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Non-invasive imaging in percutaneous mitral valve procedures

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KEYWORDS
Cardiac imaging, mitral valve, percutaneous procedures

Abstract

Novel percutaneous techniques for the treatment of mitral valve (MV) disease have recently been developed and provide an alternative to surgery in patients with high operative risk. However, the complexity of MV anatomy and the variety of mitral regurgitation mechanisms require sophisticated procedures and accurate patient selection. Non-invasive imaging (echocardiography, multislice computed tomography) provides crucial anatomical details and exact characterisation of the mechanism underlying mitral regurgitation, thereby facilitating selection of potential candidates for these procedures. Furthermore, imaging is needed for procedural guidance and assessment of long-term results; for these purposes echocardiographic techniques are mainly used.

In this review, a detailed discussion on the use of non-invasive imaging in selection, procedural guiding and follow-up of patients undergoing percutaneous MV interventions is provided.

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Introduction

Recent surveys indicated that mitral regurgitation (MR) is the second most frequent valvular heart disease (31%) in industrialised countries, caused by degenerative disease in more than 60% of the patients[1,2]. Mitral stenosis accounts for approximately 10% of valvular heart disease, most often related to rheumatic disease[1]. Both mitral regurgitation and stenosis are progressive in nature and associated with relatively high morbidity and mortality[2].

The first-line treatment in patients with symptomatic severe mitral stenosis is percutaneous valve commissurotomy, which has replaced surgery in most of the patients[3]. In patients with symptomatic severe MR, surgical mitral valve (MV) repair is currently considered the treatment of choice[3]. Mitral valve repair and/or restrictive ring annuloplasty with preservation of the subvalvular apparatus has resulted in improved intra-operative and long-term survival as compared to valve replacement. However, degenerative MV disease and particularly MR is associated with older age, substantial comorbidities and left ventricular (LV) dysfunction[4,5], and surgery is not performed in approximately 40-50% of patients, despite recent technical advances[5]. For these patients, percutaneous MV repair has been proposed as an alternative approach. The different percutaneous procedures currently available for MV treatment are summarised in Table 1 (the table is limited to procedures with clinical experience in patients). All procedures aim for a minimal invasive approach with low-risk for periprocedural complications. To select the best approach, accurate evaluation of the MV and subvalvular apparatus (summary of the different components needed to evaluate is provided in Table 2) is needed, particularly for the differentiation between primary and secondary (functional) MR[6]. In primary MR, MV abnormalities are the cause of valve malfunction. In secondary MR, however, the MV is normal, but failure of leaflet coaptation is due to global and/or regional LV dilatation and dysfunction leading to papillary muscle displacement and annular dilatation. Consequently, the therapeutic approaches are substantially different. Accordingly, non-invasive imaging (using echocardiography and multislice computed tomography, MSCT) plays an important role in patient selection by providing crucial anatomical details and the exact characterisation of the mechanism underlying MR. Furthermore, imaging is important for intra-procedural guidance to optimise procedural success and reduce perioperative complications. Fluoroscopy is the technique of choice to monitor these interventions, but this technique does not permit accurate evaluation of transvalvular flows or detailed visualisation of intracardiac structures. Echocardiography is frequently used in combination with fluoroscopy for procedural guidance and hybrid operating rooms become the preferred location for these interventions. Finally, evaluation of long-term results of these procedures is mainly performed using echocardiography.

This review will discuss in detail the role of imaging in patient selection for percutaneous MV interventions; moreover, the value of echocardiography to provide guiding during and follow-up after the procedures is addressed (Table 3).

Table 2. Different structures involved in the pathogenesis of mitral regurgitation (MR).

Structure	Relation to MR
Left ventricle and papillary muscles	Left ventricular remodelling/ papillary muscle displacement
Mitral annulus	Mitral annulus dilatation Mitral annulus calcifications
Mitral leaflets	Mitral leaflet prolapse Mitral leaflet damage
Mitral chords	Chordal rupture
Left atrium	Left atrial dilatation

MR: mitral regurgitation

Percutaneous MV commissurotomy

Percutaneous mitral commissurotomy was introduced in 1984 by Inoue et al[7] and is the treatment of choice in patients with severe mitral stenosis[3]. According to this technique, after advancing a catheter across the inter-atrial septum (transseptal puncture), one large balloon (Inoue balloon) or two smaller balloons are inflated

Table 1. Summary of the main percutaneous procedures for mitral valve (MV) treatment with clinical experience in patients. Devices with only preclinical or preliminary data are not included.

Percutaneous MV procedure	Indication	Device	Approach	Company
Valve commissurotomy	Severe symptomatic mitral stenosis	Inoue balloon or double balloon	Balloon commissurotomy	Toray Industries
Paravalvular leak closure	Significant para-prosthesis dehiscence	– Patent ductus ateriousus occluder – Atrial septal defect occluder	Occluder devices	– Amplatzer; AGA Medical Corporation – Amplatzer; AGA Medical Corporation
Leaflet repair	Severe MR originating from the central 2/3 of the coaptation line, in the absence of severe annular dilatation	MitraClip	Edge-to-edge clip	Abbott Vascular
Coronary sinus annuloplasty	Severe functional MR	– MONARC – CARILLON	– Delayed foreshortening of the device – Adjustable device length	– Edwards Lifesciences – Cardiac Dimensions

MR: mitral regurgitation

Table 3. Role of non-invasive imaging before, during and after the different percutaneous MV interventions.

