Review Article

Functional mitral regurgitation: an overview for surgical management framework

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Abstract: Functional mitral regurgitation (FMR) is one the most common complications of myocardial infarction (MI) in adults carrying a significant clinical and economic burden. Despite specific randomized controlled studies to address its treatment have been performed, there are still a number of questions remained unanswered. Outcomes of surgical repair of FMR are still hampered by a significant rate of recurrence of regurgitation and need for reoperation. Mechanisms underlying failure of repairs still need to be completely clarified and questions regarding the indications and optimal timing for intervention as well as the best suitable operative technique to be applied are still debated. This work will review the current knowledge on FMR including its pathogenic mechanisms, the available treatment strategies, the evidences from trials and observational studies and the potential future directions to address the issues related to its treatment.

Keywords: Ischemic mitral regurgitation (IMR); mitral repair; subvalvular repair

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The clinical problem

Functional mitral regurgitation (FMR) is one of the most common complications following a myocardial infarction. Randomized controlled trials to determine the optimal surgical approach have been performed (1-6), along with investigations aimed at evaluating alternative and emerging treatment strategies (7-11). Amongst patients with a history of myocardial infarction, approximately 50% and 10% develop moderate and moderate-to-severe mitral regurgitation (MR), respectively (2,4,10,11). The occurrence of FMR is responsible for more deaths and complications than all other potential consequences of a myocardial infarction combined (12). FMR results from a dysfunction of the valvular and subvalvular apparatus of the mitral valve (MV) due to displacement of one or both papillary muscles (PM) after a myocardial infarction, which leads to MV leaflet tethering and incomplete systolic MV closure. Given the complexity of its pathogenesis, a solution to correct the valvular and subvalvular dysfunction, along with the left ventricular (LV) geometric distortion associated with ischaemic mitral regurgitation (IMR), has not yet been elucidated (6,13,14).

Geometric abnormalities and tethering of any or all of the segments of the MV cause FMR by creating a so-called "vector-dependent" MV dysfunction related to the direction of the displacement vectors of the PMs. Evidence suggests that the pattern of the geometric abnormalities in FMR is variable, possibly reflecting heterogeneity in the imbalance of the tethering and closing forces, and in the biomechanical features of the valve, which may have important implications in the clinical management of this entity (8). The present article provides a review of the basic principles, recent advances, and recommendations for the surgical treatment of FMR.

Pathophysiology and effect of therapy

The prevalence of FMR ranges from 1.6 to 2.8 million in the United States (15). As mentioned, moderate or greater FMR develops progressively in more than half of patients after a myocardial infarction, and is sustained by varying degrees of disequilibrium between tethering and closing forces (16). Indeed, patients who develop heart failure from FMR also tend to have a dilated and remodeled LV, which results in PM displacement. The prevalence of LV remodeling and geometric perturbation, global dilatation, and systolic dysfunction increases with the severity of MR and are considered factors involved in worsening of the disease process (17). The extent of LV remodeling is also affected by the direction and severity of vector displacement of the PMs, regional LV dysfunction, and the degree of PM dyssynchrony (7,8,18,19). The development and perpetuation of FMR has been also attributed to reduced MV closing forces. The evidence supporting the role of closing forces in FMR includes the following observations: a reduction of LV contractility and global LV dyssynchrony is prevalent in patients with less than severe FMR, altered mitral annular systolic contraction is observed in patients with moderate leaflet tethering, and PM dyssynchrony persists in patients who received restrictive annuloplasty MV repair (20).

The interplay between reduced MV closing forces, and LV and PM dyssynchrony, has been characterized by: (I) geometrical MV abnormalities in leaflet attachments and tethering that is due to a delayed regional LV mechanical activation; (II) LV dyssynchrony itself may negatively impact systolic function, which further reduces the valvular closing forces; and (III) abnormal atrioventricular relaxation during contraction cycles causes higher left atrial pressure resulting in a positive pressure gradient within the LV chamber, affecting the mechanism of MV closure. Importantly, there is also significant dilatation and flattening of the MV annulus in patients with FMR, as well as a loss of the normal systolic folding and contraction mechanics. These characteristics worsen with disease chronicity, and it is debated as to whether they are a cause or effect of FMR. Classification schemes based on the patterns of MV leaflet tethering and closing force abnormalities, and grading of the severity mitral valvular and subvalvular apparatus dysfunction in FMR have not been established. However, differences in the vectorial displacement of the PMs have been reported, and echocardiography-based studies have identified two types of restricted systolic leaflet motion according to the tethering shape: the asymmetrical pattern with predominant posterior tethering of both leaflets that is most often observed with an inferior/posterior myocardial infarction (*Figure 1*: class 2A and 3A), and the symmetrical pattern with predominant apical tethering seen most commonly with anterior myocardial infarctions (*Figure 1*: class 2S and 3S) (20-23). Our group has successfully reproduced these patterns of FMR utilizing biomechanical models, with the hope that it may facilitate preoperative planning and postoperative management (8). The appearance of one of the two different forms of tethering depends on the relationship between the three tethering vectors observed in FMR: posterior, apical, and lateral (21-23). It is important to note that displacement of one of the PMs exerts a traction and tethering effect on both MV leaflet. In the asymmetric type, the posterior leaflet is moved more posteriorly than apically due to its parallel position in respect to the posterior LV wall. The restriction of the posterior leaflet leads to its malposition with the anterior leaflet, causing them to be in different planes during systole and resulting in asymmetric tethering and an eccentric mitral regurgitant jet (*Figure 1*: class 2A and 3A, *Figure 2*). Conversely, in the symmetrical type there is a combination of apical and medio-lateral vectorial tethering, as well as a more displaced coaptation point. The regurgitant jet is usually located centrally, and its direction reflects the equal involvement of the systolic motion in both leaflets (*Figure 1*: class 2S and 3S, *Figure 3*).

