Percutaneous Mitral Valve Intervention and modelling with multi-modality imaging

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Introduction

Functional mitral regurgitation (MR) is a common finding occurring in 20% of the general population and nearly 40% of heart failure patients exhibiting at least moderate regurgitation. Severity of MR predicts mortality and increased morbidity in ischaemic and non-ischaemic aetiologies, regardless of revascularisation techniques as well as in asymptomatic patients. Mitral valve repair, by surgical or interventional techniques, aims to restore valve competence and electromechanical synchrony to improve symptoms and survival.

Overview of mitral valve anatomy

The mitral valve apparatus consists of the MV annulus, leaflets, chordae tendinae, and papillary muscles. The aorto-mitral fibrous continuity provides an anatomical support to the anterior mitral leaflet. The normal mitral valve annulus (Figure 1) is classically described as a ‘saddle-shaped’ elliptical structure where the antero-posterior dimension is less than the commissural diameter thereby minimising leaflet strain. These normal relations are disturbed by progressive annular dilatation and papillary muscle dysfunction regardless of aetiology, resulting in progressive mitral regurgitation, a more spherical shape, changes in non-planar angle and leaflet tenting. The coronary sinus (CS) originates posteriorly from the right atrium, where it is guarded by the thebesian valve. The vein

Figure 1: Normal mitral valve and apparatus adapted from 6,8
of Marshall and the incomplete Vieussens valve mark the external and internal junctions, respectively, where the coronary sinus continues in the left atrioventricular groove as the great cardiac vein. The great cardiac vein continues as the anterior interventricular vein distally, where it runs parallel to the left anterior descending artery. The coronary sinus is predominantly adjacent to the mitral ring annulus. The CS varies in size; its length ranges from 45 to 63 mm10 and its diameter is 7 ± 1.9 mm11. Thus the proximity of the CS to the mitral ring makes it an attractive conduit for both pacing and indirect annuloplasty.

Anatomical and in-vivo imaging studies have documented the anatomical relations of the left circumflex (LCx) and its marginal branch arteries to the great cardiac vein/coronary sinus. Specifically, in normals the incidence of the LCx passing under the CS ranged from 64 to 96%12,13,15–17, increasing according to coronary artery dominance (Right dominant 74%, Left dominant 83%, co-dominant 97%)14. Maselliet al. also reported the incidence of diagonal or ramus branches of the LAD crossing under the CS in 16%. In patients with severe MR of ischaemic aetiology, the LCx crossed under the CS/GCV in 96%14. These findings have important implications for potential coronary artery compression due to percutaneous mitral annuloplasty procedures.

**Surgical or Interventional Repair?**

Medical and cardiac resynchronisation therapy reduce morbidity and mortality via after- and preload modification and reverse remodelling,18,19 but surgical and interventional techniques aim to address regurgitation via structural means. In patients with moderate ischaemic MR, MV repair with CABG conferred a survival benefit over medical therapy or revascularisation by percutaneous coronary intervention (PCI) alone. Even in those with severe functional MR, there has been documented clinical benefit in addressing MR with mitral valve repair in addition to revascularisation20. However, a substantial proportion of patients – 49% -- with moderate to severe MR are rejected for surgical consideration21.

**Surgical Approach**

Surgical repair commonly based on the ‘Alfieri stitch’ -- so-called edge-to-edge or double-orifice technique -- aims to reduce central jetregurgitant orifice area with resultant decrease in MR. This open surgical technique has evolved since its inception in 1991 when it was performed without ring annuloplasty,22 but undersize ring annuloplasty is now the accepted surgical norm23.

**Interventional approach**

Various interventional techniques have been proposed to address the problem of significant MR in patients at high surgical risk. These catheter-based approaches aim to manipulate components of the mitral valve apparatus to approximate leaflet coaptation or induce mitral annular, and subsequently, LV reverse remodelling.

Current percutaneous techniques can be sub-divided according to the target mitral valve component: leaflet, indirect (coronary sinus) annuloplasty, direct annular, and LA- and LV-tethering-based approaches, as detailed in the Table. We will focus on leaflet and CS techniques as the latter three approaches remain in nascent first-in-man or animal-model development stages.

**Indirect annuloplasty**

The Monarc (Edwards Lifesciences, previously Viking) nitinol CS implant consists of proximal and distal anchors and a spring-like bridge to displace the posterior annulus towards the anterior leaflet in order to improve coaptation. Early trials with the Edwards / Viking device achieved reduction in MR, but were complicated by device fracture and recurrence and subsequent halting of the feasibility study24. A subsequent phase I trial of the redesigned Monarc device involving 72 patients reported 82% implantation success and 18% implantation failure rate due to CS tortuosity or narrow lumen. Cardiac CT documented cardiac vein crossing over the obtuse marginal in 55% of patients; there was angiographic coronary artery compression in 15 of 72 patients (21%) resulting in 3 acute myocardial infarctions due to compression. Event-free survival was reported as 91%, 81%, 72% and 64% at 30 days, 1-, 2-, and 3 years’ follow-up, respectively (Evolution I).25

The frequent incidence of coronary artery anatomy crossing under the GCV/CS has led to the development of alternative approaches to indirect mitral annuloplasty. The NIHLU (USA) Cerclage system26 has been trialled in an animal ovine model with successful protection of coronary arteries from entrapment. MRI and cine angiogram guide interactive catheter placement and tension adjustment of the cerclage and coronary artery protection bridge.