Imaging modality	Before the procedure	Intra-procedure	Follow-up
Valve commissurotomy	Mitral stenosis severity (TTE). MV morphology/Wilkins calcium score (TTE).	Guiding catheter and balloon position (fluoroscopy, TEE, ICE). Evaluation of commissural opening (TEE). Evaluation of complications (TEE).	Potential restenosis (TTE).
Paravalvular leak closure	Regurgitation severity (TEE). Location, size and shape of the defects (TEE).	Guiding transseptal puncture and crossing the defect (fluoroscopy, TEE). Evaluation of procedure results (TEE).	Long-term procedure success (TTE).
Leaflet repair	MR severity (TTE, TEE, MRI). MV and subvalvular apparatus anatomy (TTE, TEE, MSCT).	Guiding transseptal puncture (fluoroscopy, TEE, ICE). Guidance for device steering and clip positioning (fluoroscopy, TEE). Evaluation of procedure results (TEE).	Long-term procedure success and device stability (TTE).
Coronary sinus annuloplasty	MR severity and mechanism (TTE, TEE, MRI, MSCT). Coronary sinus location in relation to MV annulus and circumflex coronary artery (MSCT). Mitral annulus calcifications (MSCT, TTE, TEE).	Evaluation of coronary sinus and circumflex coronary artery (fluoroscopy). Positioning and deployment of the device (fluoroscopy). Evaluation of procedure results (TEE).	Long-term procedure success and device stability (TTE).

ICE: intracardiac echocardiography; MR: mitral regurgitation; MRI: magnetic resonance imaging; MSCT: multi-slice computed tomography; MV: mitral valve; TEE: transesophageal echocardiography; TTE: transthoracic echocardiography

within the MV orifice, resulting in mechanical dilatation of the fused valve commissures. This approach provides similar results to surgical commissurotomy when performed in selected patients with favourable MV anatomy[7]. Therefore, patient screening relies on precise evaluation of the morphology and function of the different components of MV apparatus, which is mainly performed using transthoracic echocardiography (TTE) and semi-quantitative scores[8]. The Wilkins score is often used, and based on valve thickening, mobility, calcification and subvalvular involvement; MV morphology is considered suitable for commissurotomy in patients with a score ≤8. Particularly, commissural calcifications predict failure of commissurotomy and are associated with poor survival. Echocardiography is also fundamental for assessment of the MV area (using the pressure half-time method or by direct planimetry), pulmonary artery pressures, tricuspid regurgitation, LV and left atrium size and function. A transesophageal approach is not necessary except in patients with atrial fibrillation or history of systemic embolism to obtain better visualisation of the left atrium. Recently, real-time three-dimensional (3D) echocardiography was suggested as a more accurate approach as compared to conventional 2D echocardiography, for measurements of the MV area and assessment of the Wilkins score and MV morphology[9]. This technique provides unique orientations of the stenotic valve that permit not only a better evaluation of the funnel-shape structure of the valve and of the subvalvular apparatus, but also to obtain the optimal cut-plane for the measurement of the smallest MV orifice (Figure 1).

In addition, both 2D and 3D transesophageal echocardiography (TEE) are extremely useful during the procedure, guiding the transseptal puncture and the position of the balloon, assessing the degree of commissural opening after balloon inflation and monitoring potential complications (tamponade, MR requiring surgery). A potential alternative imaging modality is intracardiac echocardiography (ICE), which showed to be able to provide site-selective transseptal puncture and to guide the other steps of the procedure[10].

The success of the procedure during follow-up should also be monitored using echocardiography, taking into account a restenosis rate of 15% at five years and 30% at 10 years[11].

Percutaneous paravalvular leak closure

Paravalvular dehiscence is a complication that occurs in 2-15% of patients with prosthetic mitral valve replacement, particularly in mechanical prostheses[12]. When it results in a significant regurgitation or causes a persistent haemolysis, this condition is associated with worse outcome if not appropriately treated[12]. Although in these cases a prosthesis re-replacement or repair is recommended, surgical procedures are limited by an operative mortality of 6-15%[13].

Percutaneous closure of severe paravalvular leaks has been proposed as an alternative in patients considered poor surgical candidates. Although there are currently no devices specifically designed for this procedure, other occluders have been used off-label based on the size of the dehiscence: vascular coils for very small defects, patent ductus devices for medium defects, and atrial septal occluders for larger defects[14]. For multiple dehiscences, very large defects (diameter >8 mm) or lateral (internal) leaks, however, the procedure had a low success rate. To improve patient selection, it is important to have accurate pre-operative information on the severity of the regurgitation and the location, size and number of the defects. TEE provides accurate evaluation of the dehiscence (Figure 2), and is also important for guidance during the operation. Recent evidence supports the use of 3D TEE to improve the evaluation and localisation of the defects[15] (Figure 2). This technique permits more precise visualisation of the paravalvular leakage by providing an “en face” view of the prosthesis from the left atrium and any other potential views within the 3D dataset.