Clinical evidence

The initial diagnosis of FMR is made with the use of transthoracic echocardiography (TTE) (*Figures 2,3*). Although TTE is usually adequate in assessing the geometry of the valvular and subvalvular apparatus of the MV, a precise evaluation of tenting height, anterior-posterior mitral annular diameter, and interpapillary muscle distance (end-systole and end-diastole) measurements may be needed, in which case either a computed tomographic (CT) or magnetic resonance (MRI) imaging may be considered for a comprehensive assessment of the MV pathology. When contraindications to CT or MRI are present, transesophageal echocardiography can be performed. MRI is preferable to CT for serial surveillance,

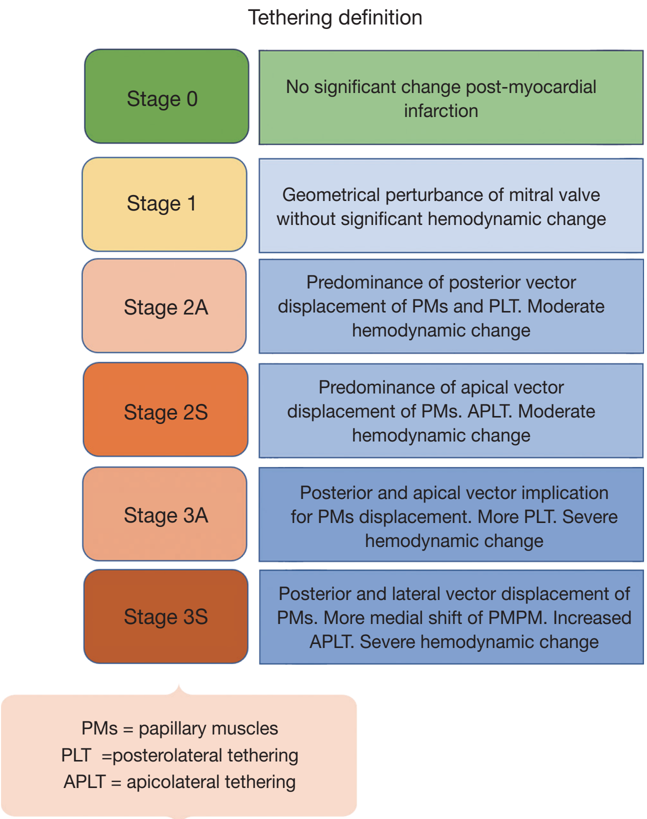

Figure 1 Schematic representation of asymmetric (A) and symmetric (S) pattern of mitral valve tethering. Asymmetric tethering pattern: a posterior vector imparts a posterior (major) and apical (minor) displacement of the posteromedial papillary muscle (PMPM) resulting in asymmetric tethering. Class 0: no Significant modification from immediate myocardial postinfarction. Class 1: geometrical abnormalities of mitral valve without significant hemodynamic change; Class 2A: predominant tenting of posterior leaflet (PL) for posterior (inferior) component of posteromedial tethering. Anterolateral papillary muscle (ALPM) tethering is less implicated and characterized by apical and posterolateral components. Effective regurgitant orifice area (EROA) <0.4 cm^2 with moderate hemodynamic change; Class 3A: more tenting of PL for implication of apical and posterior vector component. EROA ≥0.4 cm^2 with severe hemodynamic change. Symmetric tethering pattern: Predominant apical and lateral vector components. The PMPM and both mitral leaflets are medially displaced, resulting in symmetric leaflet tethering; Class 2S: primarily apical displacement of both papillary muscles (PMs) favors less leaflet tethering. EROA <0.4 cm^2 with moderate hemodynamic change; Class 3S: apical and lateral vector implicated. More medial shift results and increased tethering of both leaflets. EROA ≥0.4 cm^2 with severe hemodynamic change.

since it is not associated with radiation exposure. Yearly echocardiographic surveillance with TTE may be considered in patients with moderate FMR that do not require coronary revascularization, and who do not have an indication for MV surgery (24). If ongoing imaging surveillance, by means of echocardiography, CT, or MRI, reveals increasing MR or LV remodeling, then surgical management may be considered (25,26). In patients who have moderate to severe FMR with significant coronary artery disease, combined revascularization and mitral surgery should be offered (27,28).

If there are concomitant indications for either valvular and/or coronary surgery, then a tailored surgical approach will be required, dictated largely by the ischemic MV pattern, perioperative risk, and surgeon and center experience. In patients with higher degrees of MV leaflet tethering and LV remodeling, the surgical options include MV replacement or repair (29) (*Tables 1,2*). In the latter case, restrictive mitral annuloplasty with procedures to correct subvalvular apparatus alterations has been increasingly advocated (5,6,30-34). *Figure 4* depicts a decisional algorithm in FMR according to the revised American Association for Thoracic Surgery consensus guidelines (29).

Clinical use

The most commonly recommended surgery for patients with moderate or severe FMR are MV repair or chordal-sparing replacement, but a lack of conclusive evidence in favor of one or the other technique has left the choice largely to the surgeon's preference and expertise. Several randomized and observational studies have found that restrictive MV repair is associated with lower perioperative mortality but has high rate of MR recurrence, which is cited at 30% to 60% at mid-term follow-up (1,2). Undersizing valve repair is preferentially performed with closed rings, often with predetermined geometry, compared to partial ring or band. Conversely, replacement provides better long-term correction with a lower risk of MR recurrence and repeat surgery but has higher perioperative morbidity. In a recent meta-analysis was reported a rate of death at 35% higher in the replacement patients than in the repair subjects. This relative long-term risk has been attributed to the fact that patients undergoing mitral-valve replacement tend to be older and have more coexisting illnesses than those undergoing repair (35). When

