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VALVULAR HEART DISEASE

How to manage ischaemic mitral regurgitation

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Ischaemic heart disease is becoming an increasingly frequent cause of ischaemic mitral regurgitation (IMR). Three different clinical entities of IMR, which deeply affect the clinical decision making, are distinguishable: the acute IMR complicating an acute myocardial infarction, the true IMR secondary to a transient ischaemic phenomenon, and the chronic functional IMR (FIMR). The incidence of the two first entities is low; the third is much more frequent.

ACUTE ISCHAEMIC MITRAL REGURGITATION COMPLICATING THE ACUTE PHASE OF MYOCARDIAL INFARCTION

IMR can occur acutely in patients sustaining an acute myocardial infarction. The rupture of a papillary muscle—most frequently a head of a posteromedial papillary muscle—is a dramatic mechanical complication of acute myocardial infarction, leading to a very high mortality rate in the absence of immediate surgical intervention. Surgery, most often valve replacement, is warranted after stabilisation of the haemodynamic status using an intra-aortic balloon pump and vasodilators.[1] In the absence of such a rupture, the presence of IMR in the acute myocardial infarction phase portends a grave prognosis. Its incidence and clinical importance are largely underestimated, partly because physical examination is rather insensitive. Prompt in-hospital revascularisation can prevent or reverse acute IMR.[2] When limited to the inferior wall, early revascularisation may reduce localised left ventricular (LV) remodelling and IMR.[3] Early revascularisation also increases survival in patients with acute IMR presenting with shock.[4]

TRUE ISCHAEMIC MITRAL REGURGITATION

This second form truly defines IMR because it is secondary to an active ischaemic episode. It is clinically most often revealed by a "whistling angina" or a "flash pulmonary oedema".[5] It is linked to the presence of a significant stenosis of the right or left circumflex coronary artery. In this situation, the primary treatment is to prevent the episodes of active myocardial ischaemia by a revascularisation procedure.

CHRONIC FUNCTIONAL ISCHAEMIC MITRAL REGURGITATION

Chronic FIMR, the most common cause of IMR, broadly denotes abnormal function of normal leaflets in the context of impaired ventricular function resulting from ischaemic heart disease. It results from an imbalance between tethering forces (annular dilatation, LV dilatation, papillary muscles displacement, LV sphericity) and closing forces (reduction of LV contractility, global LV dyssynchrony, papillary muscle dyssynchrony, altered mitral systolic annular contraction).[5] Chronic FIMR results, in 95% of cases, from a type IIIb dysfunction (restricted leaflet motion). It is important to note that in the remaining 5%, an ischaemic elongation of the papillary muscle may cause prolapse in the corresponding area (type II dysfunction). When present, FIMR may exhibit a broad range of severity and, when severe (effective regurgitant orifice (ERO) $\geq$20 mm^2), conveys a poor outcome. FIMR is characteristically dynamic during exercise. It has been shown that an increase (ΔERO $\geq$13 mm^2) in FIMR during exercise identifies a subgroup of patients at higher risk of cardiac events.[6 7]

MANAGEMENT OF FUNCTIONAL ISCHAEMIC MITRAL REGURGITATION

When treating FIMR, it is important to integrate several clinical parameters—symptoms of heart failure, episodes of worsening heart failure, comorbidities—and echocardiographic elements—mitral regurgitation severity at rest and its dynamic nature at exercise, the degree of mitral valve apparatus deformation, the origin and direction of regurgitant jets, the importance of LV remodelling, the presence of LV dyssynchrony, the presence and extent of viable myocardium at jeopardy. Different clinical scenarios might thus largely modulate the clinical decision making. Practically, instead of medical treatment, unbalanced tethering can be addressed by mitral valve surgery or by LV reshaping, whereas coronary revascularisation or cardiac resynchronisation therapy can potentially reduce tethering as well as increase mitral valve closing forces (fig 1).