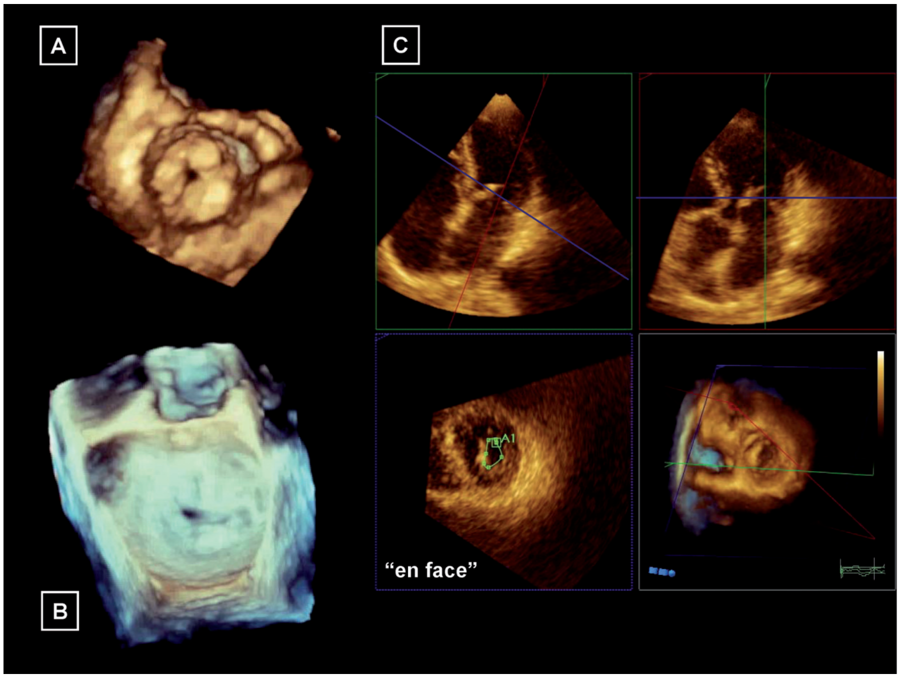

Figure 1. Example of a 3D view of a severe mitral stenosis from the left ventricle (Panel A) and from the left atrium (Panel B), for an accurate evaluation of the alterations of the mitral valve (MV) apparatus. In Panel C, an example of MV area calculation from a 3D dataset by a direct planimetry in the "en face" view: the blue line identifies the correct cut-plane ("en face") in which the smallest valve orifice can be measured.

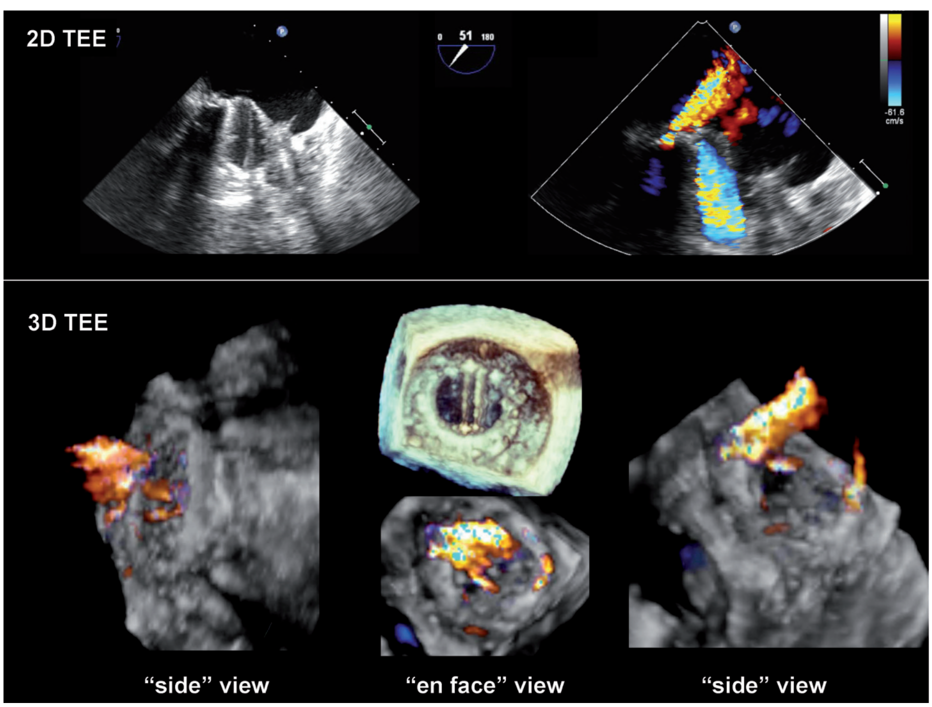

Figure 2. Echocardiographic assessment of mitral para-prosthetic leakages. Conventional 2D transesophageal echocardiography (TEE), with the use of colour Doppler, is able to identify and localise the dehiscence. However, 3D TEE, providing an "en face" view of the prosthesis from the left atrium and any other potential points-of-view, permits an intuitive and more precise picture of the paravalvular leakage.

Percutaneous leaflet repair (edge-to-edge)

The edge-to-edge MV repair using the MitraClip® device (Abbott Vascular, Structural Heart, Menlo Park, CA, USA) is the percutaneous leaflet repair procedure with the most extensive clinical data. This approach replicates the suture-based surgical technique introduced by Alfieri[16] and improves MV coaptation by opposing the centre of the two mitral leaflets with a mechanical clip, which creates a double-orifice MV opening in a "bow-tie" configuration (Figure 3). The EVEREST I trial[17] demonstrated the feasibility and safety of this procedure, with a success rate of 75%.