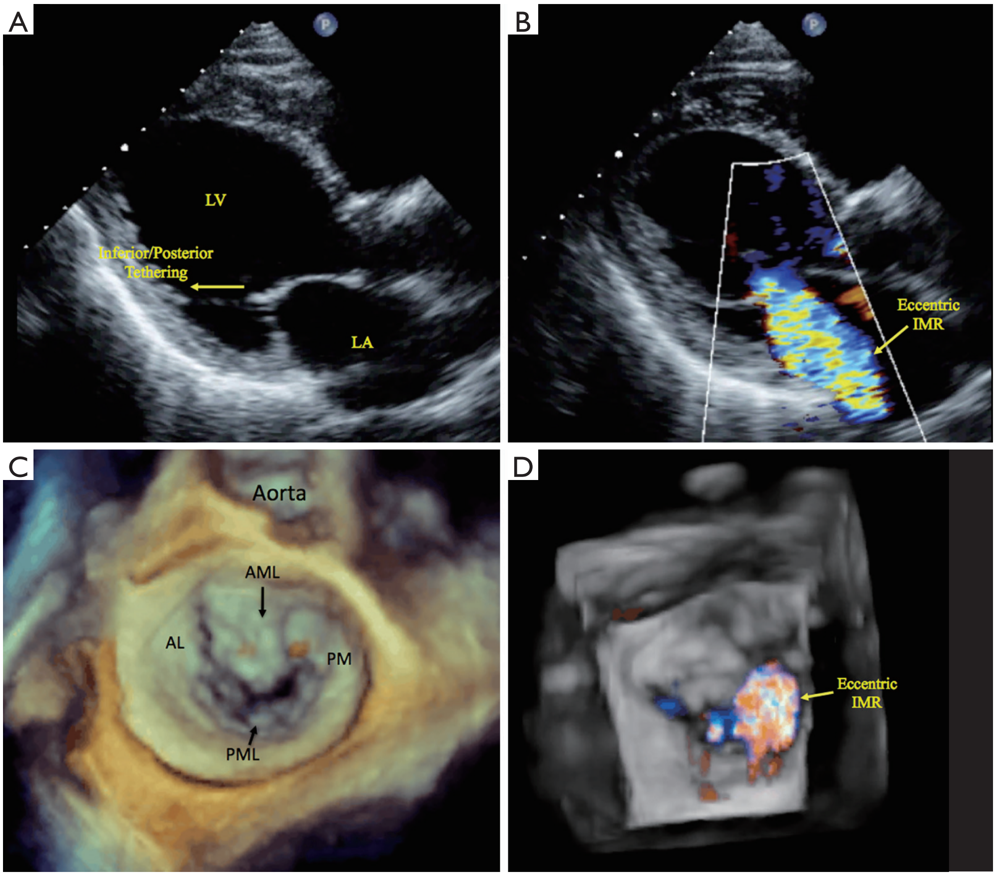

Figure 2 Asymmetric pattern of mitral valve tethering on two- and three-dimensional echocardiography. Asymmetric mitral valve leaflet tethering in the inferior/posterior direction (yellow arrow) results in posteriorly-directed eccentric ischemic mitral regurgitation (IMR) (A,B). En face (surgeon's view) of the mitral valve exemplifies the resultant regurgitant orifice, which is more medially located, and the eccentric MR (C,D). AL, anterolateral commissure; AML, anterior mitral leaflet; IMR, ischemic mitral regurgitation; LA, left atrium; LV, left ventricle; PM, posteromedial commissure; PML, posterior mitral leaflet.

performing replacement of the MV, complete preservation of the subvalvular apparatus is recommended in order to avoid further dilatation of the LV chamber related to post myocardial infarction remodeling and improve peri-operative outcomes. The MV repair technique most commonly performed is a restrictive annuloplasty with the use of a rigid or semirigid ring to downsize the annulus diameter. Combined restrictive annuloplasty and subvalvular procedures directly addressing PM displacement and leaflet tethering have also been successfully performed (5,10,30-34). Procedures involving the PMs require knowledge of their anatomy and blood flow distribution, as well as recognition of the different divisions of PMs and anatomical variants. Two main procedures are performed in this context: PM approximation or "sling", and PM relocation. The PMs anatomically classified as type I and II are approximated using a CV-4 Gore-Tex suture placed at the head of each PM. In type III, IV or V PMs, their approximation is performed with a 4-mm Gore-Tex tube encircling the bodies of each PM, which are then drawn together. In the presence of two independent posteromedial papillary muscle (PMPM) heads, both are included in the approximation to minimize MV tethering. In the relocation technique the PMs are fixed to the annular trigones, with the anterolateral papillary muscle (ALPM) to anterior and PMPM to posterior trigone, respectively. Of note, tethering by the secondary order ("strut") chordae from the ALPM to the anterior leaflet is responsible for the development of the "seagull sign" on echocardiography. The achievement of the target interpapillary distance and the effectiveness of the procedure in resolving MR are confirmed with intraoperative transesophageal echocardiography. Attempts