**Direct Leaflet Techniques**

**Mobius**

The percutaneous Mobius device (Edwards Life Sciences) employed a suture to achieve leaflet plication. Device development has since been abandoned due to suture dehiscence and technical problems27 in human trials despite initial promise in animal studies.
Mitraclip
The Mitraclip system (Abbott Vascular, USA) delivers via trans-septal puncture a rigid clip that directly plicates anterior and posterior mitral leaflets. In the EVEREST trial\(^2\), procedural success defined as device implantation and MR < grade 2 was achieved in 74% of 107 patients with < 1% hospital mortality. There were no clip embolization events although partial clip detachment occurred in 10%. The composite primary endpoint of freedom from death, MV surgery or MR > grade 2+ was achieved in 66% at one year. Survival at one and three years was 95% and 90%, respectively; freedom from surgery was 88% and 76%, respectively (p=NS). In 32 patients who subsequently required MV surgery, repair was possible in 84%, demonstrating that the surgical option remained preserved following percutaneous repair.

The EVEREST II trial\(^2\) randomised 279 patients to percutaneous Mitraclip repair or conventional MV repair surgery in a 2:1 ratio. The primary composite end point for efficacy (freedom from death, surgery for MV dysfunction, freedom from MR grade 3+ or 4+) at 12 months was achieved in 55% and 73% in the percutaneous and surgery groups, respectively (p=0.007). Death occurred in 6% in each group; MR grade > 3+ in 20% and 21%, and mitral valve surgery in 20% and 2%, respectively. Major adverse events at 30 days occurred in 15% vs 48% of patients in the percutaneous and surgery groups, respectively (p<0.001). The safety end point incorporating major adverse event criteria and blood transfusion > 2 units occurred in 9.6% vs 57%, in the percutaneous and surgical groups, respectively (p<0.005). Although percutaneous repair was less effective than surgery for reducing MR, the safety advantage of percutaneous repair was maintained even after exclusion of blood transfusion incidence. At 12 months, both groups reported similar LV dimensions, NYHA class and QoL scores.

The High Risk Surgery arm of the EVEREST II trial\(^2\) showed that the 78 patients in a high-risk surgery group (Euroscore> 12%) who received Mitraclip intervention had increased survival, 76% vs. 55% (p=0.047), at 1-year compared to the comparator group who received standard care. LVEDV fell from 172 to 140ml, and LVEF fell from 82 to 73ml (p<0.001), and NYHA functional class and QoL improved at 12 months. Meta-analysis data demonstrated that MitraClip patients were significantly older (p<0.01), had lower baseline ejection fraction (EF) (p<0.03), and had higher EuroScore values (p<0.001), with similar 30-day (1.7 vs 3.5%, p=0.54) and 1-year mortality (7.4 vs 7.3%, p=0.66).

Four-year follow-up data for the EVEREST II trial demonstrated a non-significant difference in the composite outcome of freedom from death, surgery, or MR grade 3 / 4 + (39% vs. 53%, p = 0.07) in the percutaneous vs surgical groups, respectively. Death rates were similar (17.4 vs. 17.8%, p=0.91) as was the incidence of MR grade 3 / 4 + (21.7 vs. 24.7%, p=0.745), respectively. Surgery for mitral valve dysfunction occurred in 24 vs. 5.5 %, respectively, (p<0.001) at four years. The EVEREST II trial confirmed that following MitraClip leaflet repair, the option of further MV surgery remained for patients who required it. Further imaging studies have also documented that epicardial pacemaker lead placement via the coronary sinus is possible with percutaneous leaflet repair\(^1\). The MitraClip is currently approved for symptomatic patients with degenerative MR grade 3+ who are too high risk for surgery who may benefit from fewer hospitalisations, LV remodelling and symptomatic relief.

Imaging for percutaneous MV repair
The complex mitral valve apparatus and intricate anatomical relations of the branch coronary arteries necessitate pre-implantation, intraprocedural and post-implantation by multiple imaging modalities. Multi-detector cardiac CT, and more recently cardiac MRI, are commonly used to image coronary artery and cardiac vein position. Transoesophageal 2D and real-time 3D echocardiography is typically used during device implantation to guide placement, and transthoracic echocardiograms are used to assess initial patient eligibility and post-implantation surveillance. Thus, CT and TOE are used to image structural and real-time anatomical relationships, respectively, whereas transthoracic echocardiography is used to screen leaflet morphology and grade MR severity.

