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RESEARCH ARTICLE

Lessons learned from Percutaneous Indirect Annuloplasty in the Treatment of Mitral Regurgitation and Future Perspectives

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ABSTRACT

Mitral annuloplasty is the most performed surgical procedure in the treatment of mitral valve regurgitation. However, the morbidity and mortality risks associated with this procedure limit its broader application, especially in patients with comorbidities or less severe mitral valve regurgitation. A less invasive percutaneous approach associated with lesser morbidity might offer advantages compared with mitral annuloplasty in some patients. In order to find such an approach, the use of the coronary sinus has been extensively explored. The anatomical relationship between the coronary sinus and the posterior annulus of the mitral valve inspired several creative solutions to restore mitral leaflets coaptation. Coronary sinus annuloplasty attempts to replicate the results of surgical annuloplasty by reducing the antero-posterior diameter of the mitral annulus. In the present manuscript, we performed a systematic review of the devices using the coronary sinus as a key element to correct mitral regurgitation, including two devices still in preclinical phase and those currently awaiting premarket approval. We discussed the most recently published results related to percutaneous annuloplasty, highlighted the pros and cons of each approach, and summarized the lessons learned to improve clinical results.

Key-words: Mitral valve regurgitation; mitral annuloplasty; percutaneous indirect annuloplasty; mitral valve; coronary sinus; valvular heart disease.

1. Introduction

Mitral annuloplasty alone or associated with mitral leaflets repair is the most reliable surgical procedure for treating mitral valve regurgitation.¹ Patients who underwent mitral annuloplasty showed a marked and persistent symptom and quality of life improvements.² The procedure also benefits left ventricular function by inducing a reverse remodeling as documented in long term echocardiographic studies.³ However, this surgical approach has, as any other open-heart surgery, a high morbidity and mortality rate ranging from 5 to 17%⁴, which limit broader application, especially in patients with comorbidities or less severe mitral regurgitation (MR). Within the elderly population, MR is the most common etiology of valvular heart disease, with a prevalence of 9.3% to 11%.⁵ However, those patients are often denied mitral valve surgery due to their increased surgical risk, even though this surgical intervention would significantly improve their symptoms and longevity.⁶ This surgical intervention has proven to be beneficial to some patients, but there is undoubtedly room for less invasive strategies.

A less invasive percutaneous approach to treat MR associated with lesser morbidity might offer advantages compared with a surgical procedure in selected patients, provided that the clinical results are consistent.

As with surgical annuloplasty, most percutaneous treatment approaches in the context of functional MR target annular dimensions. From a technical point of view,

the percutaneous mitral annular remodeling could be achieved by acting directly on the mitral annulus (annular plication) or by acting on the coronary sinus (CS, indirect annuloplasty). The latter is the topic of this review. Of note, percutaneous interventions directly targeting the mitral leaflets will not be discussed here.

To better understand the anatomical and functional background of percutaneous indirect annuloplasty (PIA), we refer to the Carpentier classification of MR: in Type I (normal leaflet motion and a dilated annulus) and Type IIIb (leaflet movement restriction as the consequence of ischemic disease), there are no anatomical abnormalities of the mitral leaflets. However, the lack of coaptation of central scallops of the mitral valve is due to the antero-posterior (or septal-to-lateral) annular dilatation.⁷ The usual surgical correction of functional MR is achieved by placing an undersized annuloplasty ring to reduce the diameter of the mitral annulus and allows for leaflet coaptation.⁷ The same reduction of the septal-to-lateral distance could be achieved by acting on the CS. Indeed, it runs approximately 0.5 to 1cm on the superior atrial side of the mitral valve annulus from the middle portion of P1 to the middle portion of P3. The working principle of the PIA is that any force applied on the CS towards the anterior leaflet of the mitral valve should theoretically plicate the annulus tissue and “cinch” the mitral valve leaflets by pulling together the tissue just above the mitral annulus, to reduce the septal-to-lateral distance, and eventually, the MR.

We reviewed the most relevant studies on devices performing PIA in the treatment of mitral regurgitation, highlighted the pros and cons of each approach, summarized the lessons learned, and proposed directions for future devices development.