Furthermore, event-free (death, MV surgery and MR >2+) survival was 66% at one year. The EVEREST II trial compared the percutaneous approach with conventional surgical repair or replacement in a 2:1 randomisation. The results of this trial have recently been presented[18] and revealed that the percutaneous approach met the hypothesis of superiority for safety (9.6% of major adverse events as compared to 57% in the control group, $p<0.0001$) and of non-inferiority for effectiveness (freedom from death and MV surgery or from re-operation for MV dysfunction and MR>2+ at one year was 72% versus 88% in the controls, $p=0.001$). However, patients eligible for this procedure should meet specific requirements. Particularly, only patients with severe MR and a regurgitant jet originating from the central two-thirds of the coaptation line should be selected. In patients with functional MR, leaflet coaptation length must be at least 2 mm and the depth 11 mm or less. In the presence of flail, the flail gap must be <10 mm and the flail width <15 mm (Figure 4). These rigorous criteria exclude patients with severe annular dilatation from this procedure and patients with degenerative aetiology of MR are the most suitable candidates. It is therefore crucial to obtain an accurate assessment of MR severity and MV anatomy before the procedure and TEE plays a pivotal role in this evaluation. Specifically, the 3D approach appears superior over the conventional 2D approach, providing a detailed visualisation of the scallops involved, including the commissures and the chordal anatomy[19] (Figure 5, Movie 1). In addition, dedicated software is now available to obtain quantitative 3D measures of the MV annular dimensions, leaflet coaptation length and depth, and leaflet surface, all of which are important parameters for the procedural planning (Figure 6). The application of colour Doppler with 3D echocardiography has also become available, allowing for direct planimetry of the effective regurgitant orifice area (EROA) in the "en face" view of the MV (Figure 7, Movie 2). In recent studies, this approach appeared more accurate than the conventional 2D proximal isovelocity surface area and vena contracta width methods for evaluation of MR severity[20].

Velocity-encoded magnetic resonance imaging (MRI) has also recently been proposed for transvalvular flow quantification[21]; in particular, the 3D 3-directional acquisition method provided an accurate assessment of MR severity[22] (Figure 8), and was superior over the conventional 2D one-directional approach.

Imaging is also for guidance of these sophisticated procedures, and intensive collaboration between the echocardiographer and the interventionalist is required. In fact, the delivery and the placement of the MitraClip are performed primarily under TEE guidance. In the EVEREST I trial, the investigators developed a streamlined imaging approach based on standardised TEE views, that demonstrated to optimise communication between operators and procedural efficiency[23]. First, TEE is used to guide the transseptal puncture, which should be performed according to a specific trajectory for a perpendicular alignment of the device to the MV plane. For this purpose, ICE can also be of additional value[10]. Furthermore, TEE helps steering the device with minimal endocardial contact, and positioning the clip perpendicular to the coaptation line and at the centre of the maximum MR jet. Fluoroscopy is primarily used for

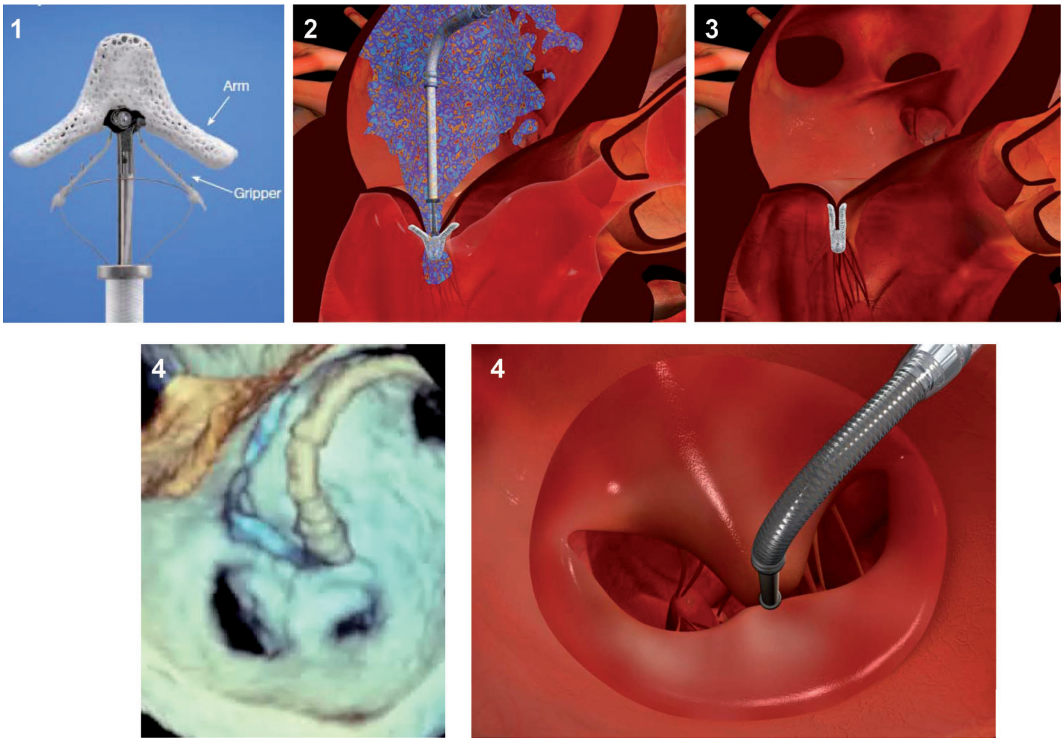

Figure 3. The MitraClip® device (Abbott Vascular) is a polyester-covered clip (1) which is positioned perpendicular to the mitral valve coaptation line and centred over the origin of the regurgitant jet (2); when the mitral leaflets are grasped, the clip is closed (3) producing a mitral double-orifice opening in a "bow-tie" configuration (4), demonstrated also with 3D transesophageal echocardiography (with a view from the left atrium). Courtesy Abbott Vascular (Structural Heart Menlo Park, CA, USA)