Cardiac CT
Cardiac CT is the primary modality for measuring anatomical relationships. Its fast acquisition times and 3D volume rendering capabilities have been used to assess anatomy relevant to annuloplasty techniques, including:

- Coronary sinus(CS) ostium area and calibre
- CS length and its course along MVA / left atrial wall
- CS to mitral annulus distance
- Anatomical relations of CS to LCx/marginal branches and MV annulus
  - Distance (CS ostium to intersection with LCx)
  - LCx branch superior/deep to Cs
- Mitral annulus diameter, circumference, area
- Left atrial volume
- Area between CS and AV groove

Sorgenteet al. 16 reported the anatomical relations between the CS and mitral annulus in 165 patients with varying LV and LA volumes. Their findings documented CS remodelling with chamber enlargement, e.g. CS shifted toward posterior aspect of MV annulus with progressive dilatation:

- frequent crossing of the LCx artery between the CS and mitral annulus in 77% of patients, and in particular, 97% of patients with severe MR.
- area between CS and AV grooves decreased in moderate-severe MR (150 v 260 mm2, p<0.001)
Cardiac MRI
Cardiac MRI has been used to evaluate in-vivo CS and MV relationships. Chiribiri reported the first accurate measurements with cardiac MRI 15 in a feasibility study in 31 participants (24 normals and 7 patients with known/suspected CAD but no CABG). Their findings showed:

- CS to LCx crossing point at 71 mm (22 to 100 mm) from ostial origin
- LCx between CS and MVA in 25/31 (80.6%)
- CS to MVA distance at LCx crossing greater in patients than normal (17 mm 9.6 mm, p<0.001)

Qualitatively, the above findings suggested CS located adjacent to LA wall rather than MV annulus, larger separation between CS and MVA in 4C view (suggestive of annulus flattening), and the LCx runs closer to CS than to MVA, and LCx between CS and MVA in majority.

Echocardiographic Imaging in percutaneous MV repair
Both transthoracic and transoesophageal echocardiography have important roles in the screening, implantation, and surveillance of percutaneous MV repair procedures.33-37 Although CT and cardiac MRI are predominantly used in anatomical assessment of the mitral valve, echocardiography is used routinely for screening entry criteria for percutaneous MV repair. Typical measurements from the EVEREST I trial included:

- MV inflow orifice area (> 4 cm²)
- MV leaflet coaptation length and depth
- MV flail gap and width
- Grading of mitral regurgitation
- ‘(integrated)’ MR – MR jet area, regurgitant volume/ fraction, pulmonary venous flow)

Functional assessment of MR severity, as proposed by the Valve Academic Research Consortium (VARC), is generally characterised by a standardised ‘integrated’ semi-quantitative approach incorporating features of MR jet area, regurgitant volume, regurgitant fraction, and pulmonary vein flow36. Transoesophageal and transthoracic 3D echocardiography allows measurement of mitral annulus geometry that is not typically measured by CT or MRI. Findings from CT and MRI have indirectly inferred mitral annulus shape change from variation of the CS to MVA distance in different view planes. These ‘non-planarity’ measures are readily assessed directly by 3D echo techniques8,33,36.

Multi-modality findings
Collating geometric findings across several anatomical, cardiac CT and MRI studies revealed consistent findings related to CS, LCx and mitral annular anatomy14. The principle findings across different modalities were as follows:

- CS-GCV behind LA in 90 to 100%
- LCx crosses between CS and MVA in 68 to 95%
- Distance from CS ostium where LCx crosses occurs at 71 to 78 mm along course of CS
- Decrease in CS to MVA distance in different views suggests flattening of MV annulus in presence of progressive moderate-severe MR and LV disease

Summary
Percutaneous MV leaflet repair may be achievable in the majority of patients, who benefit from reduced MR severity, improved quality of life and survival compared to standard medical care whilst preserving the option of future surgical and cardiovascular resynchronisation therapies. Other indirect annuloplasty techniques remain in a nascent stage where pre-procedural anatomical assessment is vital due to potential impairment of coronary vessels. Coronary CT has the largest evidence base for pre-procedural assessment of the mitral apparatus, but cardiac MRI appears equally suitable. Echocardiographic techniques maintain an important role for patient selection, regurgitation assessment and follow up, as well as intra-procedural guidance of device deployment. Current interventional devices for percutaneous mitral repair have limited approval outside research and special clinical governance arrangements. Future research should focus on modelling dynamic anatomical change of the mitral valve in motion before and after MV repair. Measurement via MRI and CT is feasible peri-procedurally, but multi-modality imaging remains essential to expand the evidence base for this promising array of techniques.

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