Update on surgical repair in functional mitral valve regurgitation.

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Abstract

Background: Functional mitral regurgitation (FMR) is common in patients with myocardial infarction or dilated cardiomyopathies, and portends a poor prognosis despite guideline-directed medical therapy. Surgical or transcatheter mitral repair for FMR from recent randomized clinical trials showed disappointing or conflicting results. Aims: To provide an update on the role of surgical repair in the management of FMR. Materials & Methods: A literature search was conducted utilizing PubMed, Ovid, Web of Science, Embase and Cochrane Library. The search terms included secondary/functional mitral regurgitation, ischemic mitral regurgitation, mitral repair, mitral replacement, mitral annuloplasty, transcatheter mitral repair, and percutaneous mitral repair. Randomized clinical trials over the past decade were the particular focus of this current review. Results: Recent data underlined the complexity and poor prognosis of FMR. Guideline-directed medical therapy and cardiac resynchronization, when indicated, should always be applied. Accurate assessment of the interplay between ventricular geometry and mitral valve function is essential to differentiate proportionate FMR from the disproportionate subgroup, which could be helpful in selecting appropriate transcatheter intervention strategies. Surgical repair, most commonly performed with an undersized ring annuloplasty, remains controversial. Adjunctive valvular or subvalvular repair techniques are evolving and may produce improved results in selected FMR patients. Conclusion: FMR resulted from complex valve-ventricular interaction and remodeling. Distinguishing proportionate FMR from disproportionate FMR is important in exploring their underlying mechanisms and to guide medical treatment with surgical or transcatheter interventions. Further studies are warranted to confirm the clinical benefit of appropriate surgical repair in selected FMR patients.

Update on Surgical Repair in Functional Mitral Regurgitation

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ABSTRACT

Background: Functional mitral regurgitation (FMR) is common in patients with myocardial infarction or dilated cardiomyopathies, and portends a poor prognosis despite guideline-directed medical therapy. Surgical or transcatheter mitral repair for FMR from recent randomized clinical trials showed disappointing or conflicting results.

Aims: To provide an update on the role of surgical repair in the management of FMR.

Materials & Methods: A literature search was conducted utilizing PubMed, Ovid, Web of Science, Embase and Cochrane Library. The search terms included secondary/functional mitral regurgitation, ischemic mitral regurgitation, mitral repair, mitral replacement, mitral annuloplasty, transcatheter mitral repair, and percutaneous mitral repair. Randomized clinical trials over the past decade were the particular focus of this current review.

Results: Recent data underlined the complexity and poor prognosis of FMR. Guideline-directed medical therapy and cardiac resynchronization, when indicated, should always be applied. Accurate assessment of the interplay between ventricular geometry and mitral valve function is essential to differentiate proportionate FMR from the disproportionate subgroup, which could be helpful in selecting appropriate transcatheter intervention strategies. Surgical repair, most commonly performed with an undersized ring annuloplasty, remains controversial. Adjunctive valvular or subvalvular repair techniques are evolving and may produce improved results in selected FMR patients.

Conclusion: FMR resulted from complex valve-ventricular interaction and remodeling. Distinguishing proportionate FMR from disproportionate FMR is important in exploring their underlying mechanisms and to guide medical treatment with surgical or transcatheter interventions. Further studies are warranted to confirm the clinical benefit of appropriate surgical repair in selected FMR patients.

K EYWORDS

Functional mitral regurgitation, secondary mitral regurgitation; mitral repair, valve surgery

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Introduction

Functional (or secondary) mitral regurgitation (FMR) traditionally refers to the incompetency of a structurally normal mitral valve (MV) that derives from geometrical or electrical abnormalities of the left cardiac chambers, displacement of papillary muscles (PM), leaflet tethering (Carpentier type IIIb), and annular dilatation (Carpentier type I). [1,2] Unlike primary mitral regurgitation (MR), wherein components of the leaflets or apparatus are the source of the disease, FMR is more common and hemodynamically significant in patients after acute myocardial infarction (AMI) and in patients with all subgroups of systolic heart failure (HF)–be it with preserved, mid-range, or reduced ejection fraction (EF).[1-5] This prevalence is expected

to rise exponentially over the next few decades due to the aging population and the increasing survival of patients with ischemic heart disease or HF.[2-4]