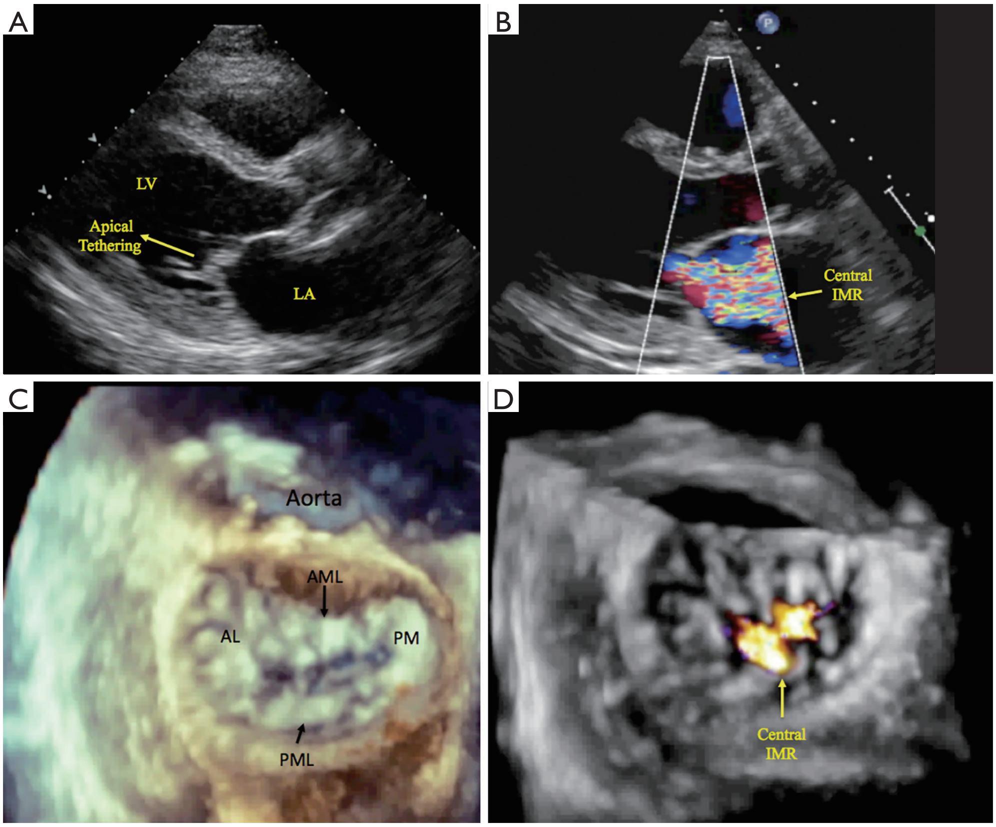

Figure 3 Symmetric pattern of mitral valve tethering on two- and three-dimensional echocardiography. Symmetric mitral valve leaflet tethering in primarily the apical direction results in a central ischemic mitral regurgitant jet (A,B). En face (surgeon's view) of the mitral valve exemplifies a central, crescentic-shaped regurgitant orifice and MR jet (C,D). AL, anterolateral commissure; AML, anterior mitral leaflet; IMR, ischemic mitral regurgitation; LA, left atrium; LV, left ventricle; PM, posteromedial commissure; PML, posterior mitral leaflet.

have been made to achieve the benefits of MV repair or replacement with the use of less invasive methods. Generally, patients undergoing surgery for FMR require concomitant coronary artery revascularization. Hybrid surgical and percutaneous revascularization performed with MV surgery have been reported (36). Additionally, approaches involving percutaneous revascularization in combination with minimally invasive access valve surgery to avoid median sternotomy have been described with encouraging results (37).

Results from randomized controlled trials and observational studies

The results of the Cardiothoracic Surgical Trials Network (CTSN) randomized studies (*Table 1*) advanced the knowledge of the outcomes of surgery for the management of FMR. In one trial, 251 one patients with severe IMR were allocated to receive MV repair with a restrictive annuloplasty or chordal-sparing replacement (1,2). When comparing MV repair versus replacement at 2-year follow-up, there was no difference in the extent of LV reverse remodeling, LV ejection fraction or rate of death (19.0% *vs.* 23.2%). However, patients undergoing MV repair had a significantly higher incidence of recurrent MR (defined as moderate or greater) when compared with replacement (58% *vs.* 3.8%). Chan *et al.*, reported similar findings, in a propensity-matched analysis of 130 patients in which the 5-year actuarial freedom from moderate or greater recurrent MR was 41% for MV repair versus 86% for replacement (38). Interestingly, echocardiographic evidence from the CTSN trial showed that in patients receiving MV repair that did not experience recurrent MR, LV reverse remodeling was significantly improved when compared with those who had recurrence. While analysis of these subgroups was not performed, it is important to note that

Table 1 Studies of mitral valve repair versus replacement and combined coronary artery bypass grafting and valve repair versus coronary artery bypass grafting alone for ischemic mitral regurgitation

Study	N	Age (years)	Male	LV ejection fraction (%)	MR grade/ severity	In-hospital mortality	Follow-up	Study and follow-up outcomes
Randomized-controlled trials								
Goldstein 2016							2 years	CABG performed in 74% MVp and 75% MVR (P=0.8)
MVp	126	69±10	77 (61%)	42±12	0.4±0.17 cm^2 (EROA)	2 (2%)		MVp associated with greater recurrence of moderate-to-severe MR as compared with MVR (58% *vs.* 3.8%; P<0.001)
MVR	125	68±9	78 (62%)	40±11	0.39±0.11 cm^2 (EROA)	5 (4%)		No difference in LV reverse remodeling between groups; however, MVp without recurrent MR associated with significantly smaller LV end-systolic volume index
								2-year survival: 81% MVp *vs.* 77% MVR (P=0.39)
Michler 2016							2 years	CABG performed in all patients
CABG + MVp	151	64±10	106 (71%)	39±11	0.2±0.1 cm^2 (EROA)	10 (7%)		CABG alone associated with greater recurrence of moderate or greater MR as compared with CABG + MVp (32.3% *vs.* 11.2%; P<0.001)
CABG alone	150	65±11	99 (66%)	41±12	0.2±0.1 cm^2 (EROA)	11 (7%)		Improvement in inferior-posterior-lateral wall motion was associated with freedom from recurrent MR
								2-year survival: 90% CABG + MVp *vs.* 89.4% CABG (P=0.78)
Chan 2012							1 year	CABG performed in all patients
CABG + MVp	38	71±11	25 (74%)	40±17	0.21±0.09 cm^2 (EROA)	1 (3%)		CABG + MVp was associated with a 4% recurrence of moderate or greater MR *vs.* 50% in CABG alone (P= N/A)
CABG alone	38	70±8	29 (74%)	40±16	0.18±0.1 cm^2 (EROA)	1 (3%)		CABG + MVp was associated with greater LV reverse remodeling and improved peak oxygen consumption as compared with CABG alone
								1-year survival: 91% CABG + MVp *vs.* 95% CABG (P=0.66)
Fattouch 2009							32±18 months	CABG performed in all patients
CABG + MVp	48	64±9	30 (63%)	42±10	2±0 (grade)	2 (4%)		CABG + MVp was associated no recurrence of moderate or greater MR *vs.* 60% in CABG alone (P= N/A)
CABG	54	66±7	35 (65%)	43±9	2±0 (grade)	1 (2%)		CABG + MVp experiences LV reverse remodeling and improvement in LV ejection fraction at follow-up
								5-year actuarial survival: 94% CABG + MVp *vs.* 89% MVp (P= NS)

Table 1 (*continued*)