2. Methods

Pubmed and Cochrane Database of Systematic Review were consulted and articles containing preclinical and clinical data on devices achieving PIA were selected. The following keywords were used: indirect annuloplasty; functional mitral regurgitation; mitral valve; percutaneous annuloplasty; transcatheter mitral valve intervention. Single center experience and multicenter randomized trials for market approval clearance were included, whereas case reports were excluded from the analysis. For each clinical report we analyzed study designs, patient selection, and outcomes (primary, secondary, and complications). For preclinical studies including feasibility studies, we analyzed the technical challenges and complications. When several studies reported data on the same device, we selected the most updated and relevant.

3. Results

Eleven studies describing five different systems have been identified and analyzed (Table 1). One device (Carillon Mitral Contour System® by Cardiac Dimensions, Kirkland, WA) got a "Conformité Européenne" (CE) mark approval; three others, the MONARC (Edwards Lifesciences, Irvine, California, USA), the PTMA (Viacor Inc., Wilmington,

Massachusetts, USA), and the ARTO system (MVRx Inc., San Mateo, CA, USA) have been evaluated in clinical multicenter trials with the aim of receiving market approval. For one device, the selected study demonstrated the feasibility of a novel procedure in an animal model. The relevant characteristics and results concerning each device are reported in Table 2.

Table 1. Publications on percutaneous indirect mitral annuloplasty considered in this study

Article	Study name	Device	Type of study	Patients enrolled /implanted	Follow-up duration (months)
Schofer J <i>et al.</i> (2009)	AMADEUS	Carillon	Prospective Single arm	48/30	6
Siminiak T <i>et al.</i> (2012)	TITAN	Carillon	Prospective Case-controlled Non-randomized	36/17	12
Lipiecki J <i>et al.</i> (2016)	TITAN II	Carillon	Prospective Single arm	36/30	12
Witte KK <i>et al.</i> (2019)	REDUCE-FMR	Carillon	Prospective, Randomized (3:1)	120/87	12
Harnek J <i>et al.</i> (2011)	EVOLUTION	Monarc	Prospective Single arm	72/59	12
Rogers JH <i>et al.</i> (2015)	MAVERIC	ARTO	Prospective Non-randomized First-in-human	11	1
Patterson T <i>et al.</i> (2021)	MAVERIC	ARTO	Multicentre, Prospective Single arm	45	24
Sack S <i>et al.</i> (2009)	-	Viacor	First-in-human	27/19	1
Sack S <i>et al.</i> (2009)	-	Viacor	Prospective Non-randomized	31/11	12
Tozzi P <i>et al.</i> (2022)	-	-	Experimental	-	-
Kaye DM <i>et al.</i> (2003)	-	-	Experimental	-	-

Table 2. Main characteristics and development stage of devices analyzed.

Device	Anchoring mean	Type of implant	Area of implant	Development stage
Carillon	Yes	Permanent	Only CS	CE marked
Monarc	Non	Resorbable	Only CS	Suspended
Viacor	Yes	Permanent	CS and subclavian vein	Suspended
PS3 / ARTO	Yes	Permanent	CS and interatrial septum	CE marked
Unnamed	Yes	Permanent	CS and trigon	Pre-clinical

CS: coronary sinus.

4. Discussion

Transcatheter edge-to-edge repair with the MitraClip system (Abbott Vascular Inc, Menlo, CA, USA) is currently the most advanced technology available for clinical use, with proven safety and efficacy profiles in selected patients with either functional or degenerative MR (8). However, up to 30% of patients screened for MitraClip have been refused due to anatomic contraindication, including annular dilatation.⁸ Moreover, and about a quarter to a third of patients did not respond as expected to MitraClip therapy because of important residual MR after the procedure. This is probably due to the concomitant annular dilatation that is not corrected by the MitraClip.

Importantly, the surgical experience has shown that long-term results of surgical edge-to-edge repair in the absence of annuloplasty are suboptimal.⁹ Therefore, the absence of

mitral annuloplasty is a major concern regarding patient's eligibility and long-term durability of MitraClip therapy. The combination of transcatheter annuloplasty and MitraClip has the potential to improve durability and expand the indication toward a lower risk population. We believe there is a clinical need for a transcatheter mitral repair approach to address annular dilatation.

In 2003, Kaye *et al.*¹⁰ demonstrated the feasibility of reducing the mitral annulus diameter inserting a device directly into the CS using a fully percutaneous approach. This is possible because the CS is in close relationship with the posterior aspect of the mitral annulus, and is easily accessible through the venous system and right atrium. The technique was defined as indirect mitral annuloplasty and for the first time, it was possible to correct functional MR by reducing the septal-to-lateral distance without opening

the thorax and on beating heart. The only limitation was the absence of annular calcifications.