Despite this prevalence and the consensus that FMR portends poor prognosis, only 5-22% of patients with isolated FMR undergo interventional treatment,[5,6] and the optimal choice of treatment for FMR remains controversial within the cardiology and cardiac surgery community.[7-9] Firstly, a large proportion of these FMR patients have multiple comorbidities and increased operative risks, with about 40-50% of patients responding favorably to guideline-directed medical therapy (GDMT) or cardiac resynchronization therapy (CRT) alone.[2,3,5] Secondly, although surgical or transcatheter interventions targeting MV may improve symptoms and quality of life, a substantial mortality benefit has not been demonstrated.[10-16] Thirdly, for surgical candidates with FMR, MV repair (usually with a down-sized annuloplasty ring) that enhances leaflet coaptation and preserves sub-annular apparatus has long been the preferred approach, this approach nevertheless has failed to achieve pre-specified benefits on cardiac geometry and long-term MV competency due in part to ongoing leaflet tethering caused by continued left ventricle (LV) remodeling, in spite of annular size reduction. Although mitral replacement could provide durable FMR correction results, it makes little sense to routinely replace "structurally normal" valves with artificial prostheses.[17] Accordingly, the questions that have befuddled cardiac surgeons are: (1) If FMR is the consequence of LV dilatation and dysfunction, can surgical interventions that target the MV still be effective in certain patients? (2) How to select the right patients that would authentically benefit from surgical repair? and (3) What are the optimal surgical repairing techniques for these FMR patients?

Presenting an update of several recent studies on pathophysiology and mechanical interventions of FMR, this article aims to deepen our understandings of surgical strategies and outcomes of this challenging entity, and to provide insights in guiding the most appropriate surgical strategies for selective patients.

Epidemiology and prognostic impact of FMR

FMR is one of the most common valvular diseases in the developed world, with an incidence in the United States estimated less than 1% before age 55 years but rising to 9.3% in those greater than 75 years of age.[18] Moreover, approximately 20-35% of patients after AMI have ischemic MR (IMR) that is considered to be clinically meaningful, and in up to 50% in patients with HF of either ischemic (>70% cases) or non-ischemic origin.[2-6]The prevalence of symptomatic HF is estimated to range from 1-2% in the general European population.[19] Moderate/severe MR is common after HF and AMI, which was reported in 16-43% of patients.[20-23] In China, 4 million people had been estimated to be living with HF and by 2030 the country is estimated to have over 23 million patients with AMIs each year (nearly 3 times as many as those in 2010).[24-26] In HF and AMI cohorts, moderate or severe FMR affects up to 30% of patients.[25,26] Given an aging population and lifestyle changes that are associated with increases in hypertension, body mass index, and metabolic syndrome, combined with improved survival of patients with coronary artery disease, the burden of FMR is expected to increase substantially in China.[27]

Closely related to poor prognosis, FMR is an independent predictor of mortality with more than 2.5 times higher than that of community patients.[6] In patients with ischemic cardiomyopathy, the presence of MR of any grade results in worse long-term prognosis while severe IMR is even an indicator of short-term mortality. In a retrospective study of 4005 ST-segment elevation myocardial infarction (STEMI) patients in the United States, 9.5% of them presented with moderate/severe FMR. The 1-year mortality rates of moderate, moderate-severe, and severe FMR were 20.8%, 37.4%, and 37.1%, respectively.[28] In another hospital-based cohort in Japan, among a total of 1701 symptomatic HF patients while 104 FMR patients (who had moderate to severe FMR) and 1597 non-FMR patients (who had no or mild FMR) were compared, Kaplan–Meier curves and Cox regression analysis revealed that significant FMR was associated with higher incidence of all-cause death, cardiovascular death, and repeated admissions for HF.[29] An effective regurgitant orifice area (EROA) >20 mm^2 has also been shown to be a predictor of adverse outcomes in patients with FMR. In an observational study in Europe, 138 adult patients were subjected to echocardiography evaluation after AMI whereas moderate/severe MR was found in 70% of patients.[30] Five-year mortality in patients with moderate/severe FMR were higher than that in those with mild FMR, while mortality in patients with