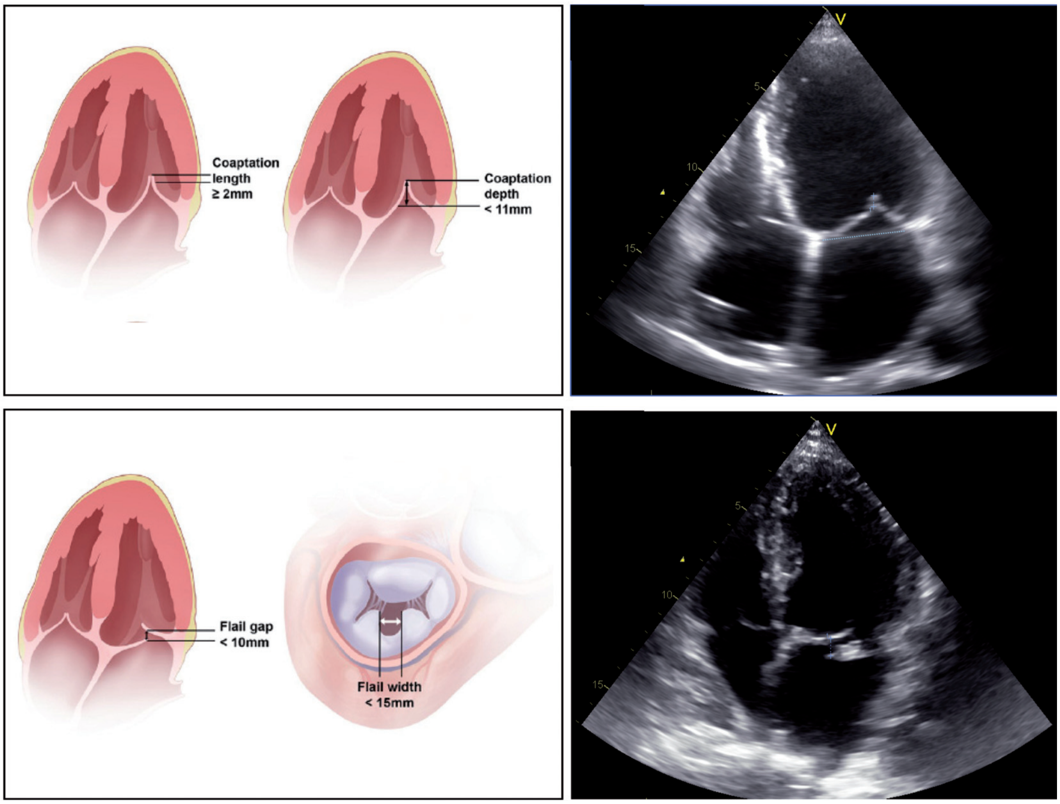

Figure 4. Key anatomic eligibility criteria for the mitral edge-to-edge procedure (drawing adapted with the courtesy of Abbott Vascular, Structural Heart Menlo Park, CA, USA).

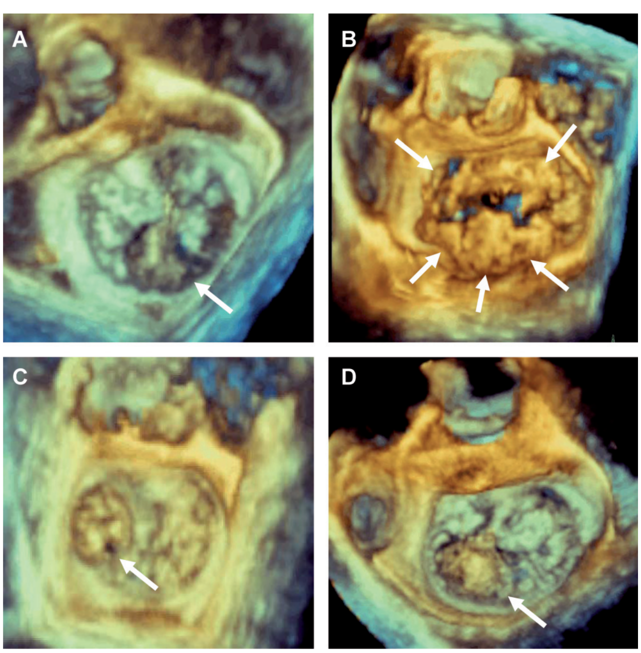

Figure 5. Real-time 3D transesophageal echocardiography allows for an accurate assessment of mitral valve prolapse, providing a detailed visualisation of the scallops involved (white arrows) and optimising the selection of the patients suitable for an edge-to-edge repair or other percutaneous procedures. Panel A: patient with a flail of P2 with a chordal rupture; Panel B: Barlow's disease with a diffuse involvement of both leaflets; Panel C: patient with a prolapse of P1 involving the antero-lateral commissure; Panel D: prolapse of P1 and P2.

assessing the opening angle of the clip arms and plays a lesser role in the steering and positioning of the clip.
The procedural success is evaluated using TEE, and defined as a significant reduction of MR grade (final result <grade 2) with a double-orifice MV opening. Finally during longer follow-up, TTE can evaluate MR severity, device stability and the potential effect on LV size and function.