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Study	N	Age (years)	Male	LV ejection fraction (%)	MR grade/ severity	In-hospital mortality	Follow-up	Study and follow-up outcomes
Bouchard 2014							1 year	CABG performed in all patients
CABG + MVp	15	N/A	12 (75%)	46±11	0.2±0.03 cm^2 (EROA)	1 (7%)		Freedom from moderate or greater recurrent MR was 85% in both groups.
CABG alone	16	N/A	14 (88%)	42±17	0.23±0.05 cm^2 (EROA)	0 (0%)		No difference in LV reverse remodeling or LV ejection fraction between groups
								1-year survival: 93% CABG + MVp *vs.* 94% CABG alone (P=0.42)
Propensity-matched studies								
ISTIMIR 2013							5 and 8 years	CABG performed in all patients
CABG + MVp	244	67±9	178 (73%)	35±3	2.8±0.5 (grade)	8 (3%)		No difference in LV ejection fraction between groups
CABG + MVR	244	69±10	169 (69%)	35±3	2.8±0.5 (grade)	13 (5%)		8-year actuarial survival: 82% CABG + MVp *vs.* 80% CABG + MVR (P=0.42)
Chan 2011							2.5±2.1 years	CABG performed in 75% MVp and 86% MVR (P=0.1)
MVp	65	63±11	35 (59%)	37±10	N/A	2 (3%)		5-year actuarial freedom from moderate or greater recurrent MR: 41% MVp *vs.* 86% MVR (P=0.04)
MVR	65	62±9	33 (56%)	37±13	N/A	3 (5%)		5-year actuarial survival: 79% MVp *vs.* 61% MVR (P=0.4)
Observational/retrospective studies								
Magne 2009							3.8±3.9 years	CABG performed more often in MVp *vs.* MVR (94% *vs.* 84%; P=0.002)
MVp	186	66±9	128 (69%)	45±15	163 (88%) (severe)	19 (10%)		6-year actuarial survival: 73% MVp *vs.* 67% MVR (P=0.17)
MVR	184	66±10	110 (60%)	40±14	179 (97%) (severe)	31 (17%)		No benefit of MVp for operative or overall mortality in multivariable analyses
Gillinov 2001						63 (13%) (cohort)	3.8±2.4 years	CABG was performed more commonly in the MVp versus MVR group (97% *vs.* 88%; P=0.002)
MVp	397	77% (≥60)	221 (56%)	N/A	397 (100%) (≥ moderate)			Time-related survival rates were 71% at 1 year and 55% at 5 years
MVR	85	84% (≥60)	40 (47%)	N/A	85 (100%) (≥ moderate)			Survival was better with MVp in the lowest quartile risk patients (P=0.003)
								Lack of an internal thoracic artery conduit and a complex MR regurgitant jet attenuated the benefit of MVp

Table 1 (*continued*)

Table 1 (*continued*)

Study	N	Age (years)	Male	LV ejection fraction (%)	MR grade/ severity	In-hospital mortality	Follow-up	Study and follow-up outcomes
Meta-analyses								
Dayan 2014							N/A	44% reduction in the odds of operative mortality with MVp (P=0.001)
MVp	903	62–71	55–74%	27–45	903 (100%) (severe)	N/A		7.5-fold increased risk of moderate or greater recurrent MR with MVp (P<0.001)
MVR	1,605	66–72	47–93%	27–44	1,605 (100%) (severe)	N/A		No difference in left ventricular reverse remodeling, mitral valve reoperation, or survival between groups
Vassileva 2011							N/A	Short-term mortality 2.7 times greater with MVR (P=0.001)
MVp	1,058	61–66	41–74%	29–45	N/A	N/A		35% increase in long-term mortality with MVR (P=0.001)
MVR	678	62–69	47–93%	36–44	N/A	N/A		

Numbers expressed as mean (± standard deviation), mean (range), or number (percentage) as reported in the cited studies. Variables included in the meta-analyses for which individual values were not available to summarize are presented as range. CABG, coronary artery bypass grafting; EROA, effective regurgitant orifice area; LV, left ventricle; MR, mitral regurgitation; MVp, MV repair; MVR, mitral valve replacement; N, number; N/A, not available; ISTIMIR, The Italian Study on the Treatment of Ischemic Mitral Regurgitation; RIME, Randomized Ischemic Mitral Evaluation trial.

late freedom from recurrent MR after MV repair for IMR is approximately 90% in LV reverse remodeling “responders”, which is defined as a reduction in the LV end-systolic volume index >15%. A second CTSN randomized trial evaluated 301 patients with moderate FMR, comparing those who received coronary artery bypass grafting (CABG) alone with patients who underwent combined CABG plus MV repair with a restrictive annuloplasty (3,4). While patients undergoing combined CABG plus MV repair had significantly less recurrent MR than CABG alone at 2-year follow-up (11.2% *vs.* 32.3%), there was no difference in LV reverse remodeling or rate of death (10% *vs.* 10.6%) and an increased incidence of adverse neurologic events (5.5% *vs.* 1.7%) and supraventricular arrhythmias. Similar outcomes were reported in three smaller randomized studies, including the RIME (Randomized Ischemic Mitral Evaluation) trial, in which combined CABG plus MV repair resulted in less recurrence of MR when compared with CABG alone at early to mid-term follow-up (0–15% *vs.* 15–60%) (39). However, this did not translate into a benefit in clinical outcomes. Finally, long-term follow-up data at 8 years from the ISTIMIR (The Italian Study on the Treatment of Ischemic Mitral Regurgitation) propensity-matched study found similar LV function and survival between a strategy of CABG plus MV repair versus CABG alone (40). Important limitations to the data regarding the efficacy of MV repair in FMR are centered on valvular anatomy and the technical aspects of the repair itself. Firstly, a restrictive annuloplasty addresses annular dilatation as the sole mechanism of FMR, when in fact the underlying substrate is LV dilatation and dysfunction leading to PM displacement and leaflet tethering. Indeed, the annular size may exceed more than 1.5 times its normal dimension prior to the development of FMR. Secondly, with a restrictive annuloplasty the fibrous posterior annulus is displaced anteriorly, which increases the annulo-papillary muscle distance and further tethers and restricts posterior mitral leaflet motion. Increased myocardial stress is also observed in the lateral LV wall, and these factors contribute to the high MR recurrence rates observed with MV repair. Thirdly, the hemodynamic MR burden may have been underestimated in these studies. An effective regurgitant orifice area of 0.2 cm^2 has been associated with increased mortality in patients with FMR, and this cutoff was exceeded in most of the trials, particularly in the severe FMR CTSN trial where it measured approximately 0.4 cm^2 in both the repair and replacement groups. Finally, the sample sizes limited the statistical power to evaluate the

