Percutaneous correction of Mitral Regurgitation using the MitraClip device: A Literature Review

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Introduction

Throughout the last 18 months I have shadowed a team of interventional cardiologists, led by Consultant Interventional Cardiologist, Dr F. Alamgir, based at Castle Hill Hospital, Hull and East Yorkshire Hospitals NHS trust. The team was the first centre in the United Kingdom to implement a new experimental technique designed to help reduce mitral regurgitation (MR)[1]. Population-based evidence documents that MR is the most common form of valvular heart disease[2].

The device used to reduce MR was granted CE approval in Europe in September 2008 following successful trials in America however FDA approval in the United States is still awaited[3].

Background

MR is the process of systolic retrograde flow from the left ventricle (LV) to the left atrium (LA) and is graded both functionally through the New York Heart Association (NYHA) grading score and clinically through echocardiography (see Table 1)[4,5].

Significant MR is classified[6] as having a severity score of 3+ to 4+.

Significant MR currently affects over four million Europeans and a similar number of Americans with an additional 250,000 people diagnosed annually[2,7]. Currently surgery provides a clinically effective method of correcting this dysfunction, so why change it? I was fortunate to be involved with Dr Alamgir's team who perform this procedure and completed a world first percutaneous mitral valve repair and simultaneous left anterior descending coronary artery revascularisation.

Table 1: *MR grade criteria*[6]

Variable	Mild 1+	Moderate 2+	Moderate to Severe 3+	Severe 4+
Colour flow Doppler	Small Central $<4 cm^2$ or <10% of LA area	Moderate Central 4-6 cm^2 or 10-30% of LA area	Large Central 6- <8cm^2 or 30-40% of LA area or eccentric to first Pulmonary Vein	Large Central ≥8cm^2 or ≥40% of LA area or eccentric to second Pulmonary Vein
Pulmonary Vein flow	Systolic	Diastolic dominant	All diastolic	Systolic reversal
Regurgitant volume (ml/beat)	<30	30-44	45-59	≥60
Regurgitant fraction (%)	<30	30-39	40-49	≥50

Pathophysiology

To understand fully how to improve a current method of therapy it is essential to consider the pathophysiology and anatomy of MR.

Effective functioning of the mitral valve requires co-ordinated anatomical interaction of the leaflets, valve annulus, chordae tendineae and papillary muscles as well as both the LA and LV[4,8].

MR is the result of the malfunction of one or more of these structures causing inadequate leaflet closure[4].

This co-ordinated functioning can be altered when a patient suffers from coronary artery disease, infective endocarditis, rheumatic fever, myxomatous degeneration, chordal rupture or a cardiomyopathy[4,10].

Mild to moderate, primary MR can remain asymptomatic for a prolonged length of time however the LV undergoes eccentric hypertrophy

as volume load increases to maintain cardiac output[11]. Remodelling through myocardial fibre elongation eventually leads to LV dysfunction and the development of an increased LV end diastolic volume[12,13].

Functional MR originates from chronic volume overload and results in LV dysfunction, increased end systolic diameter, symptomatic heart failure and heightened sudden death risk[13]. Excess volume load leads to LA dilatation consequently causing atrial fibrillation (AF) and thromboembolism[13].

There are three main categories, which classify MR aetiologies, which include degenerative disease (20-70%), ischaemic disease (13-30%) and non-ischaemic disease consisting of rheumatic heart disease (3-40%) and endocarditic heart disease (10-12%)[14]. Both ischaemic and non-ischaemic causes of MR are associated with functional MR.

Functional MR is multi-factorial, due to ventricular dysfunction (hypokinesis and dilatation), papillary muscle dysfunction, annular dilation and leaflet teathering[15,16].

Degenerative mitral valve disease is associated with structural abnormality of the valve or associated sub-valvular structures (rupture or stretching of the chordae tendinae)[16].

Despite a reduction in surgical mortality, long-term outcome is still poor in this cohort. MR correction alone cannot correct the underlying muscle dysfunction. Best management for secondary MR includes heart failure therapy and cardiac resynchronisation therapy in selected patients, however there is a potential role for percutaneous devices[17].