EROA[?]20 $mm^2$was also higher than that in those with EROA <20 mm^2.[30] In another multivariable analysis that included parameters such as LV volume, LV ejection fraction (LVEF), renal function, etc., FMR was an independent predictor of adverse prognosis.[9]

Pathophysiology of FMR: an evolving conceptual framework

The long-held view that MR could be distinguishingly classified as primary or secondary according to the underlying pathophysiology is important for decision-making in treatment.[18] MR is considered as "primary" (also known as organic) when principally due to a structural or degenerative abnormality of the mitral leaflets, annulus, chordae tendineae and PMs.[37] The adverse remodeling of the ventricle is the consequence of valve dysfunction, and patients with primary MR would benefit from MV repair or replacement.[37] In contrast, patients with FMR have largely normal mitral leaflets and regurgitation occurs as a consequence of left cardiac chambers remodeling and dysfunction. Regional MI or global LV remodeling and dysfunction (caused by hypertension or dilated cardiomyopathy) may lead to apical and/or lateral PM displacement that results in leaflets tethering and reduced closing forces, annulus dilation and flattening, and loss of leaflet coaptation.[38] Occasionally, patients with global LV systolic dysfunction may have left bundle branch block, which can further exacerbate regurgitation due to dyssynchronous PMs contraction.[39] Consequently, the management of FMR has largely focused on the restoration of LV structure and function with neurohormonal antagonists and resynchronization devices, and surgical MV intervention is generally reserved as the final option.[40]

The conceptual outline that is traditionally utilized to characterize MR overlooks the fact that the maintenance of a competent MV requires dynamic and complex interactions among the leaflets and the entire apparatus, which include the annulus, chordae, PMs, and the function and loading condition of segmental or global ventricular muscles that support normal leaflet coaptation.[15] Therefore, a restricted focus on static anatomy and the sequence of events over time (original lesions of MV or LV that initiated the disease process) may not provide a sufficient framework for selecting the optimal management, and the distinction between "primary" and "secondary" MR can be blurred in many clinical scenarios: 1) during the decompensated phase of primary MR, LV dilatation and dysfunction could contribute to progressive MR via secondary mechanisms; 2) in the setting of global LV dysfunction without left bundle branch block, some patients with non-ischemic cardiomyopathy have selective delayed activation of one PM (e.g., the anterolateral insertion), and others presenting with PM dysfunction or even rupture due to posteromedial or inferior MI. In these circumstances, asymmetrical tethering or significant prolapse of a single leaflet could lead to severe MR that could be corrected by surgical interventions – a response that can be clinically identical to primary MR, even though the MR is secondary to structural alterations of the LV.[15,16,41]

Current technological advances have greatly enhanced the ability to characterize the dynamics of MR, allowing quantitative estimation of regurgitant volume (RVol) as well as the EROA.[42,43] By interpreting the relationship of EROA and the estimated LV end-diastolic volume (LVEDV) based on the Gorlin hydraulic orifice equation, some investigators have proposed a novel conceptual framework that classifies patients with FMR according to the causal mechanism rather than the severity of the regurgitant lesion and thus identifies patients in whom MR is a direct factor in the disease process among patients with LV dilatation and dysfunction.[37-39] For instance, in patients with primary MR or FMR that occurs as a result of regional LV dysfunction/remodeling, severe degrees of MR are usually accompanied by only modest increases in LVEDV, and the magnitude of MR would greatly exceed that predicted by LV volumes (disproportionate MR). In contrast, in patients with FMR that occurs entirely due to global LV dilatation, the severity of MR is proportional to the amount of LV dilatation. This principle may be of great value in selecting optimal treatment since "proportionate" FMR may respond favorably to GDMT aimed at reducing LVEDV (neurohormonal antagonists), while "disproportionate" FMR may benefit selectively from interventions that are directed toward the improvement of leaflet coaptation (cardiac resynchronization therapy or mechanical interventions). Serendipitously, the validity of this novel concept of proportionate and disproportionate MR appears to have been inadvertently tested in 2 recently completed randomized controlled trials (RCTs) of transcatheter mitral valve repair (TMVr) in patients with FMR.[15,16,37-39]