A CS approach is technically appealing, and as a result four devices for PIA have reached the clinical phase of investigation in the last 10 years. However, for two of them, the related company ended the trial and suspended device production because of high unexpected death and complication rates. In addition, typical complications of catheter-

based procedures such as access-site trauma and cardiac chamber perforation were reported.

The increasing clinical experience with those new devices has raised some concerns regarding the use of CS to address MR, questioning both the efficacy of the procedure and the durability of the results.¹¹ The main concerns that clinical trials revealed can be summarized as follow (Figure 1):

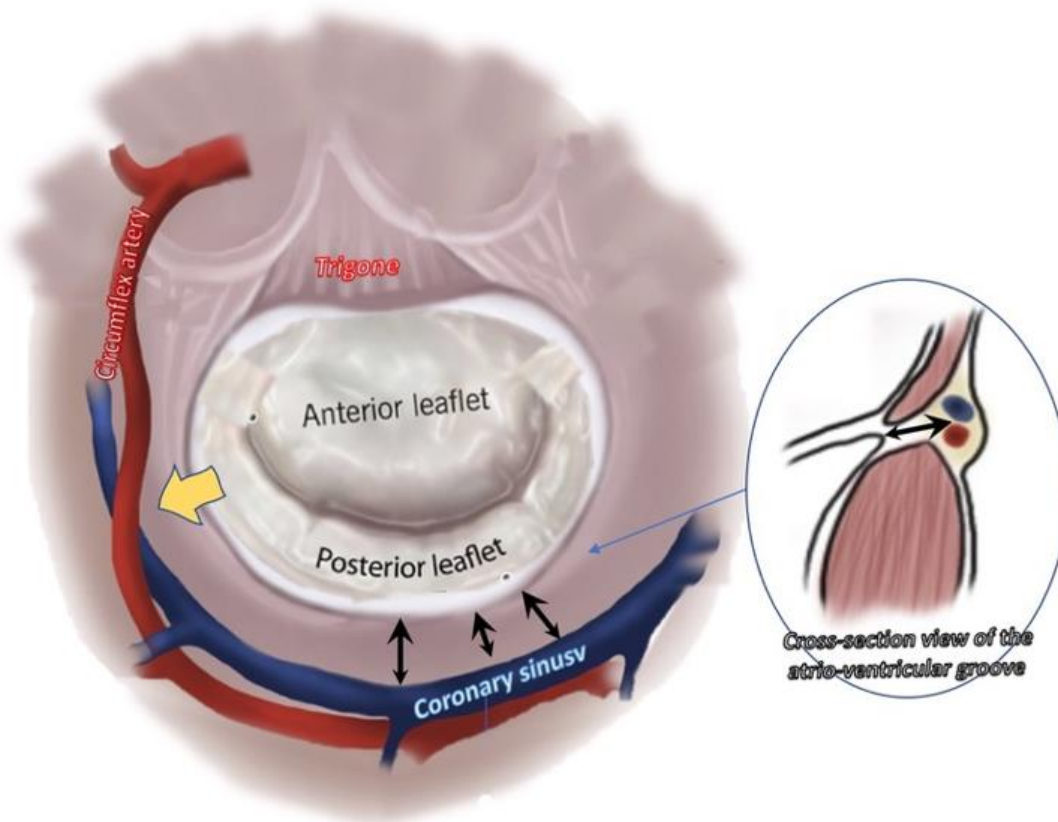


Figure 1. Schematic representation of anatomical key elements implicated in successful percutaneous indirect mitral annuloplasty. Yellow arrows identify the potential impingement of the circumflex artery when traction is applied on the coronary sinus towards the anterior leaflet of the mitral valve. Black arrows indicate the distance between the coronary sinus and the mitral annulus, that has to be <10mm to achieve the displacement of the mitral annulus when force is applied onto the coronary sinus.