Medical treatment

The scope of medical treatment, which remains the first step in the management of these patients, is to prevent myocardial ischaemia, reduce the severity of FIMR, and revert or delay the LV remodelling process. However, presently no pharmacological approach has been shown to improve the patient clinical outcome. Usual medical treatment of heart failure, including angiotensin converting enzyme

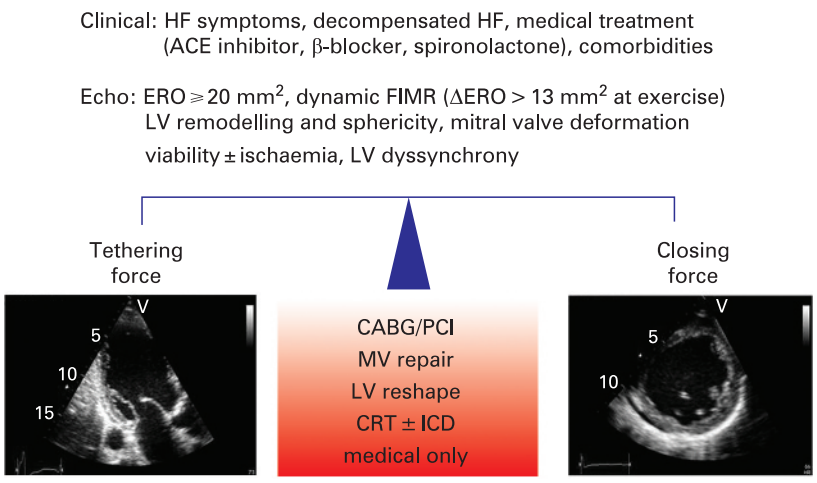

Figure 1 Global management of functional ischaemic mitral regurgitation. ACE, angiotensin converting enzyme; CABG, coronary artery bypass grafting; CRT, cardiac resynchronisation therapy; ERO, effective regurgitant orifice; FIMR, functional ischaemic mitral regurgitation; HF, heart failure; ICD, implantable cardioverter-defibrillator; LV, left ventricle; MV, mitral valve; PCI, percutaneous coronary intervention.

(ACE) inhibitors, β-blockers and spironolactone, should be prescribed according to the official recommendations. All these drugs gradually lead to a fundamental reshaping of the LV. Diuretics are administered according to the signs of water retention. In cases of acute dyspnoea, sublingual nitrates seem to be beneficial. In practice, FIMR appears to remain common despite the use of these drugs.[8]

Cardiac resynchronisation therapy

Currently, when a revascularisation procedure is not indicated or insufficient to improve the clinical status, the use of biventricular pacing is justified (European Society of Cardiology (ESC) guidelines class I level of evidence A) in heart failure patients with significant ventricular conduction delay (QRS >120 ms) who remain symptomatic despite optimal drug treatment.[9] The effects of cardiac resynchronisation therapy (CRT) on FIMR can be observed acutely or only late after implantation. This treatment is associated with an immediate reduction in the quantified degree of FIMR (expected reduction of 35%), which is directly correlated to the improvement in LV systolic performance (greater mitral closing force)—increase in LV dP/dt—and the reduction in the interpapillary muscle activation time delay (less tension on mitral leaflets).[10 11] Reduction in mitral regurgitation severity also results from a more effective mitral annulus contraction and a significant decrease in systolic tenting area—the systolic displacement of the body of the mitral leaflets into the LV cavity. Thus, in the acute stage, CRT corrects the imbalance between forces acting on the mitral valve and enhances the sphincteric action of the annulus. It should be noted that these changes are often insufficient to remove regurgitation. Persistent residual FIMR is determined by the extent of residual deformation of the mitral valve.[12]

Besides these acute effects, an additional 10–20% reduction in FIMR, that parallels the decrease in LV volumes and the increase in LV dP/dt, occurs some months after CRT. Although this improvement is sustained at 1 year follow-up, it could be attenuated in some patients secondary to the progression of the ischaemic disease.[13] The benefit of CRT appears to be dependent on continued pacing because withholding pacing results in an immediate loss of efficacy and recurrence of FIMR. Indeed, the transient interruption of CRT after long term results in acute deterioration of FIMR as a consequence of a pronounced decline in LV dP/dt and the reappearance of significant papillary muscle dyssynchrony.[14] This supports the notion of maintaining CRT indefinitely. The effect of CRT on dynamic FIMR is also progressive and appears in the chronic stage of stimulation. Indeed, CRT reduces not only FIMR at rest but also its dynamic component during exercise. The expected attenuation of exercise induced FIMR is about 30%.[12 15] However, CRT reduces the amount of increase in FIMR but does not avoid the development of at least some dynamic component in most patients.