Mechanical intervention of FMR: the game changers

Although long-term outcomes of surgical repair for primary MR have been excellent, treatment for FMR with valve repair or replacement has produced less favorable results. Both US and European guidelines currently recommend medical therapy as the initial strategy and mainstay of FMR management with CRT and revascularization as appropriate.[7-9] In the 2017 American College of Cardiology/American Heart Association (ACC/AHA) valvular guidelines, the biggest change was a new recommendation that "it is reasonable to choose chordal-sparing MV replacement over downsized annuloplasty repair if an operation is considered for severely symptomatic patients (New York Heart Association (NYHA) class III-IV) with chronic severe ischemic MR (stage D) and persistent symptoms despite GDMT".[8]This was based on remarkable findings of a cardiothoracic surgical trials network (CTSN) multicenter RCT showing that the recurrence rate of moderate-to-severe MR over 1 and 2 years was significantly higher in the restrictive annuloplasty repair group than in the replacement group, associated with a higher incidence of HF and rehospitalization.[11,12] In addition, the recommendation for MV repair in patients with chronic, moderate ischemic MR undergoing coronary artery bypass grafting (CABG) changed from "may be considered" to "usefulness of MV repair is uncertain" (2b, Level B-R).[8] This modification was largely based on another CTSN study demonstrating that the addition of restrictive MV annuloplasty to CABG did not add any survival benefit or reduce overall adverse events or readmissions.[13,14] A superficial interpretation of these two CTSN trials favors replacement in patients with severe FMR. For moderate FMR, leaving it alone at the time of CABG seems to be reasonable.

The reality of the poor prognosis despite rigorous GDMT (and CRT when indicated) and the high proportion of advanced HF patients who are too risky or unsuitable for conventional surgery have stimulated rapid development of less-invasive transcatheter technologies. Currently, the most widely used TMVr device is the MitraClip (Abbott Vascular, Santa Clara, California). This transcatheter intervention produces an edge-to-edge leaflet coaptation and creates a double-orifice MV.[44] The efficacy and safety of Mitraclip for moderate-to-severe FMR were evaluated in 2 large RCTs: MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) and COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy).[15,16] Both trials randomized patients to MitraClip along with GDMT vs. GDMT alone. The MITRA-FR trial found no differences in a composite of death from any cause and readmissions for HF at 1 year, while the COAPT trial found a significant reduction in hospital readmissions for HF at 2 years and overall mortality. On the basis of the results of the COAPT trial, the FDA approved the MitraClip for the treatment of FMR in patients with HF who remain symptomatic despite GDMT.[9] Consequently, new changes have been made in the most recently published "2020 Focused update of the 2017 ACC expert consensus decision pathway on the management of mitral regurgitation",[9] which supported the consideration of TMVr in the management of FMR.

However, the strikingly opposed findings across the 2 MitraClip RCTs, which used precisely the same device to reduce MR, have generated intense debate because these results cannot be simply explained by differences in trial design, length of follow-up, or statistical power.[37] Intriguingly, an examination of the baseline characteristics of the patients participating in the 2 trials indicated that the studies included 2 distinctly different populations of patients with FMR.[45,46] Patients enrolled in the COAPT trial had more severe FMR (EROA $41mm^2$ vs. $31mm^2$; RVol 60ml vs. 45ml) and less dilated ventricles (LVEDV index $101ml/m^2$ vs. $135ml/m^2$) than those in the MITRA-FR trial. According to the concepts of proportionate and disproportionate MR, it is evident that the patients in the MITRA-FR trial represent a population in which the MR is proportional to the ventricular dilatation and is a consequence, not a cause, of the ventricular disease. Therefore, these patients would generally respond favorably with an improved prognosis when treated with GDMT aiming at reducing the ventricular volume. In contrast, the patients in the COAPT trial had disproportionate degrees of FMR, with higher RVol for smaller ventricles, in which proper functioning of the MV apparatus is disproportionately undermined, leading to severe MR that cannot be explained by the degree of LV enlargement. These patients would be ideal candidates for mechanical interventions aimed at correcting the MR.[37-39]