4.1 Coronary sinus to mitral annulus distance

This is the main anatomical determinant of device efficacy in reducing MR. The CS is not immediately adjacent to the annulus, but rather courses along the free wall of the left atrium and can be up to 14mm above the annulus. Therefore, in some patients, the force applied onto the CS is not transferred to the mitral annulus.^{11,12} The analysis of cardiac computed tomography (CT) scans of competent and regurgitant mitral valves demonstrated that the distance between the CS and mitral valve annulus increases among patients with functional MR. This is mainly because the regurgitant valve has lost its typical saddle shape in favor of flatter configuration.¹³ Thus, this anatomical configuration potentially compromises the effect of CS reshaping on the mitral annulus, and therefore on MR. The cardiac CT provides information on the position of the CS with respect to the mitral annulus. If the CS is located >10mm from the mitral annulus on the atrial side, then the therapy targeting the CS may not be able to provide reliable remodeling of the mitral annulus.

4.2 Circumflex artery impingement

Choure *et al.*¹³ analyzed CT scan images of more than 100 patients and demonstrated that the circumflex artery (Cx) crosses between the CS and MV annulus in 80% of them. The distance between the CS and circumflex coronary artery at P1 level ranges from 3 to 13mm. This proximity could result in coronary impingement when a device is inserted into the CS, being a source of

myocardial infarction of the lateral wall of the left ventricle. This dreadful complication could cause ischemic MR, when not fatal. Therefore, the preoperative workup of patients candidate to indirect mitral annuloplasty should include a coronary CT scan to predict Cx impingement if a device is to be placed into the CS. The device landing zone into the CS could be identified on the CT scan 3D reconstruction and the distance between the landing zone and Cx was measured: CS to Cx distance of >8.6mm might help preventing Cx occlusion.^{12,13} Coronary compression precluded device placement in 10–15% of patients as reported in the different studies.^{8,10,11}

4.3 Coronary sinus thrombosis

Theoretically, any device positioned into the CS is a potential source of CS thrombosis. However, studies on cardiac resynchronization therapy have reported a CS thrombosis risk so low that patients do not need to be placed on long-term anticoagulation or anti-platelet therapy, unless otherwise indicated.¹⁵ The same approach has been used when designing the clinical studies on percutaneous indirect mitral annuloplasty, and this complication was anecdotal.

4.4 Device migration

Any device permanently deployed into the CS implies the risk of CS displacement/migration with perforation, and potentially fatal outcome. As a venous structure, the CS is thin walled. Dissection and perforation could be due to tortuous anatomy, forceful

catheter/device manipulation, or injection into the wall of the vessel. If we refer to the experience of left ventricular lead placement for cardiac resynchronization therapy, cardiac venous structure injury is not common, with an occurring rate of 0.7%, and pericardial tamponade needing drainage seems rare (0.04%).¹⁵ However, device migration occurred frequently with the MONARC and PTMA devices.

The MONARC device (Edwards Lifesciences, Irvine, California, USA) consisted of two self-expandable nitinol stent-like anchors connected by a bridge. One anchor was deployed distally in the posterior interventricular vein, and the second anchor was deployed proximally in the CS adjacent to the ostium. The bridge connecting the two anchors was fashioned like a spring with biodegradable spacers. Over the first 4 weeks after implantation, dissolution of the biodegradable elements allowed for the bridge to shorten by as much as one-third of its original length, drawing the anchors together and shortening the coronary sinus.

A pilot study was conducted in five patients with significant MR.¹⁶ Although there was a significant reduction in MR, late device failure occurred because of separation of the bridge and anchor. Thus, the benefit induced by this device was not sustained. Subsequently, a second-generation reinforced device was evaluated in the EVOLUTION Phase I trial. Although the initial results were promising, the device had a high rate of bridge fractures and device migration causing unexpected deaths.¹⁶

Similar observations were made with the PTMA device (Viacor Inc., Wilmington, Massachusetts, USA). It consisted of a catheter housing metallic rods pushed from the subclavian vein into the CS. The metallic rods were of various stiffness in order to apply a tailored effect on the posterior portion of the annulus. The proximal hub of the catheter was left in a subclavian pocket and could be re-accessed for further adjustment. A first-in-man study was performed on four patients with at least Grade 2+ MR and no primary leaflet anomaly.¹⁷ However, two patients experienced fatal displacement of the device into the CS. As a result, the company ended the trial and ceased its activity.^{18,19}

Both devices share the same design limitation: the lack of anchoring or retaining systems that should prevent device migration. Anchoring/retaining systems should be considered when designing devices for percutaneous indirect mitral annuloplasty to prevent fatal complications such as CS perforation.

4.5 Durability and cardiac remodeling

Based on the limited number of patients treated and data available from clinical trials, it is difficult to comment accurately on the durability of the indirect annuloplasty. The only two devices for which long-term results are available are the Carillon and the ARTO system.