Coronary sinus annuloplasty

Another percutaneous approach, specifically for the treatment of secondary MR, is based on the possibility of reducing the mitral annular circumference, mainly along the antero-posterior diameter, mimicking surgical annuloplasty. For this purpose, various devices have been developed (Table 1) and rely on the anatomical relationship between the posterior mitral annulus and the coronary sinus. For example, the MONARC™ device (Edwards Lifesciences, Inc., Irvine, CA, USA) consists of a distal self-expanding anchor, which is deployed in the great cardiac vein, and a spring-like bridge with biodegradable elements that connects the distal anchor to a proximal anchor deployed at the level of the coronary sinus ostium (Figure 9). A few weeks after implantation, the spring shortens and constraints the coronary sinus, thereby reducing the mitral annulus circumference. Similarly, the CARILLON device (Cardiac Dimensions, Kirkland, WA, USA) is a steel wire connected to a distal and proximal stent which are also positioned in the coronary sinus; the length of the connector can be adjusted during implantation until an appropriate MR reduction has been achieved.

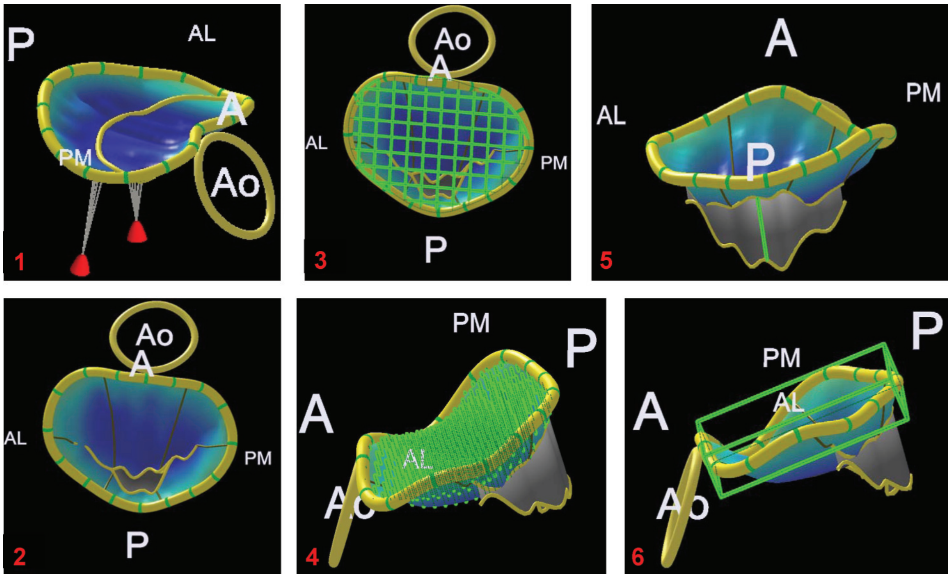

Figure 6. 3D model of mitral valve (MV) anatomy obtained using MV-Quantification software (Philips Medical System, Bothell, WA, USA) from transesophageal 3D images. In the first panel an example of normal MV anatomy. In the second panel an example of a functional ischaemic mitral regurgitation with a restrictive movement of mitral leaflets. From these models, several 3D measurements can be derived (in light green), such as MV annulus and leaflet surface (Panel 3), tenting volume (Panel 4), coaptation length (Panel 5) and annular height (Panel 6). A: anterior leaflet; AL: antero-lateral commissure; Ao: aortic valve; P: posterior leaflet; PM: postero-medial commissure

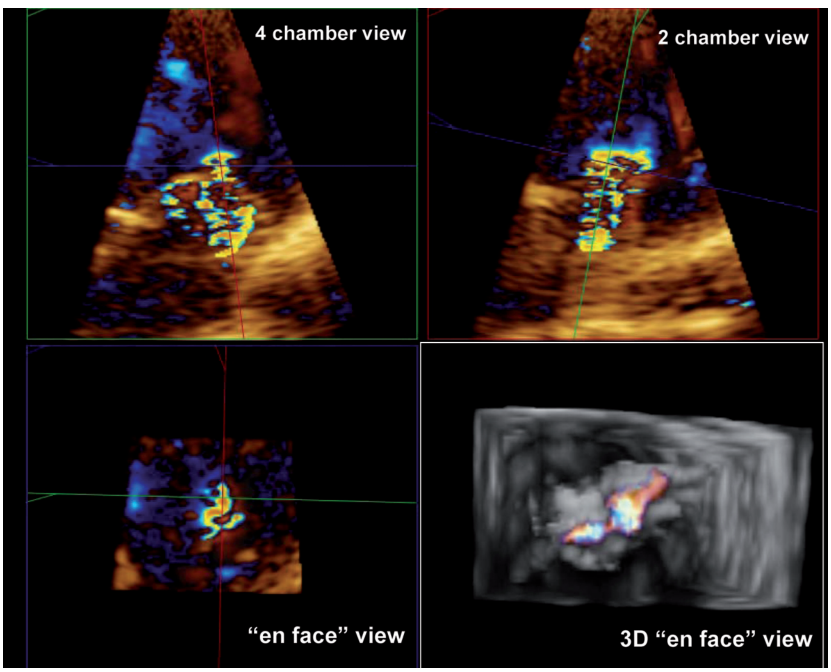

Figure 7. Direct assessment of the mitral valve effective regurgitant orifice area (EROA). The 3D dataset is manually cropped by an image plane (blue plane) perpendicular to the jet direction until the narrowest cross-sectional area of the jet. EROA is measured by manual planimetry of the colour Doppler signal, tilting the image in an "en face" view.