Traditionally MR has been corrected through median sternotomy arrested surgical intervention and whilst this is clinically effective there are significant morbidity and mortality risks.

This associated risk is calculated using either the euroSCORE or Society of Thoracic Surgeons (STS) risk calculator. The euroSCORE includes LV function data whilst the STS risk calculator considers preoperative myocardial infarction (MI) information, valvular disease and relevant coronary vessel disease[18]. The STS calculator generates a lower risk score than the euroSCORE regarding mitral valve repair or replacement[18].

Those with high EuroSCORE values are usually denied surgery and instead develop heart failure. Only 20% of patients with significant MR undergo mitral valve surgery[19,20].

This group of patients have a poor prognosis with an annual mortality rate of 5% either through progressive heart failure, sudden death, stroke or endocarditis[21,22]. During this time they suffer from a poor quality of life and often experience repeated hospitalisation alongside vast amounts of primary care and social service support[23].

Current Treatment Methods

Medical

Currently there is very little medical therapy for MR. Studies have evidenced improved haemodynamics in acute MR by administrating nitroprusside and nitroglycerin which reduces afterload, MR and pulmonary pressures[24]. Acute patients can be stabilised using an intra-aortic balloon pump prior to urgent mitral valve repair or replacement[25]. No equivalent study exists which demonstrates these benefits for patients with chronic MR.

For chronic, asymptomatic MR, literature suggests there is no benefit for regular administration of medication in delaying surgery or restricting LV dysfunction[26]. For this group of patients it is important to decide the appropriate timing for surgery before there is irreversible LV dysfunction.

Currently the recognised treatment consists of treating identifiable reversible aetiology and regularly assessing every 6 to 12 months MR severity, LV ejection fraction and LV end-systolic

dimension through echocardiolograhy[9,25].

Functional MR can be medically managed through therapeutic agents including anti-hypertensives, beta- blockers, angiotensin-converting enzyme inhibitors and diuretics[25]. Anti-anginals can be combined when MR is intensified because of ischemia[27].

If the MR is related to a dilated cardiomyopathy there is evidence that suggests biventricular pacing can reduce the MR severity[28].

Surgical

The STS's database states that mitral valve surgery (repair or replacement) is the second most common valvular surgery in the United States and more than 100,000 procedures are completed annually worldwide[29].

Surgery is indicated for patients with either symptomatic and severe primary MR or asymptomatic patients with severe primary MR and LV dysfunction, or pulmonary hypertension or AF[25].

Early surgical intervention is beneficial in symptomatic patients whilst asymptomatic patients are difficult to manage due to the difficulties faced when assessing the LV contractile function[30].

The standard protocol is an LV end-systolic dimension greater than 40mm and a resting LV ejection fraction of 60% or less. For functional MR, surgery is considered for severe symptoms. Those suffering ischaemic MR are also considered for revascularisation either through CABG or percutaneous coronary intervention (PCI), if there is significant myocardial viability or ischemia[25].

Surgery is linked to many complications and risks as well as an extended post-operative recovery period. Patients recovering from mitral valve surgery may take several months to fully recover from their surgery[31].

There are two available surgical options mitral valve repair or mitral valve replacement. When there is degenerative MR, mitral valve repair is the procedure of choice, due to reduced infective endocarditis risk, lower operative and long-term mortality, better LV function preservation and no chronic anti-coagulation therapy[32].

Repair techniques are relatively complex, especially anterior leaflet repair, and were designed for degenerative mitral valve disease and may be unsuitable for other MR causes.

There are several mitral valve repair techniques, which include triangular resection for posterior leaflet prolapse, chordal or Gore-Tex transfer to treat anterior leaflet prolapse, sliding leaflet repair or Edge-to-Edge repair.

The edge-to-edge repair, pioneered by Professor Ottavio Alfieri in Milan, is a surgical technique requiring median sternotomy arrested surgery since the early 1990s for the treatment of MR[33]. The double orifice procedure has over 1,500 cases in peer reviewed journals with a ten year follow up showing mortality is no greater than other methods of mitral valve repair and is successful for all primary aetiologies of MR[33-35].