The response to CRT might be modulated by the severity of FIMR and the extent of LV remodelling before implantation. Severe FIMR (ERO ⩾20 mm²) in the setting of an enlarged LV is associated with lack of reverse remodelling during follow-up. Patients with more severe disease are thus less likely to respond to CRT. Moreover, the degree to which the reduction in FIMR plays a role in reverse LV remodelling remains currently unclear. CRT reduces but does not abolish FMR in most patients. The persistence of a critical level of regurgitation might thus be able to perpetuate the LV remodelling process. Data concerning long term effects are limited. Importantly, this mode of treatment is restricted to patients who fulfil the classical criteria for CRT.

Table 1 Indications for surgery in ischaemic mitral regurgitation (IMR)

Clinical situation	Mitral valve surgery (ESC guidelines 2007)
Patients with severe IMR (ERO ⩾20 mm²)	
Ruptured papillary muscle due to acute MI	Immediate
LV ejection fraction ⩾30% undergoing CABG	Recommended (IC)
LV ejection fraction <30% and option for CABG	Reasonable if symptomatic (IIaC)
LV ejection fraction ⩾30%, no option for CABG	To consider if symptomatic and low morbidity (IIbC)
Patients with moderate IMR (ERO <20 mm²)	
Undergoing CABG	Reasonable if repair is feasible (IIaC)
No option for CABG or undergoing PCI	Uncertain ("a priori not")
Patients with trace IMR	
Undergoing CABG	Not recommended

CABG, coronary bypass grafting; ERO, effective regurgitant orifice; ESC, European Society of Cardiology; LV, left ventricular; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Surgical treatment

The indication for surgical correction of FIMR is a source of debate. In most cases, coronary bypass grafting alone is not sufficient to remove regurgitation or even to reduce its severity.[16] However,

Table 2 Predictors of outcome after mitral valve surgery

History	Condition	Echocardiography	Surgery
Older age		LV ejection fraction <30%	
Diabetes mellitus	High Euroscore	Extensive scar + no viability	Left main stenosis
Cardiac heart failure	Emergent operation	Severe LV remodelling	Three vessel disease
Increasing NYHA class	Cardiogenic shock	Severe MV deformation	MV replacement
Renal failure		Complex regurgitant jet	Residual IMR
Associated diseases		Restrictive diastolic filling	

IMR, ischaemic mitral regurgitation; LV, left ventricular; MV, mitral valve; NYHA, New York Heart Association.

not treating FIMR exposes the patient to a higher risk of hospitalisation for heart failure.[17] The possible survival impact of mitral valve surgery is poorly known; mortality at 5 years remains high.[18] Results from the literature unfortunately reflect their retrospective nature, the inevitable patient selection bias, and unresolved issues such as the best surgical technique to use. So far, the added value of valve repair compared to bypass surgery alone is thus uncertain. Table 1 lists the indications for surgery, and table 2 the predictors of outcome following surgery.