Table 2 Studies of combined mitral valve repair plus papillary muscle intervention versus mitral valve repair alone for ischemic mitral regurgitation

Study	N	Age (years)	Male	LV ejection fraction (%)	MR grade/ severity	In-hospital mortality	Follow-up	Study and follow-up outcomes
Randomized-controlled trials								
Nappi 2016							5 years	All patients underwent concomitant CABG
MVp + PMA	48	63±7	28 (58%)	35±5.3	48 (100%) (≥3+)	3 (6%)		MVp + PMA associated with less recurrence of moderate-to-severe MR as compared with Ring (29% *vs.* 56%; P=0.01)
MVp	48	65±7	30 (63%)	36.7±3.7	48 (100%) (≥3+)	4 (8%)		Greater LV reverse remodeling, improved LV ejection fraction, and improved mitral valve geometry observed with MVp + PMA
								5-year survival: 77% MVp + PMA *vs.* 71% MVp (P=0.64)
Propensity-matched studies								
Langer 2009								All patients underwent concomitant CABG
MVp + PMR	30	68±11	19 (63%)	37±14	3 [3–4] (grade)	2 (7%)	26 [5–48] months	MVp + PMR associated with less recurrence of moderate or greater MR as compared with MVp (6% *vs.* 29%; P=0.01)
MVp	30	70±6	20 (67%)	41±15	3 [3–4] (grade)	4 (13%)	69 [23–82] months	Greater LV reverse remodeling observed with MVp + PMR
								2-year survival: 89% MVp + PMR *vs.* 73% MVp (P=0.13)
Fattouch 2012							42±12 months	All patients underwent concomitant CABG
MVp + PMR	69	63±11	39 (57%)	43±8	69 (100%) (EROA ≥0.2 cm^2)	3 (4%)		MVp + PMR associated with less recurrence of moderate or greater MR as compared with MVp (3% *vs.* 12%; P=0.02)
MVp	69	62±9	41 (59%)	43±5	69 (100%) (EROA ≥0.2 cm^2)	4 (6%)		Greater LV reverse remodeling and improved mitral valve geometry observed with MVp + PMR
								5-year freedom from cardiac-related event: 83% MVp + PMR *vs.* 65% MVp (P<0.001)
Mihos 2016							10.1 [0.25–42][a] months	Note: 38% of MVp + PMA had NICMP; CABG performed in 59% of MVp, with prior revascularization in all for both groups
MVp + PMA	34	64±11	31 (91%)	29±7	3.7±0.4 (grade)	2 (6%)		MVp + PMA associated with less recurrence of moderate or greater MR as compared with MVp (15% *vs.* 35%; P<0.001)
MVp	17	66±11	15 (88%)	30±7	3.4±0.8 (grade)	2 (12%)		Improved mitral valve geometry observed with RA + PMA
								3-year survival: 87% MVp + PMA *vs.* 82% MVp (P=0.49)

Table 2 (*continued*)

Table 2 (*continued*)

Study	N	Age (years)	Male	LV ejection fraction (%)	MR grade/ severity	In-hospital mortality	Follow-up	Study and follow-up outcomes
Calafiore 2014							33±15 months	All patients underwent concomitant CABG
MVp + CC	26	61±9	17 (65%)	31±5	3.6±0.6 (grade)	N/A		MVp + CC associated with a smaller MR grade as compared with MVp (0.6±0.6 *vs.* 1.1±0.8; P=0.014)
MVp	26	62±10	18 (69%)	29±8	3.3±0.8 (grade)	N/A		Greater LV ejection fraction and reverse remodeling, and improved New York Heart Association functional class observed with MVp + CC
Observational/retrospective studies								
Borger 2007							2 years	92% of patients in both groups underwent concomitant CABG
MVp + CC	43	66±8	27 (62%)	33±11	2.8±0.8 (grade)	4 (9%)		MVp + CC associated with less recurrence of moderate or greater MR as compared with MVp (15% *vs.* 37%; P=0.04) No difference in LV reverse remodeling between groups
MVp	49	63±8	35 (71%)	44±15	3.0±0.9 (grade)	5 (10%)		2-year survival: 82% MVp + CC *vs.* 79% MVp (P=0.09)
Roshanali 2013							41±13 months	All patients underwent concomitant CABG
MVp + PMA	31	48±12	17 (55%)	28±3	3.7±0.5 (grade)	2 (6%)		MVp + PMA associated with a smaller MR grade (1.3±0.7 *vs.* 1.6±1.1; P=0.06) and a lower LV ejection fraction (32%±4% *vs.* 33%±4%; P=0.05) as compared with MVp
MVp	69	47±15	44 (64%)	29±3	3.8±0.4 (grade)	2 (3%)		No difference in the recurrence rate of moderate or greater MR, LV reverse remodeling, or New York Heart Association functional class between groups
Meta-analyses								
Mihos 2017							10.1–69 months	Included only randomized controlled and propensity-matched studies
MVp + PMi[b]	207	61–68	57–91%	29–43	≥ moderate	4–6%		MVp + PMi associated with 57% reduced risk of recurrent MR (P=0.0002)
MVp	190	62–70	59–88%	29–43	≥ moderate	6–13%		Greater LV reverse remodeling, and improved LV ejection fraction, and mitral valve geometry observed with MVp + PMA

Numbers expressed as mean (± standard deviation), median (interquartile range), or number (percentage) as reported in the cited studies. Variables included in the meta-analyses for which individual values were not available to summarize are presented as range. [a], follow-up is presented as mean and range; [b], PMi included papillary muscle approximation or relocation, or secondary order chordal cutting. All patients underwent concomitant CABG, except for the study by Mihos *et al.* (see text). CABG, coronary artery bypass grafting; CC, secondary order chordal cutting; EROA, effective regurgitant orifice area; LV, left ventricle; MR, mitral regurgitation; MVp, mitral valve repair; N, number; NICMP, non-ischemic cardiomyopathy; PMA, papillary muscle approximation; PMi, papillary muscle intervention; PMR, papillary muscle relocation.

