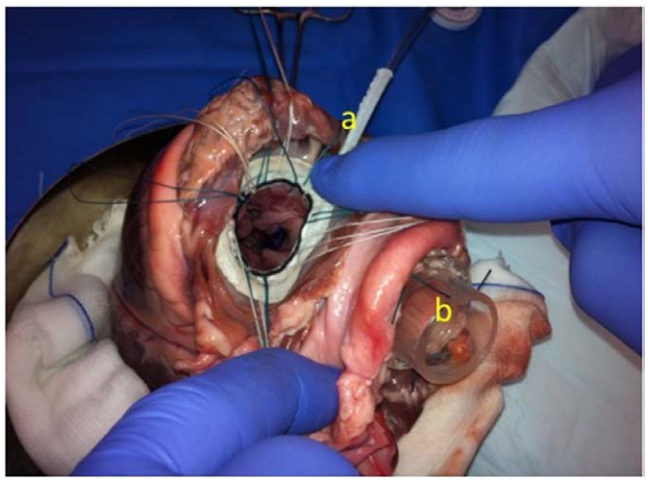

Figure 5. Integrity of the mitral valve has been assessed. Intertrigonal distance is 32 mm. The ring (size 30) is sutured on the mitral annulus using interrupted 2/0 Tycron sutures. **A**: The connecting line exits the left atrium at the level of the right end of the atrial incision. **B**: A plastic flange 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.

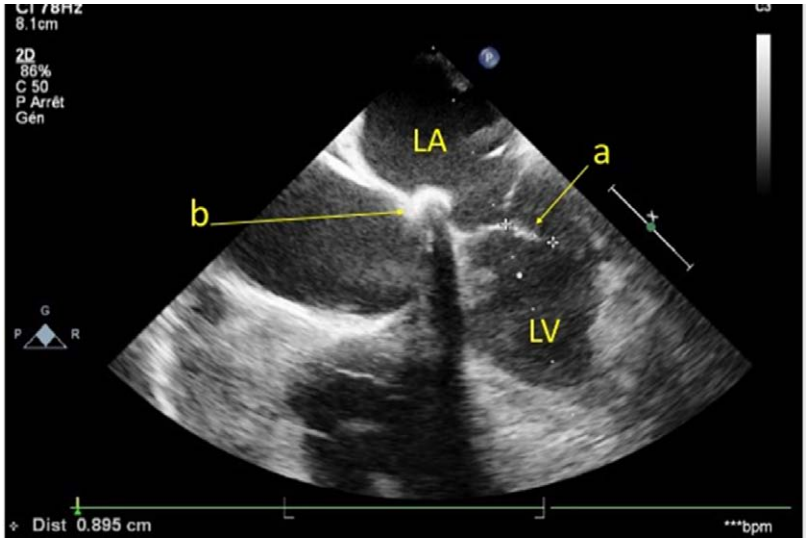

Figure 6. Echocardiogram with epicardic view of the four cavities. a, height of mitral leaflets coaptation; b, ring at the level of A2. LA, left atrium; LV, left ventricle.

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 Video, Supplemental Digital Content 1, http://links.lww.com/ASAIO/A119). The coaptation in P1 and P3 segments was difficult to measure because of 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 toward 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 toward the anterior could be the displacement of the leaflets coaptation plane toward the left ventricle outflow tract inducing systolic anterior motion (SAM) effect.[9] Any of the heart treated showed SAM effect; however, we cannot exclude that, in patients with small left ventricle chamber, hypertrophy of the interventricular septum, and acute mitroaortic junction, SAM could appear after complete activation of the device.

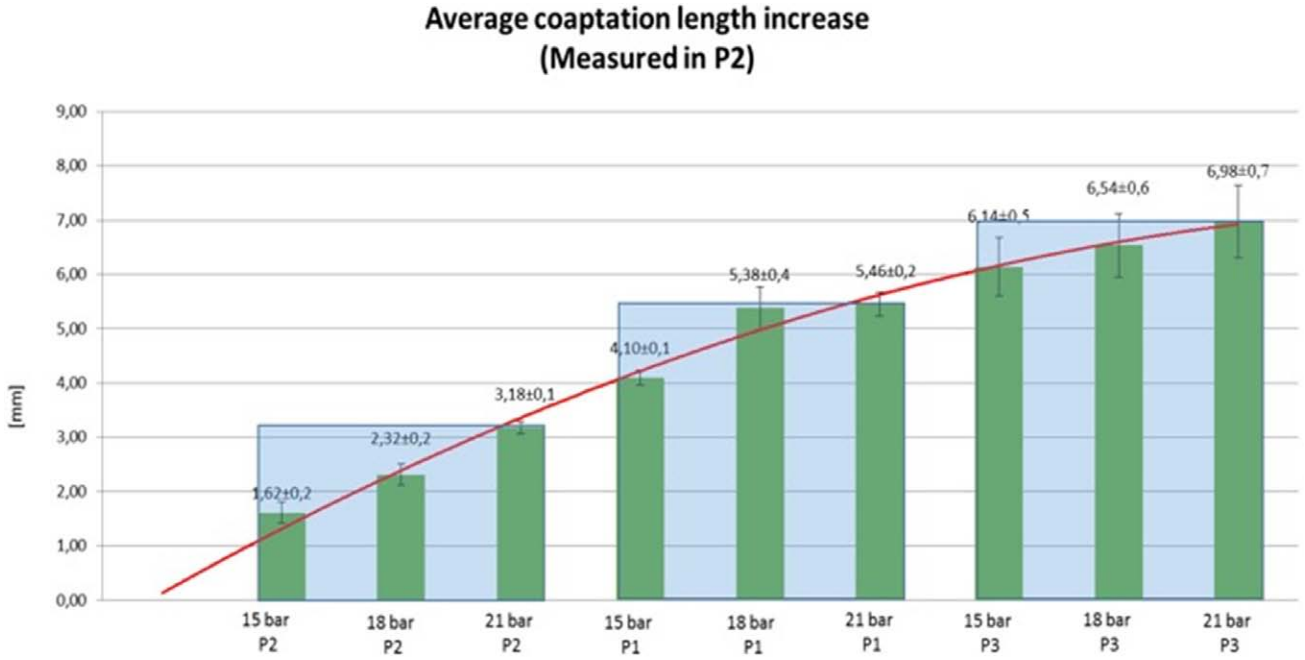

Figure 7. Detailed results on average coaptation increase (height of mitral leaflets coaptation) associated with small, medium, and large deformation of each P segments. The amount of deformation depends on inflation balloon pressure.

The possibility of progressively correct the MR 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 because of 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 transcatheter 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 left ventricle dilatation possibly associated 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 left ventricle 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 transcatheter 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 MR after surgical repair. It could also allow to surgically treat MR in low LVEF patients, possibly reducing the complication rate associated with standard repair. Only the ongoing clinical studies will possibly demonstrate that MiMa improves long-term results of mitral repair, avoids reoperation and rehospitalization due to MR, and allows to treat MR in patients with poor ventricular function.

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