The safety and feasibility of the MONARC™ device was evaluated in the EVOLUTION I trial, that enrolled 55 patients with moderate-severe functional MR and LV ejection fraction ≥25%. Presented but unpublished interim results showed a procedural success of 76% and a reduction of at least 1 grade of MR at six months follow-up in 92% of patients[24]. The CARILLON device was also tested in the AMADEUS trial, which enrolled patients with moderate to severe MR and LV ejection fraction <40%[25]. Of the 48 patients enrolled, only 30 received the device with a major adverse event rate of 13% at 30 days; at six months follow-up, a significant reduction in MR was achieved, associated with significant improvements in 6-minute walk distance and quality of life score.

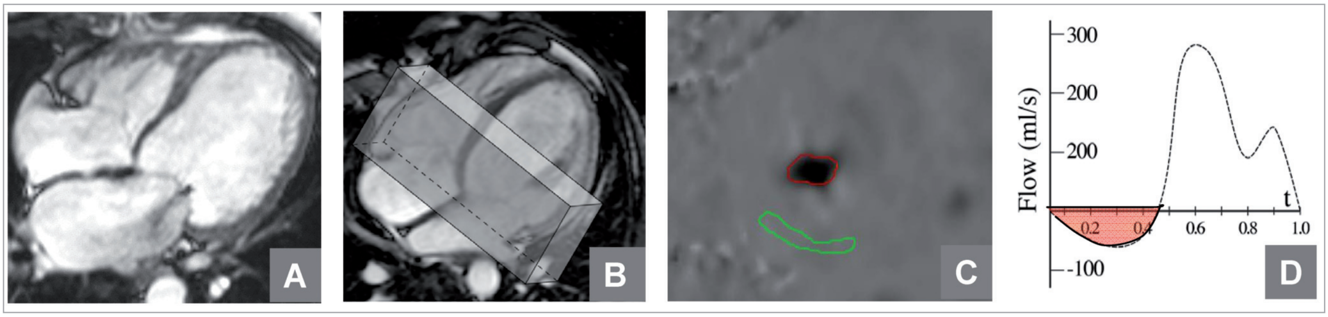

Figure 8. Velocity-encoded magnetic resonance imaging has been recently proposed as a reference method for mitral regurgitation severity assessment (Panel A). For the quantification of transvalvular flow, the acquisition is performed in a volume positioned at the basal level of the heart (Panel B), covering the full excursion of the MV during contraction and relaxation, and the 3 velocity vector components of blood flow (Panel C) are reformatted for the calculation of the regurgitant volume (Panel D, red area under the curve).

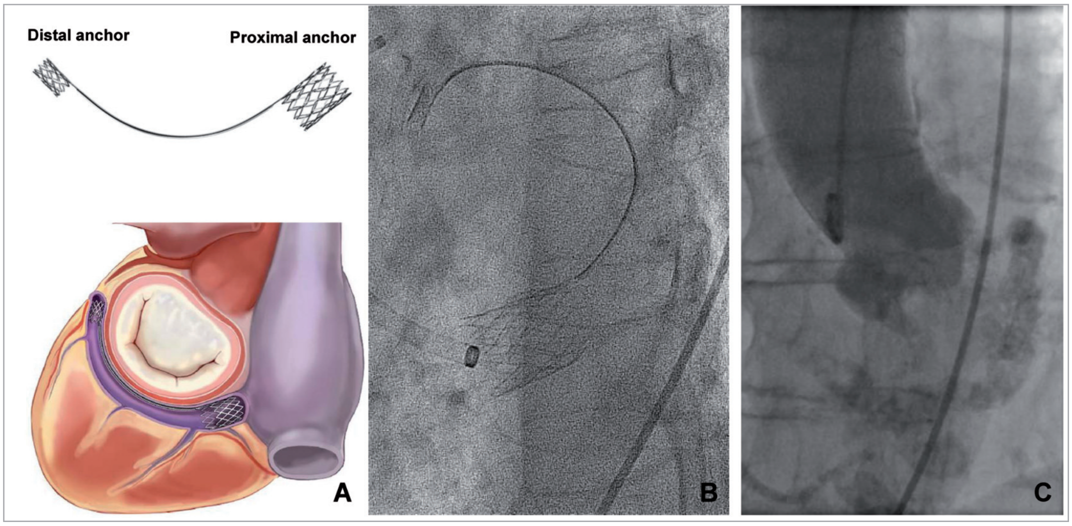

Figure 9. The MONARC™ device (Edwards Lifesciences, Inc., Irvine, CA, USA) consists of a distal self-expanding anchor, which is deployed in the great cardiac vein, and a spring-like bridge with biodegradable elements that connects the distal anchor to a proximal anchor deployed at the level of the coronary sinus ostium (Panel A). Fluoroscopy (Panel B) is the main guidance for the positioning and the deployment of the anchors; furthermore, it can visualise significant mitral annulus calcifications (Panel C) which may limit the effectiveness of the procedure. (Drawings courtesy of Edwards Lifesciences, Inc., Irvine, CA, USA).