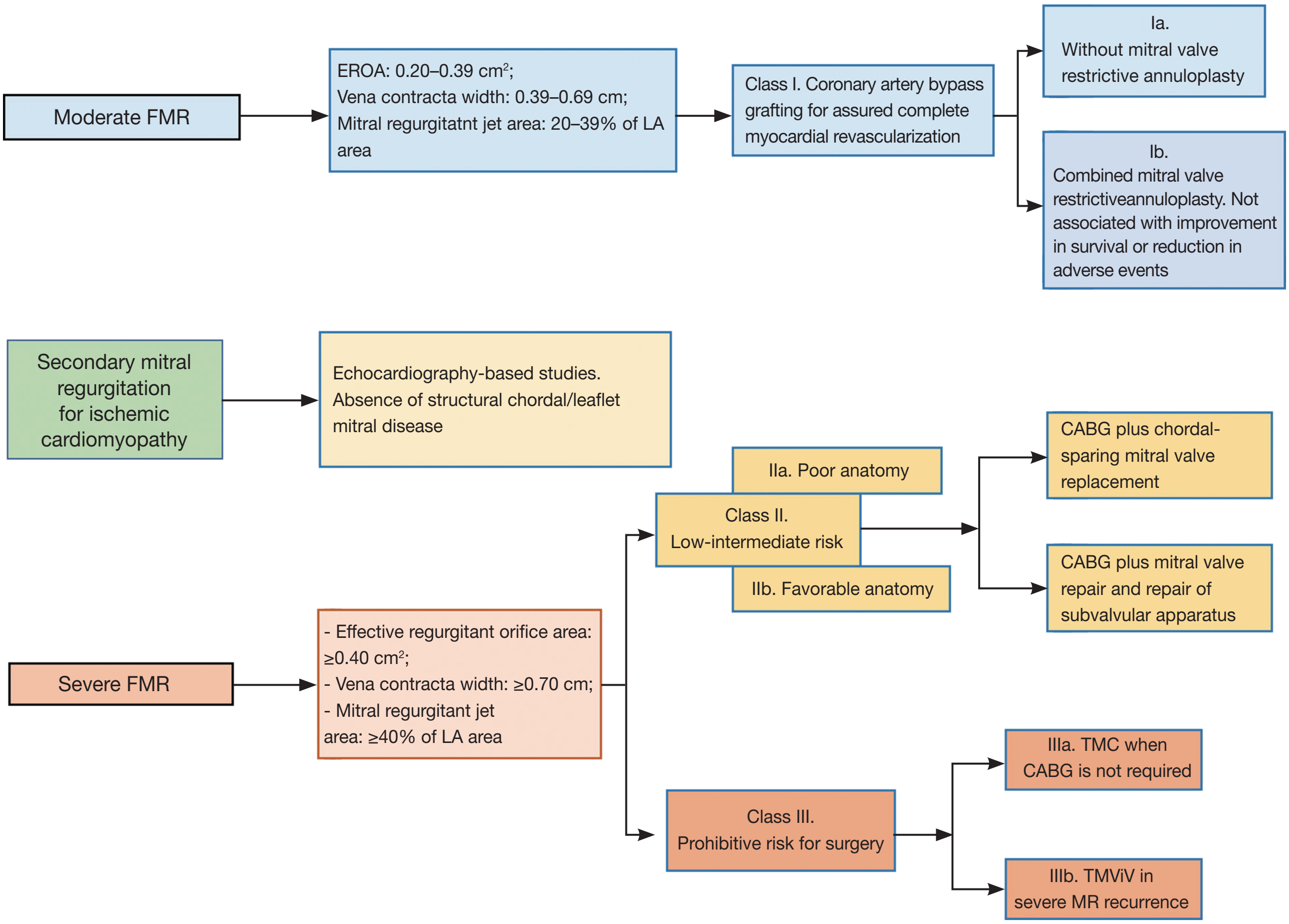

Figure 4 Decision-making algorithm in FMR. A flow chart for the management of this condition and indications for surgery is depicted. On the basis of the updated 2017 AATS AHA/ACC focused update of the 2014 AHA/ACC guideline for the Management of Patients with Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. FMR, functional mitral regurgitation; EROA, effective regurgitation orifice area; LA, left atrium; CAGG, coronary artery bypass grafting; TMC, transcatheter mitraClip; TMViV, transcatheter mitral valve in valve; MR, mitral regurgitation.

effects of surgical strategy on mortality, with reliance on surrogate clinical and echocardiographic endpoints.

The major clinical trial comparing MV repair versus replacement was limited because it involved a consistent number of patients who did not received CABG (26.2%) (2) and patients who underwent mitral-valve replacement tended to be older as reported by Milano *et al.* (41). The majority of the currently available randomized controlled or not-randomized evidences on IMR are based on small sample sizes and concomitant CABG procedures, the only interventions actually able to provide the necessary improvement of regional and global LV function to correct IMR, are not equally distributed among the subgroups. Despite the American College of Cardiology/American Heart Association and European Society of Cardiology/European Association for Cardiothoracic Surgery guidelines have been recommending surgical treatment of severe IMR for a long time, the debate still cannot reach a standing point as differences in the baseline characteristics of the patients harness the statistical power of the results. Indeed, it has been more than 40 years since the first FMR papers were published and now more than 50 papers are added each year under the key words “Surgery of Moderate or Severe IMR”. Despite this abundant and growing body of literature, particular risk factors that are unknown or unmeasured cannot adjust for the differences in baseline.

Therefore, some studies have shown no differences in short- and long-term outcomes between repair and replacement groups, although the majority of studies favoring repair as emerged in work of Thourani *et al.* and Micovic *et al.* (42,43).