Hence, the outcomes of recent surgical and transcatheter RCTs emphasized the importance of patient selec-

tion and, taken together, have delineated the beneficial role of MV intervention in FMR patients who have disproportionate regurgitation despite GDMT (or CRT when indicated). Concurrently, the effectiveness of MV intervention in patients with proportionate or non-severe MR is yet to be proven.[47]

Role of surgical repair in FMR

The current role of surgical repair in FMR appears limited due to the conservative recommendations given by the 2017 U.S. and European guidelines and the position papers of professional societies,[7,8,46] which are predominantly based on the results of 2 CTSN randomized studies.[7,8,12,14]Observational, non-randomized, and single-center experiences often lack robustness in study design with non-rigorous definitions of the degree of MR especially in patients with moderate and severe MR.[48] Although RCTs are less susceptible to confounders and non-homogeneity of the samples, insufficient power and methodological or operational flaws might fail to generate evidence that can reliably be used to guide patient care.[41]

In the CTSN moderate IMR trial, the negative results after 2-year follow-up might be reasonably explained by the novel conceptual framework that all the enrolled patients were presented with proportionate MR (EROA of 0.2±0.1 cm^2 and LV end-systolic volume index (LVESVI) of 54.8±24.9ml/m^2).[13,14] The contribution of CABG targeting ischemic ventricular muscles, not the restrictive annuloplasty targeting at mitral annulus, for alleviating MR is fundamental, and the results show that adding MR correction procedures to CABG showed no additional benefit in death and major adverse events.[14] However, several flaws in this trial should be noted. Firstly, given the fact that 35.8% of patients in the CABG only group and 31.3% in the combined procedure group had no AMI, mixing patients with myocardial ischemia and infarction made the results inconsistent because pure IMR is reversible with revascularization and MR secondary to infarction-induced LV remodeling responds poorly to CABG;[49] Secondly, the gradation of severity of IMR as moderate (EROA 0.20-0.39 cm^2, vena contracta 0.3-0.69 cm and color Doppler jet area from 20% to 40% of the left atrial area) in this study now have been defined as severe in 2017 European guideline.[7] As a result, these discrepancies cast shadow on the way the study was built and on its conclusions. Moreover, whether a survival benefit beyond 2 years in adding MV repair to CABG could be translated from better cardiac physical function, less IMR grade and higher reverse LV remodeling observed during 2-years follow-up is pending.[14] Therefore, the impact of surgical MV repair in moderate IMR remains to be re-evaluated.

In the CTSN severe IMR trial, although a substantially recurrence of at least moderate MR developed in 58.8% of the patients in the repair group, the patients who did not have recurrent MR had greater LV reverse remodeling than patients who underwent replacement (LVESVI 42.7±26.4ml vs. 60.6±39.0ml) at 2 years.[12] This outcome validates the well-proven principle that a "good repair" (with durable correction of MR) outperforms the best replacement in the setting of FMR.[50] However, the high prevalence of recurrent MR in this cohort of patients contrasts with apparent durability of the same restrictive annuloplasty in patients with moderate MR (11.2%) studied by the same group of investigators.[14] It is logically to attribute these differences to the larger LV in patients with severe MR. However, baseline LVESVI were only modestly greater in patients with severe MR (61.1±26.2 ml/m2)[12] than in those with moderate MR (59.6±25.7 ml/m2).[14] More importantly, among patients with severe MR, preoperative LV cavity size was not different between those who did or did not develop recurrent MR. Therefore, several authors have suggested the recurrence of MR was most likely related to a mismatch between LV end-systolic dimension (LVESD) and the mitral ring size. If the PMs remain laterally displaced relative to the mitral ring, tethering of the posterior leaflet can be exacerbated following restrictive annuloplasty.[51,52] A post-hoc analysis by the CTSN authors indicated that a LVESD/ring size ratio >2 was associated with increased risk of persistent or recurrent IMR.[51] Recent echocardiography-based studies have identified several valvular (e.g., coaptation depth >1.5 cm, posterior mitral leaflet angle >45°, distal anterior mitral leaflet angle >25°, systolic tenting area >2.5cm^2) and ventricular (e.g., LVEDV >65mm, coaptation depth >1.5 cm, end-systolic interpapillary muscle distance >20 mm, and systolic specificity index >0.7) determinants failure of undersized annuloplasty in those with FMR.[48,53] Given that these factors were not considered as inclusion or exclusion criteria for randomization, a crucial bias exists.[50]If these cases and those with a mismatch between the LV and mitral ring size were detected at the time of surgery, consideration should be given to an intervention directed to improving