Regarding the feasibility of coronary sinus annuloplasty, several issues need to be considered. First, the procedure is particularly suited for patients with functional MR and accurate assessment of the mechanism causing regurgitation should be performed using echocardiography. Alternatively, multislice computed tomography (MSCT) also provides detailed anatomic and geometric information on the MV apparatus, which may increase insight into the mechanism underlying MR[26].

Furthermore, the exact location of the coronary sinus relative to the MV annulus and the circumflex coronary artery should be carefully assessed in order to evaluate the feasibility of the procedure and to avoid myocardial ischaemia due to coronary artery compression. Transesophageal echocardiography does not allow for the assessment of the entire length of the coronary sinus and its relationship with the mitral annulus and the coronary arteries. Recently, MSCT has been proposed as an alternative method for 3D reconstruction of these structures and analysis of their spatial relationship (Figure 10). Tops et al[27] used 64-slice MSCT to study 105 patients, including 34 patients with heart failure and different degrees of functional MR. In 90% of these patients the coronary sinus was located above the mitral annulus and the distance between these two structures was increased (approximately 9 mm) in the presence of severe MR, thereby potentially compromising the efficacy of percutaneous annuloplasty. Furthermore, in 68% of patients the circumflex coronary artery was located between the coronary sinus and the mitral annulus with a potential risk of compression during percutaneous annuloplasty. Another issue limiting the potential success of this procedure is the presence of severe calcifications of the mitral annulus that can be visualised by MSCT, echocardiography or fluoroscopy (Figure 9).

Fluoroscopy and echocardiography are also crucial during the procedure. Fluoroscopy is used for arterio- and venography to assess the anatomical details of the coronary sinus and the circumflex coronary artery; moreover, fluoroscopy is also used to guide the positioning and the deployment of the anchors. Echocardiography provides information on acute and long-term reduction of mitral annular dimensions and its potential beneficial effect on MR severity.

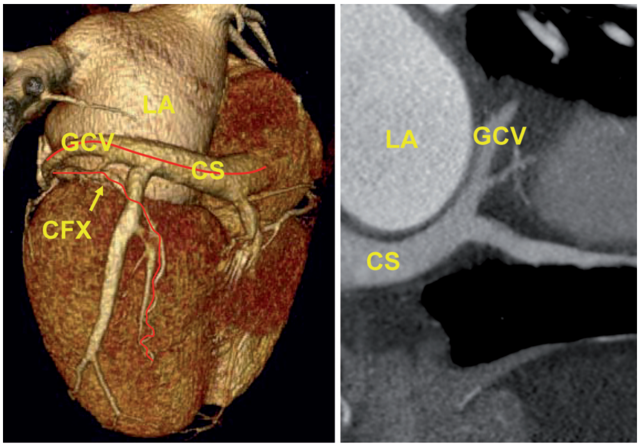

Figure 10. Example of multislice computed tomography volume-rendered reconstruction (left panel, dorsal view) and multiplanar reformatted image (right panel) of the heart in order to visualise (highlighted in red) the coronary sinus (CS) and the great cardiac vein (GCV) and to study their relationship with the circumflex coronary artery (CFX, highlighted in red) and the left atrium (LA).

Direct remodelling and other percutaneous MV procedures

Several other percutaneous procedures are in development and use different approaches, such as direct mitral annuloplasty or direct LV or left atrium remodelling. The Quantam Cor (Quantam Cor, Inc., San Clemente, CA, USA), for example, proposes to shrink the posterior annulus of the mitral valve by a percutaneous application of radiofrequency energy directly on the annular tissue. The iCoapsys (Myocor, Maple Grove, MN, USA), places two pads on the anterior and inferior walls of the LV with a cord passing through the cavity (using a transpericardial subxyphoid approach), which applies tension to the mitral annulus via a change in LV chamber configuration. The PS3 system (Percutaneous Septal Shortening System, Ample Medical Inc., Foster City, CA, USA) is designed to reduce the mitral annulus size by connecting the fossa ovalis located superior to the annulus, with the great cardiac vein on the opposite side of the atrium. Although only preclinical or preliminary data are available on the use of these devices, non-invasive imaging may be of great importance for these procedures, both for patient selection and intra-procedural guidance. A detailed assessment of the mitral annulus and LV geometry is crucial in these interventions and can be provided by 2D echocardiography, although 3D imaging techniques (3D echocardiography, MRI and MSCT) may be preferred.

Conclusions

Recent studies have reported promising results of percutaneous procedures for the treatment of MV disease. However, the complexity of the MV anatomy and the variety of mechanisms causing MR, require sophisticated devices and accurate patient selection. Non-invasive imaging plays a pivotal role in patient selection, guidance of the procedures and long-term follow-up. Particularly in the patient selection, sophisticated 3D imaging techniques (3D echocardiography, MSCT and MRI) are preferred. Guidance of the procedures and long-term follow-up is mainly performed with echocardiography.

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Online data supplement

Movie 1. Barlow's disease with a diffuse involvement of both mitral valve leaflets, in a 3D view from the left atrium (surgical view). See also Figure 5.

Movie 2. Example of a colour Doppler 3D dataset for a direct assessment of the mitral valve effective regurgitant orifice area (EROA). See also Figure 7.