Practically, the decision to intervene in the mitral valve will depend on the severity of FIMR and whether or not bypass grafting will be scheduled. Unanimously, severe FIMR (ERO $\geq$20 mm^2) should be corrected at the time of bypass surgery (ESC level IC),[8] while trivial FIMR (ERO <10 mm^2) can be neglected. Remodelling annuloplasty using a prosthetic undersized ring (one or two sizes) is the technique of choice in type IIIb dysfunction.[19] If the repair is unfeasible (limited cases) or there is type II dysfunction in which stringent annuloplasty will be often inefficient, it is reasonable to advocate mitral valve replacement (bioprosthesis) with preservation of the subvalvular apparatus. In symptomatic patients with severe FIMR and no option for revascularisation, mitral valve repair may be considered (ESC level IIbC). However, when the LV function is severely impaired, surgery is more likely to be considered if myocardial viability is present, if comorbidity is low, if FIMR increases dynamically during exercise, if the LV is not severely remodelled, and if the revascularisation can be almost complete. In the other cases, cardiac transplantation (ESC level IC) remains the preferable approach since it is associated with a better 5 year outcome (fig 2).

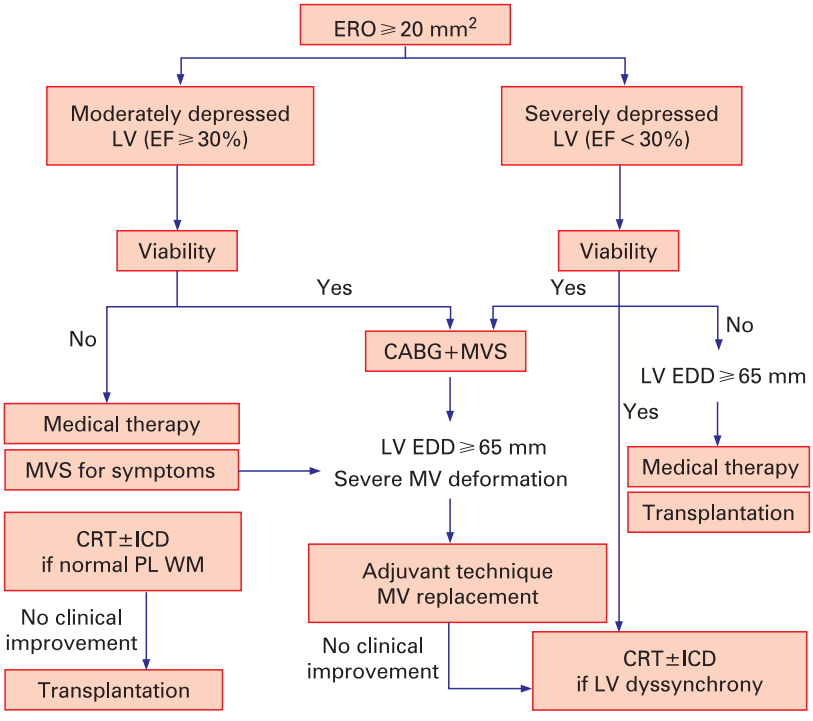

Figure 2 Management of patients with severe functional ischaemic mitral regurgitation. CABG, coronary artery bypass grafting; CRT, cardiac resynchronisation therapy; EDD, end-diastolic diameter; EF, ejection fraction; ERO, effective regurgitant orifice; ICD, implantable cardioverter-defibrillator; LV, left ventricle; MV, mitral valve; MVS, mitral valve surgery; PL WM, posterolateral wall motion.

In patients with moderate FIMR (ERO <20 mm^2), the ischaemic symptoms usually dictate the treatment strategy. For example, mildly symptomatic patients with no residual myocardial ischaemia and mild to moderate FIMR will be usually treated medically, whereas symptomatic patients with active or inducible ischaemia will be oriented towards a revascularisation procedure. When percutaneous coronary revascularisation is performed, mitral valve surgery is rarely proposed. In this situation, the patient should be carefully followed up to detect any FIMR progression and ongoing LV remodelling process. Conversely, when bypass grafting is planned, the decision to repair the mitral valve remains a matter of controversy. In such cases, if the mitral valve is repairable, combined surgery is reasonable (ESC level IIaC). However, the additional risk of mitral valve surgery is not negligible, particularly in patients with comorbidities and poor LV function. Very ill patients should be treated conservatively with revascularisation alone.[17] In the future percutaneous annuloplasty may possibly be proposed for these patients.[20] Low risk patients can be further stratified with exercise echocardiography.[16] Although this technique is of growing interest, its value to predict the results of surgery still remains to be evaluated. Patients with a dynamic increase in FIMR (ΔERO $\geq$13 mm^2) during exercise might be submitted for combined surgery, while patients with either no significant changes or exercise induced reduction in FIMR as a result of recruitable function in the inferobasal wall might be referred for bypass grafting alone (fig 3).