The Carillon Mitral Contour System® (Cardiac Dimensions, Kirkland, WA) is the device with the largest clinical experience and most robust long term results for indirect mitral

annuloplasty. It is made of a nitinol band with self-expanding anchors on both ends, and is delivered through a 9-Fr sheath in the right internal jugular vein. The device is sized on the basis of both CS diameter and length as defined by procedural venography. The distal anchor is placed as far as possible toward the lateral annulus, and then tension is applied in order to “cinch” the annulus (figure 2) the

degree of tension necessary to correct the functional MR is decided on the basis of procedural echocardiography. Then, the proximal anchor is deployed and coronary angiography is performed to evaluate for Cx compression. If necessary, the Carillon can be retrieved at any point until the final release from the delivery system.²⁰⁻²²

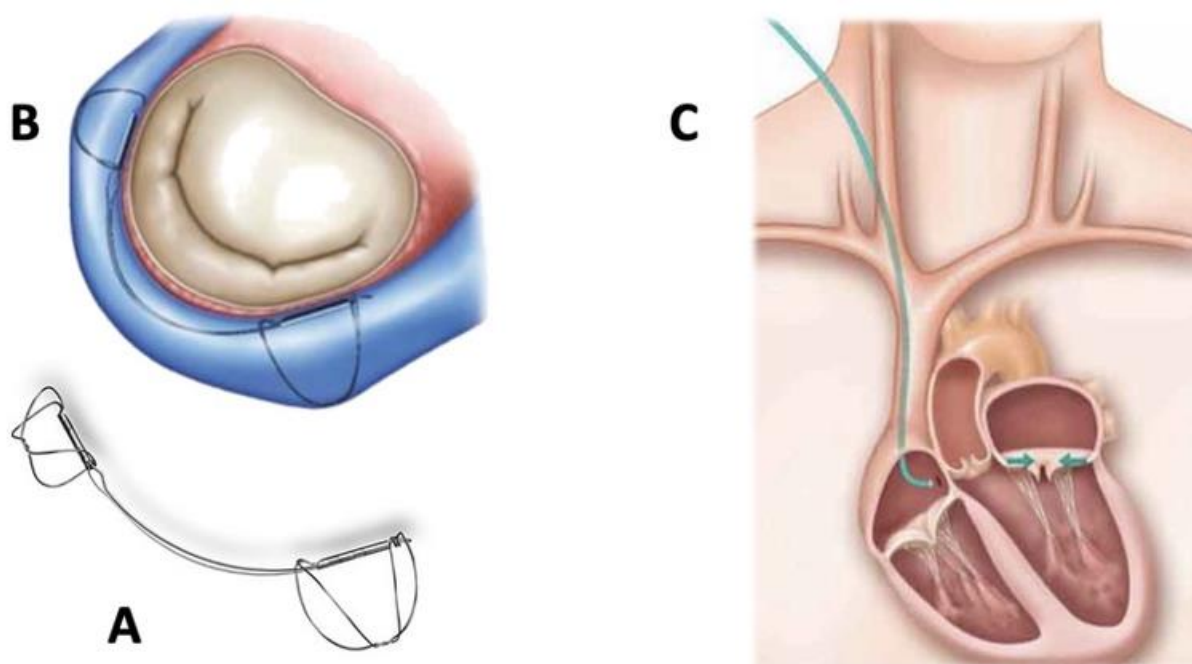


Figure 2. (A) The Carillon device. (B) The device inserted into the coronary sinus improves leaflet coaptation. (C) Single venous access (jugular vein) is required to deploy the device.

The most recent published data regarding the Carillon system has been provided by Witte *et al.* in 2019.²³ In this randomized double-blind REDUCE-FMR trial, 120 patients with an average age of 70 years and mean left ventricular ejection fraction (LVEF) of 34% were randomized in a 3:1 fashion to device vs. optimal heart failure guideline-directed medical therapy alone. Only 12 patients (14%) could not be implanted due to anatomic

issues (eight with left Cx impingement, two with CS dissection, and two with failure of the distal anchor to maintain tension). At 12 months, the primary endpoint of regurgitant volume (Rvol) reduction was significantly better in the treatment group (-7.1mL/beat vs. +3.3mL/beat, $p=0.049$). There was also significant improvement in left ventricle (LV) remodeling as demonstrated by a LV diastolic volume 10.4mL decrease vs. a 6.5mL

decrease ($p=0.03$), and a LV systolic volume decrease of 6.2mL vs. an increase of 6.1mL ($p=0.04$). Secondary functional outcome measures demonstrated statistically significant improvements in New-York Heart Association (NYHA) class and 6-minute walk testing. Importantly, there were no procedural perforations, device fracture, or embolization. Three patients in the device group suffered from a myocardial infarction within 30 days, one of which was due to Cx compression.