Understanding the anatomy of the mitral valve is essential to consider now. For the Edge-to-Edge repair, sutures are placed from the largest central anterior leaflet to the second posterior leaflet (A2 and P2) allowing adequate diastolic blood flow through the valve, whilst enabling correct valvular function throughout systole. The effective diastolic orifice is reduced by 40-50%, to around 3cm^2; clinically significant mitral stenosis does not develop until the area drops below 1.5cm^2 [34,35]. Over time the need for mechanical support provided by the suture is reduced due to endothelial migration occurring between the approximated leaflets.

The large median sternotomy scar is one of the disadvantages of mitral valve surgery. Professor Ottavio Alfieri developed a novel trans-thoracic

technique to overcome this and Dr Hugo Vanermen in Belgium has pioneered the field of robotic minimally invasive surgery to correct MR[36].

The minimally invasive robotic approach has proved to be safer than traditional surgery and provides the patient with a shorter recovery time and this approach has been adopted at numerous specialist centres around the world[37].

Percutaneous approach

As with the advantages of PCI, pioneered Dr Andreas Gruentzig in Zurich in 1977, compared with CABG, a percutaneous method for valve repair would further reduce length of stay, reduce infection risk, leave a small scar and reduce recovery time.

Dr Alain Cribier in France, pioneered the percutaneous valve approach in 2002 and since then numerous methods have been suggested including leaflet repair, coronary sinus annuloplasty, direct remodelling, annular plication, annular shrinking using radio frequencies and valve replacement[38].

Annuloplasty

There are two device designs currently in phase two trials.

Firstly the MONARC device, designed for the treatment of functional MR, consisting of two self-expanding stent-like anchors deployed via the right internal jugular vein distally into the great cardiac vein and proximal coronary sinus with a bridging structure.

Following implantation the bridging structure reduces in size, drawing the anchors together, reducing the coronary sinus and adjacent mitral annulus[38,39].

The results from the EVOLUTION phase 1 study looking at the MONARC device were promising, showing successful implantation in 82% of patients (n=59).

However after 3-months following implantation angiography displayed compression in 30% of patients' coronary arteries, with three MIs resulting in one death.

At 18 months there had also been two coronary sinus perforations, one anchor displacement and four anchor separations. These concerns will be reviewed with designed modifications in the non-randomised multicentre EVOLUTION phase two trial[38,39].

The CARILLION is a similar device to the MONARC device, consists of a proximal and distal anchor and a curved nitinol connecting bridge; implanted in the coronary sinus[38,40].

Studies designed to demonstrate animal feasibility and safety provided evidence of acute and chronic reductions in mitral annulus diameter alongside a reduced MR:LA area ratio[38,40].

Phase 1 AMADEUS trials showed implantation success in 70% (n=30) of patients with 80% of patients showing at least 1-grade reduction in MR severity, however at one month there had been two MIs, one death, two coronary sinus perforations, one anchor displacement and one dissection[38,40].

MitraClip

The second of the two phase two trials looked at correction of functional or degenerative MR[40]. Functional MR is corrected by coaptation of the teathered leaflets, whilst anchoring flail and prolapsed leaflets repairs degenerative MR.

By reducing MR the LV volume is also reduced. The MitraClip device builds on the surgical Edge-to-Edge repair technique to reduce MR[33,40,41]. It is the MitraClip device that the team at Castle Hill Hospital are currently using to correct MR percutaneously.

The MitraClip device is inserted using a catheter via the femoral vein under general anaesthesia. The device is then delivered trans-septally and placed into the left atrium over the mitral valve

using trans-oesophageal echocardiography and fluoroscopy[42]. The device is placed whilst the heart is still beating, allowing for accurate identification of the optimum position for the coaptation of the P2 and A2 mitral leaflet scallops[43].

The repositionable and removable nature allows emulation of the Edge-to-Edge repair without arresting the heart enabling continual assessment of the degree of regurgitation providing optimal MR reduction.

This is a clear advantage over the arrested surgical technique where cardiopulmonary bypass would have to be restarted to assess valvular function fully.

The device is coated in polyester promoting endothelial migration, generating a tissue bridge and is safe in up to 3 tesla MRI. The repair limits the dilatation of the annulus, restrains the LV wall and limits LV dilatation.