Several groups have used transoesophageal echocardiography at the beginning of the intervention to make this decision. However, because of changes in loading conditions, general anaesthesia leads almost systematically to underestimation of FIMR severity (reduction of moderate FIMR to trace amounts).[21] Accordingly, to minimise the effects of anaesthetic induction on FIMR some groups perform a preload and afterload challenge test. A rapid fluid filling is performed until the mean capillary wedge pressure reaches 15–18 mm Hg. If the regurgitation does not

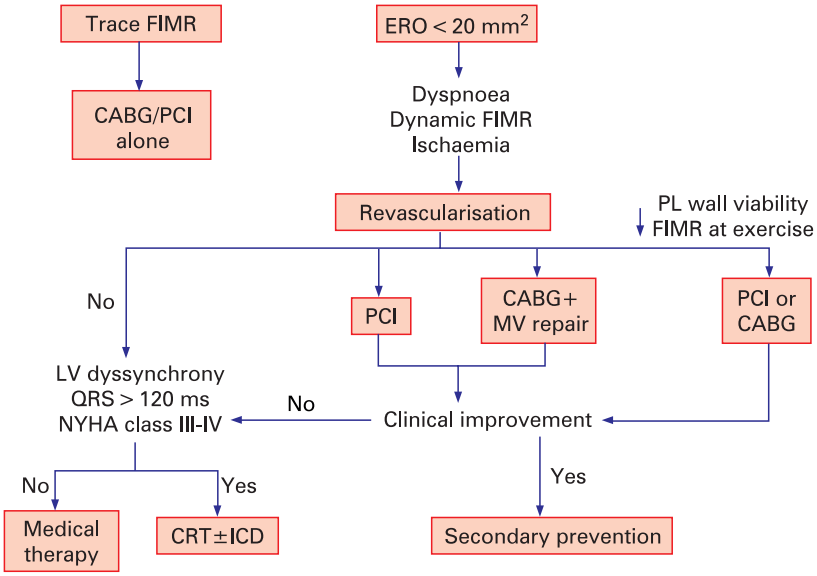

Figure 3 Management of patients with moderate functional ischaemic mitral regurgitation. CABG, coronary artery bypass grafting; CRT, cardiac resynchronisation therapy; ERO, effective regurgitant orifice; FIMR, functional ischaemic mitral regurgitation; ICD, implantable cardioverter-defibrillator; LV, left ventricle; MV, mitral valve; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PL, posterolateral.

increase, phenylephrine is administered until the mean arterial blood pressure reaches 100 mm Hg.[18 21] This approach provides a rough assessment of the dynamic behaviour of FIMR. Indeed, the level of increase in the FIMR associated with the need for repair is not yet validated.