Another study, the EMPOWER Trial (The Carillon Mitral Contour System® in Treating Heart Failure With at Least Mild FMR) is currently ongoing, and first data release is expected in 2025.²⁴ This will be largest trial using this device, with the aim of enrolling 400 patients in 50 centers located in the US and Europe. This trial is meant to be a demonstration of “real-world” practice, with the possibility to better understand sequential annular and edge-to-edge repair. In fact, patients who remain symptomatic with severe MR, both in the treatment and control group, could receive advanced treatment including surgery, advanced heart failure mechanical support, or MitraClip at any time.

The PS3 system, also known as the ARTO system, achieves septal-to-lateral distance shortening through direct traction between the interatrial septum at the fossa ovalis and the CS at the level of the mid-P2 scallop by the means of a trans-atrial suture connecting the two holding elements.²⁵ Given that the PS3 system applies traction primarily at the P2 level, this force is only transmitted across a relatively short distance to trigger a mitral

annular shape change (figure 3). In comparison with the Carillon device, this system has the advantage of addressing the antero-posterior axis of the mitral annulus more directly, and could intuitively provide better long-term restriction of the annulus.

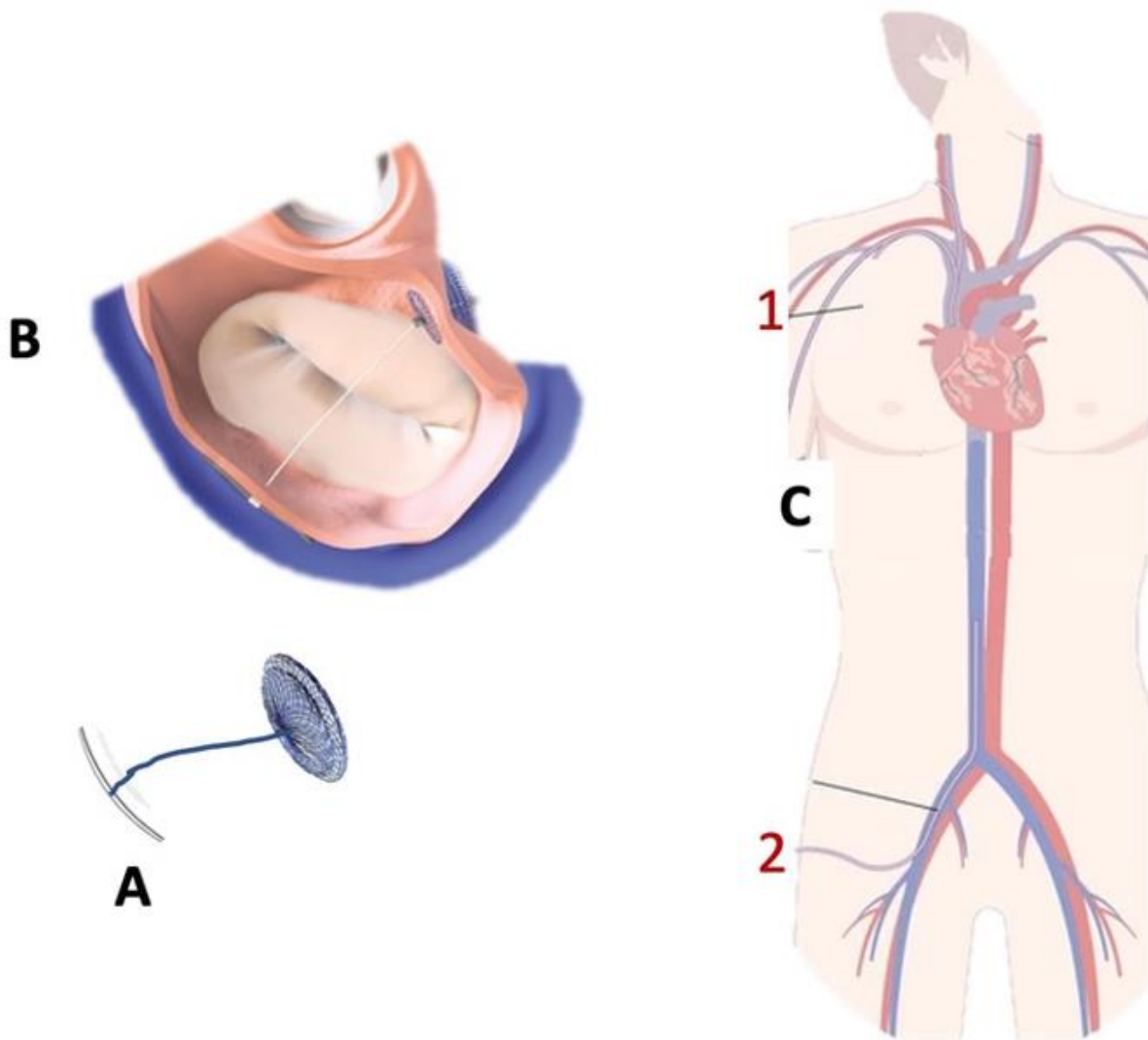


Figure 3. (A) The ARTO system. (B) One element is deployed into the coronary sinus and a second element across the interatrial septum. A connecting wire links both elements. (C) Double venous access (jugular and femoral veins) is required to deploy the device.

This system has been assessed in an international, multicenter, prospective, single-arm study²⁶ on 45 patients with symptomatic Grade 2+ ischemic MR over a 1-year follow-up. The effective regurgitant orifice area decreased from $30.3 \pm 11.1 \text{ mm}^2$ to $13.5 \pm 7.1 \text{ mm}^2$ and regurgitant volumes from $45.4 \pm 15.0 \text{ mL}$ to $19.5 \pm 10.2 \text{ mL}$. Mitral annular anteroposterior distance decreased from