Results from randomized controlled trials and propensity score analysis: MV repair versus combined valvular and subvalvular repair

First described by Hvass, Kron and Rama and colleagues, a combined MV and subvalvular repair for FMR has been utilized with the aim of improving repair durability and decreasing the incidence of recurrent MR (5,18, 30-33,44-46). Fattouch *et al.* reported the clinical and echocardiographic outcomes of PM relocation combined with MV repair using a non-restrictive mitral annuloplasty in a propensity-matched analysis of 138 patients with severe FMR (33). PM relocation plus MV repair was associated with a significantly smaller LV end-diastolic diameter, less recurrence of MR (3% *vs.* 12%), and a considerable improvement in MV geometry, when compared with MV repair alone at 42-month follow-up (47). Similar outcomes with combined PM relocation and MV repair for severe FMR were reported in a 60-patient propensity-matched study by Langer *et al.* (48), in which recurrent MR was observed in 6% of the combined PM relocation and MV repair patients *vs.* 29% of the MV repair alone group at mid-term follow-up (*Table 2*). In the only randomized trial evaluating the efficacy of subvalvular intervention in FMR, Nappi *et al.*, allocated 96 patients to receive either MV repair with a restrictive annuloplasty alone or in combination with PM approximation. At 5-year follow-up, PM approximation in addition to MV repair resulted in a significantly smaller LV end-diastolic diameter, a greater LV ejection fraction, less recurrence of MR (27.9% *vs.* 55%), and improved MV geometry, with a similar survival rate (77.1% *vs.* 70.8%) when compared with MV repair alone (5,6). A multi-center propensity matched analysis of MV repair versus combined MV repair and PM approximation in the setting of ischemic or non-ischemic cardiomyopathy also revealed a lower prevalence of recurrent MR (15% *vs.* 35%) and improved MV geometry at early follow-up with the addition of PM approximation, with no difference observed between the types of cardiomyopathic substrate (49). Finally, a 2017 meta-analysis of five studies, which included 397 patients undergoing MV repair alone versus in combination with a subvalvular intervention, suggested the superiority of a combined valvular and subvalvular repair with regards to reduced risk of recurrent moderate or greater MR, MV geometry, and LV reverse remodeling (10). A subanalysis of the randomized trial by Nappi *et al.*, demonstrated that PM approximation was beneficial in both symmetrical and asymmetrical tethering patterns of FMR by primarily correcting the posterior and lateral displacement of the PMs. PM approximation improved LV remodeling and MR recurrence rate in both tethering subgroups, but was also associated with a reduced risk of MV reoperation in patients with symmetric tethering, when compared with MV repair alone (0% *vs.* 16.7%) (6). These data are in accord with studies from Gelsomino *et al.*, which highlighted that symmetric tethering is a negative predictor of LV reverse remodeling after annuloplasty MV repair, and that this condition requires a more comprehensive intervention to restore LV and subvalvular geometry (20,23,50-52). As performed in the trial, it is proposed that a 30% reduction in the interpapillary muscle distance by the approximation is sufficient to restore an adequate LV geometry and favorable redistribution of forces within the valvular and subvalvular apparatus. The reinforcement of the posterior annulus by means of a double row of overlapping sutures may also be beneficial to reduce the tension on the portion of the annulus experiencing the greatest stress (53,54). As stated earlier, the small sample sizes are important limitations in the studies of combined MV and subvalvular repair, owing in part to the difficulty in recruitment and randomization of patients with specific MV geometric or subvalvular apparatus abnormalities. Furthermore, most of the studies included a relatively heterogeneous population in terms of tethering pattern, regional wall motion abnormalities, and extent of coronary artery disease. Tethering and wall motion abnormality characteristics have important implications the selection of the PM intervention performed. For example, while the dysfunction and posterior PM displacement associated with an inferior wall myocardial infarction can be corrected by PM approximation, an overwhelming lateral displacement secondary to an anterior or lateral wall myocardial infarction may not be compensated by this approach, and these patients may be better suited with PM relocation stabilizing the PMs with fixation to the mitral trigones. Finally, the utilization of pre-operative echocardiography may help in identifying patients at high risk of MV repair failure, in whom the addition of a subvalvular intervention or performance of chordal-sparing replacement may be warranted. Several echocardiographic parameters reflecting the extent of MV tethering and LV geometric distortion and remodeling have been described, and are presented in *Figure 1* (55,56).

IMR and coronary artery disease

Complete myocardial revascularization via concomitant CABG or staged percutaneous coronary intervention is an important and necessary step in the management of FMR In regards to surgical revascularization, the performance of CABG or CABG plus MV surgery are associated with a 44% and 31% reduction in long-term mortality, respectively, when compared with medical therapy alone (57).

The importance of myocardial revascularization and improvement in regional wall motion was also highlighted in the CTSN moderate IMR trial. It was shown that the percent improvement in global and in posterior-inferior-lateral wall motion was greater in patients who did not experience recurrent MR after CABG or CABG plus MV repair as compared with those who did have recurrent MR (3,4,58,59). Importantly, in patients with severe FMR and advanced post-ischemic LV remodeling, non-viable infarcted myocardium or PM dyssynchrony, coronary revascularization alone is typically insufficient to correct FMR, and concomitant chordal-sparing replacement or reparative strategies addressing both the annular and subvalvular components of the MV apparatus should be considered.

Unanswered questions and future directions

FMR is a complex pathological entity characterized by the presence of concomitant and interconnected abnormalities of the MV, subvalvular apparatus, and LV structure and function. A "holistic" approach to comprehensively address each of the components is required. For this purpose, a full understanding of the pathological changes and mechanisms of dysfunction is crucial. This way can satisfy a better understanding of the role of transcatheter MV therapy for treatment of ischemic versus degenerative cardiomyopathy in patients at prohibitive risk surgery. These evaluations are necessary without prejudice to the progressive affirmation of the transcatheter procedure for MV pathologies that is suitable in high risk patients with severe MR (60). Mathematical modeling of the MV along with the intriguing insight provided by finite element analysis aims to enable precise mapping of the pathogenesis of FMR in individual patients, and to analyze the potential changes induced by the application of different operative techniques (61). Questions regarding the indications and timing of MV intervention, the best suitable operative technique to be applied, and in cases of PM handling, the extent of the geometrical correction needed (48), still remain unanswered. Surely, *in vitro* and *in silico* studies may provide further insight; however, larger randomized clinical trials and targeted subgroup analyses with significant sample sizes are warranted in order on outcomes prediction and to enhance the comprehensive engineering and mathematical modeling of this disease.

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Footnote

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