leaflet coaptation at valvular (e.g., leaflet augmentation plus true-size annuloplasty,[17,54] Figures 1 and 2) and subvalvular levels (e.g., papillary muscle approximation or relocation)[55,56]. Since the life-expectancy of patients undergoing replacement is endangered by the incremental risk of thromboembolic/hemorrhagic and prostheses-related events, well-designed RCTs without significant operational flaws are required to reconfirm the role of surgical MV repair in treating severe FMR.

In the era of fast-evolving transcatheter therapy, apart from the MitraClip, many other transcatheter devices designed to imitate surgical repairing techniques, including direct or indirect annuloplasty, have already been shown to be promising in reducing MR in experimental or ongoing clinical trials. Further studies will determine whether selected FMR patients (with or without different risk profile and predictors of repair failure) might benefit from tailored surgical or transcatheter repair.

Summary

Regardless of its etiology, FMR is provoked by progressive remodeling and dysfunction of the left cardiac chambers. Accurate assessment of the dynamic interactions among MV, its entire apparatus and left ventricle/atrium is critically important to help define patient risk and their response to tailored therapies.[57,58] GDMT and CRT, when indicated, remain the initial treatment strategy. The exact role of surgical and transcatheter interventions in the treatment of FMR will continue to be elucidated as the recognition of the critical importance of LV geometry in determining valvular function and clinical outcomes evolve. Recently proposed new conceptual framework of proportionate and disproportionate MR help identify which patients benefit from treatments that can decrease LV volumes and reverse LV remodeling (e.g., neurohormonal antagonists) or from interventions that are directed toward the restoration of normal MV function, such as CRT or MV repair, particularly when appropriate annular and adjunct leaflet or subvalvular reconstructions are utilized. Future well-designed RCTs are needed to evaluate the real benefit of surgical or transcatheter repair in FMR.

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Figure legends

Figure 1. Anterior mitral valve leaflet patch augmentation with true-sized annuloplasty. *Reproduced with permission from reference #17.*

[A] After the true-size annular measurement according to the usual principle (i.e., based on the size of the anterior leaflet and on the inter-trigonal distance), an incision is made along the anterior mitral annulus (the dashed line).

[B and C] A CardioCel (LeMaitre Vascular, Burlington, Mass., USA) patch slightly larger than the space area succeeding the "fall" of the anterior mitral leaflet is prepared and sutured on the leaflet, followed by a true-sized semirigid ring annuloplasty.

[D] Systolic anterior motion is never a concern, as the patch-augmented anterior mitral valve leaflet is always "pushed" toward the left atrium during the systolic phase.

Figure 2. Posterior mitral valve leaflet patch augmentation with true-sized annuloplasty in patients with severe ischemic mitral regurgitation due to significant posterior leaflet (i.e., P_3) tethering. *Reproduced with permission from reference #54.*

[A] A commissure-to-commissure incision is made along the posterior mitral annulus (the dashed line).

[B] A CardioCel patch slightly larger than the space area succeeding the "fall" of the posterior mitral leaflet (whereas deferring to its shape and curvature) is prepared and sutured on the leaflet, followed by a true-sized semirigid ring annuloplasty.

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