To increase the area of coaptation a second clip can also be placed and does not compromise future surgical review if required. This concept applies regardless of the aetiology, but does have certain patho-anatomical constraints[42].

Anatomical Viability

For functional MR, the valvular coaptation length needs to be considered.

For effective repair, the coaptation length should be greater than 2mm with coaptation depth less than 11 mm.

Flail also needs to be considered. The flail gap should be less than 10mm, whilst flail width should be less than 15mm[42].

There are further considerations for mitral clip insertion including an ejection fraction of less than 25% or LV end systolic dimension of greater than 55mm, severe mitral annular calcification, renal insufficiency, previous mitral valve surgery, evidence of intra-cardiac mass, thrombus, endocarditis, rheumatic heart disease, vegetation or the presence of a permanent pacemaker[42].

In the event that one of patients has inappropriate criteria for the MitraClip the decision of the patient's care would be decided at a multidisciplinary team meeting.

Evidence

The safety of the MitraClip was displayed originally in porcine models[44,45]. The phase 1 EVEREST (Endovascular Valve Edge-to-Edge Repair Study) enrolled 55 nonrandomized patients, confirming the safety and feasilibilty of the MitraClip, also reporting a reduced LV chamber dimension at 12 months[6,46].

The EVEREST II trial randomised 279 patients (device n=184 vs control n=95) over 37 centres with severe MR (3+ to 4+) (degenerative 73% vs functional 27%) in a 2:1 ratio with surgical repair (n=59) or replacement (n=8) depending on the cardiac surgeon's preference.

To participate within the trial, patients had to be symptomatic with correct anatomical criteria; if they were asymptomatic they had to display LV dysfunction. The primary end points of the study looking at the major adverse event rate at 30 days and clinical success rate were both achieved[20,47].

Regarding safety, the MitraClip demonstrated that it was safer than surgery when comparing major adverse events at 30 days following treatment (9.6% vs 57.0%). The main reason for this was the inclusion of a blood transfusion greater than two units, which contributed 8.8% to the MitraClip and 57.0% for the control. Despite this it has been reported that if the preferred cardiothoracic bleeding parameter had been used there would have been little relative change. It was also demonstrated statistically that it was non-inferior to surgery in effectiveness (72.4% vs 87.8%)[20,47].

Clinically, surgery still is more effective, 95.7%

of patients in the device group had MR severity of 3+ to 4+, which at 12 months follow up, had reduced to 18.5% in the 3+ to 4+ group, 33.6% in the 2+ group, 11.1% in the 1+ to 2+ group and 36.1% in the 1+ group. There were no deaths, stroke or urgent-reoperation in the device group[47].

Those in the control group with MR originally 3+ to 4+ (92.6%) had a larger reduction with 17.9% having no MR at 12 month follow up, 58.2% having severity of 1+, 7.5% having 1+ to 2+ and 3.0% having severity of 3+.

Despite the clinical effectiveness of the surgical technique the study failed to show a significant symptomatic benefit for those undergoing surgical treatment.

The baseline NYHA functional class was comparable between groups however at 12 month follow up 97.6% of patients in the device group had NYHA class I/II compared with 87.9% of the surgical control group.

Patients in the device group were also shown to have improved LV volume and dimension at 12 months when compared to the surgical approach[47].

Patients were evaluated on their quality of life using the SF-36 form and those in the device group displayed significantly improved quality of life following the procedure both mentally and physically at both 30 days and 12 months compared with the surgical patients[47].

In summary the MitraClip demonstrated that it is safer than conventional surgery with no reduced efficacy, producing improved clinical benefits for the patient. Surgery is still an option for those undergoing the MitraClip procedure.

In Europe 472 procedures have been carried out from the 1,115 performed worldwide[47].

Conclusion

The MitraClip is a safe, feasible and unique device, which can positively change the prognosis for many individuals suffering from MR without the need for invasive surgery.

It is paramount however that for this technique to be successful patient selection is adhered to and that there is a multidisciplinary team, including both cardiothoracic surgeons and interventional cardiologists, to evaluate each case.

From my own personal experience, being involved with Dr. Alamgir's team at Castle Hill Hospital, where such advanced procedures are performed, has been an incredible insight into the future of the rapidly expanding field of interventional cardiology.

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