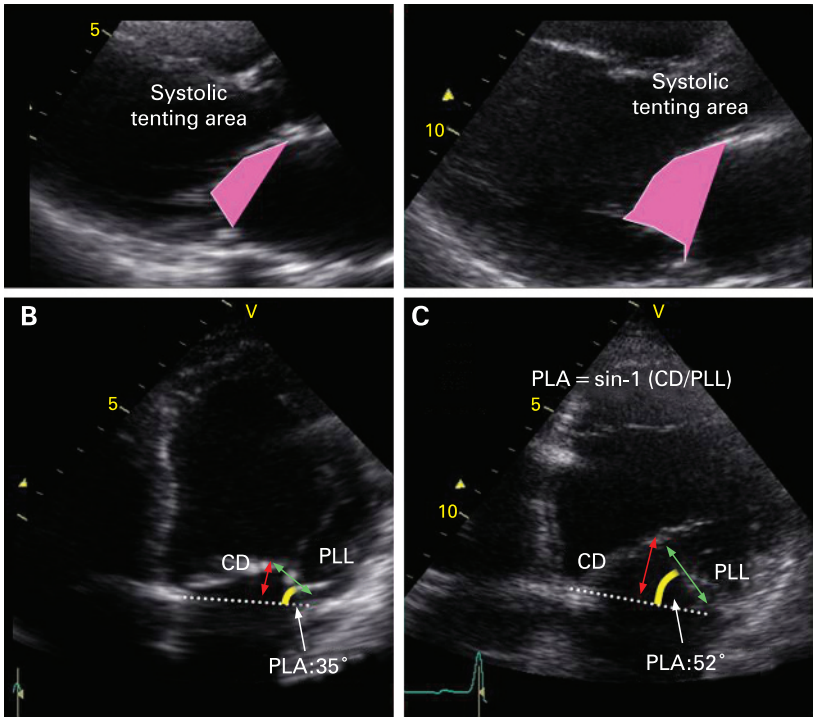

Figure 4 Echocardiographic assessment of mitral valve deformation. CD, coaptation distance (red arrow); PLA, posterior leaflet angle; PLL, posterior leaflet length (green arrow).

Table 3 Preoperative predictors of mitral valve repair failure (transthoracic echocardiography)

Parameters	Threshold
Coaptation distance	⩾1 cm
Systolic tenting area	>2.5–3 cm²
Posterolateral angle	⩾45°
Lateral wall motion abnormality	Scar
Central regurgitant jet	–
Complex regurgitant jets	Multiple
Left ventricular end-diastolic diameter	⩾65 mm
Left ventricular end-systolic diameter	⩾51 mm

Practically, it is probably best to identify potential candidates for combined surgery before intervention.

Residual or recurrent FIMR after mitral valve surgery

It has become increasingly clear that a ventricular problem cannot be resolved by a single annular procedure—that does not directly address tethering by the remodelled LV—in every case.[5] Persistence or recurrence of FIMR is observed in approximately one third of patients, the risk being more significant during the first 6 months after surgery (table 3).[5 16] The persistence of FIMR—which can perpetuate the LV remodelling process and adversely affect the patient's outcome—could be explained by the postoperative persistence and/or worsening of mitral leaflets tethering.[5] In most instances, mitral ring annuloplasty reduces the anterior–posterior annular dimension and contributes to restoring a surface of coaptation.[19] By doing so, it always induces, for geometrical reasons, a further tethering of the posterior leaflet, but also of the anterior leaflet, and frequently converts the valve into a monocusp with sometimes a restricted anterior leaflet motion as well.[22] This pattern of coaptation of the edge of the anterior leaflet against the body of the even more tethered posterior leaflet usually accounts for a mild residual leak postoperatively. This is particularly more pronounced in patients with an asymmetrical mitral orifice (P2–P3 are more restricted) who received a symmetrical ring. If the remodelling process is not halted by the procedure, a further tethering of both the anterior and posterior leaflet is expected with a recurrence of FIMR.[5]

Several echocardiographic parameters can help to identify patients at risk of treatment failure (fig 4). Preoperatively (transoesophageal echocardiography), patients with a mitral diastolic annulus diameter ⩾37 mm, a systolic tenting area ⩾1.6 cm² and an FIMR grade >3.5 have a 50% probability of failure during follow-up.[23] Preoperatively (transthoracic echocardiography), a coaptation distance >1 cm (distance between the leaflet coaptation point and the mitral annulus plane in the apical four chamber view), a systolic tenting area >2.5 cm² (the area enclosed between the annular plane and mitral leaflets in the parasternal long axis view), a posterior leaflet angle ⩾45° (indicating a high posterior leaflet

How to manage ischaemic mitral regurgitation: key points

- Bypass grafting (CABG) alone does not correct functional ischaemic mitral regurgitation (FIMR) in most patients.
- The candidate for combined surgery (mitral valve replacement + CABG) should be selected preoperatively.
- Undersized mitral annuloplasty is the technique of choice.
- Recurrent FIMR is frequent in patients with severe mitral valve deformation/left ventricular remodelling.
- Survival advantage from repair rather than mitral valve replacement is evident in most patients.
- The precise role of subvalvular adjuncts needs to be studied.
- Prospective registries and randomised trials are necessary.