$45.0 \pm 3.3 \text{ mm}$ to $38.7 \pm 3.0 \text{ mm}$. At 30 days, there were two adverse events: one pericardial effusion requiring surgical drainage and one asymptomatic device dislodgement. Significant improvements in NYHA functional class and in the 6-minute walk test were observed at 30 days, which remained stable at 1 year (26). Mortality was 8/45 (18%) after 2 years, with no deaths

attributable to the device or the procedure. Echocardiographic assessment at 2 years demonstrated that MR Grade had been reduced to ≤ 1 in 68% of patients, and that no patients exhibited Grade 4+ MR compared to one third (35%) of the population at baseline.²⁷ These data demonstrate that after 2 years following ARTO implantation, there was a sustained improvement in LV dimensions and reduction in MR.

4.6 Coming soon device

A promising device for indirect mitral annuloplasty is still in the pre-clinical phase of development (MitralTechnologies SA, Liège, Belgium). It has an anchor shape and consists of three elements: the "saddle" that is inserted into the CS; the "plug" that is positioned in aortic-mitral curtain just below the commissure between non-coronary and left coronary leaflets of the aortic valve; the "bridge" that connects the saddle and the plug.²⁸ The length of the bridge can be adjusted in order to reduce the septal-to-lateral mitral annular distance under echocardiographic control. The device is fully positioned through venous access into the right atrium, where catheterization of the coronary sinus is performed and the transseptal puncture is conducted to access the aortic-mitral curtain and deploy the plug element (figure 4). The procedure was successful in an animal model and showed a decrease of the septal-to-lateral distance of 35%. This device reproduces the working principle already seen in the ARTO system, with a significant improvement concerning the durability of the CS deformation.