restriction), a central regurgitant jet (indicating a severe restriction of both leaflets in patients with severe FIMR), the presence of complex jets originating centrally and posteromedially, a restrictive diastolic filling profile (suggesting a more advanced LV disease process and associated with further negative LV remodelling after repair), and a severe LV enlargement (low likelihood of reverse LV remodelling after repair and poor late outcome) increase the risk of mitral valve repair failure. Taking these parameters altogether could reduce the frequency of postoperative FIMR.[24] For example, using a two sizes stringent ring (ring 24–26), in conjunction with obtaining a coaptation distance $\leqslant$8 mm at the end of intervention in selected patients with a preoperative LV end diastolic volume $\leqslant$65 mm, leads to a dramatic decrease in the incidence of recurrent FIMR as low as 2.3%.[18] This could, however, increase the risk of inducing mitral stenosis.[25] When the mitral valve is severely deformed and the LV significantly enlarged, it would be reasonable also to restore the geometry of the LV and/or to reduce directly the leaflets tethering by a complementary subvalvular or ventricular approach. In some cases, mitral valve replacement is defendable.

New treatment modalities

This intrinsic limitation of simple reductive annuloplasty has been challenged by different techniques which aim at reducing the traction exerted from the LV on the mitral valve.[26] Enlargement of the posterior leaflet, especially in the area of the posteromedial commissure, may enable the placement of a normal ring and restore a surface of coaptation by reducing the tethering. The surgical relocation of the posterior papillary muscle is another approach to correct the tethering at the ventricular level.[27] Resection of secondary strut cords that account in some cases for bending of the anterior leaflet and reduced coaptation, although appealing, has not led to conclusive clinical results.[28] The association of the edge-to-edge Alfieri procedure to an undersized annuloplasty seems to reduce the incidence of repair failure in patients with excessive tethering (coaptation distance $\geqslant$1 cm).[29] Asymmetrical tethering could be solved by using an asymmetrical ring annuloplasty. Severe LV remodelling could be challenged by an LV restoration using the modified Dor procedure or by applying the "Acorn" or the "Myosplint" system.[30]

More recently, various companies have launched studies on percutaneous approaches of mitral valve repair. The majority of devices (for example, MitraLife-Edwards, Edwards Monarc, Cardiac Dimensions, Viacor) take advantage of the proximity of the coronary sinus to the posterior mitral annulus to deliver devices (anchors that are placed in the anterior and posterior portions of the coronary sinus) that remodel the mitral annulus.[31–33] The Edwards Monarc device consists of a pair of self expanding nitinol anchoring stents located at the ends of the device and joined to each other by a connecting element that undergoes delayed shortening over 3–4 weeks after placement. The Cardiac Dimensions Carillon device consists of two different sized, self expanding figure-of-eight nitinol loops located at either end of a fixed length stainless steel connector. The Viacor device is used to place one or more straightening rods within a catheter that is positioned in the coronary sinus via the subclavian vein. Although these rods do not plicate the coronary sinus per se, they do "bend" the sinus in a manner that pushes the posterior leaflet forward relative to the location of the commissures. Other devices such as the Mitralign perform septal lateral cinching by direct placement of several almost-stapled-like anchors around the mitral annulus to reduce the diameter of the orifice. The percutaneous septal sinus shortening approach (Ample Medical), the Quantun Cor, and the minimally invasive iCoapsys device are new percutaneous devices under evaluation. Finally, in an experimental model, it has been shown that cell transplantation in the infarcted area can also potentially reduce IMR through a decrease in localised LV wall

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deformation.[34] So far, these techniques—which stress the importance of addressing the ventricular factors that cause FIMR—have only been applied in small clinical cohorts or are still limited to experimental models. Thus, definitive recommendations cannot be made at present.

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