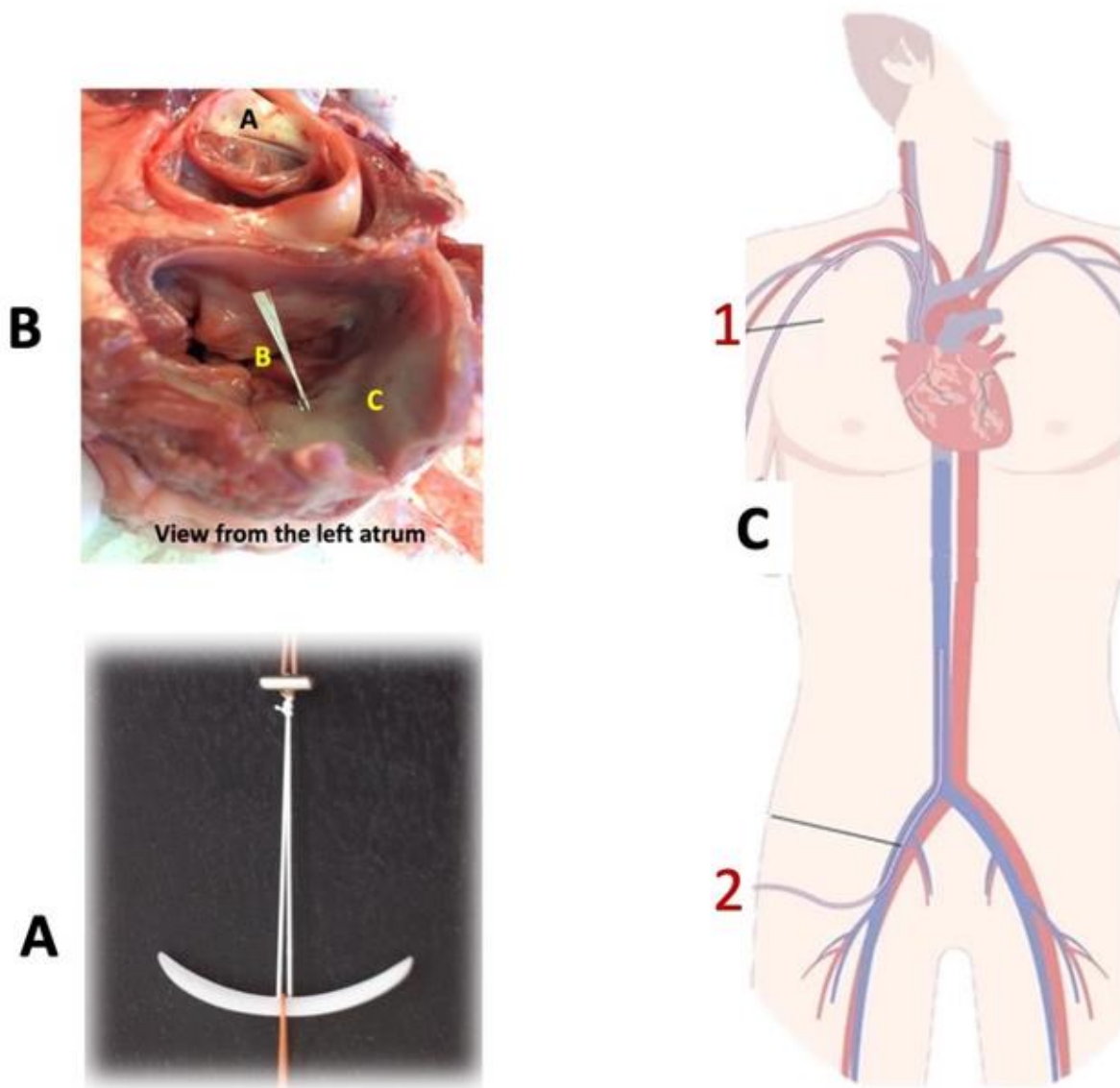


Figure 4. (A) MitralTechnology's device. (B) The device has been implanted into sheep heart and the roof of the left atrium has been removed. The connecting wire (yellow B) is clearly visible. The yellow C indicates the position of the coronary sinus hosting the "saddle" element. (C) Double venous access (jugular and femoral veins) is required to deploy the device.

The traction applied over time on the interatrial septum seen in the ARTO system could induce progressive displacement of the interatrial septum towards the great cardiac vein and eventually override the reduction in septal-to-lateral distance, thus compromising

the durability of mitral annulus reshaping. The aortic-mitral curtain is part of the heart fibrous skeleton and represents a more solid point of attachment than the interatrial septum. This should provide a longer durability of the annulus deformation, but clinical studies have

to endorse this assumption first. The need for anticoagulant treatment with a permanent left atrium implant has not been addressed.

5. Conclusions

PIA represents a compelling option in the treatment of functional MR if patients are screened for CS to mitral annulus distance and coronary impingement, and if the device has

anchoring/retaining systems to avoid its migration and provide consistent and durable results. The availability of a reliable annuloplasty device will certainly increase the overall clinical applicability for transcatheter mitral interventions, making them a true alternative to open-heart surgery in well-selected patients.

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