Therapeutic decision-making for patients with fluctuating mitral regurgitation

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Abstract | Mitral regurgitation (MR) is a common, progressive, and difficult-to-manage disease. MR is dynamic in nature, with physiological fluctuations occurring in response to various stimuli such as exercise and ischaemia, which can precipitate the development of symptoms and subsequent cardiac events. In both chronic primary and secondary MR, the dynamic behaviour of MR can be reliably examined during stress echocardiography. Dynamic fluctuation of MR can also have prognostic value; patients with a marked increase in regurgitant volume or who exhibit increased systolic pulmonary artery pressure during exercise have lower symptom-free survival than those who do not experience significant changes in MR and systolic pulmonary artery pressure during exercise. Identifying patients who have dynamic MR, and understanding the mechanisms underlying the condition, can potentially influence revascularization strategies (such as the surgical restoration of coronary blood flow) and interventional treatment (including cardiac resynchronization therapy and new approaches targeted to the mitral valve).

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Introduction

Mitral regurgitation (MR) is a common and progressive condition that is difficult to manage clinically.[1,2] MR results from several heterogeneous conditions, including disorders of the mitral valve leaflets, mitral annulus, chordae tendineae, papillary muscles, and the left ventricle.[3] Strategies for the treatment of MR are typically based on a patient's symptomatic status, and the aetiology and the consequences of MR, as assessed during echocardiography at rest.[1,2] MR is dynamic, with physiological fluctuations occurring in response to haemodynamic changes in the cardiocirculatory system, which can precipitate the development of symptoms and subsequent cardiac events.[4–6] The dynamic nature of MR has been investigated in patients with various acute cardiac conditions, particularly those with chronic degenerative or secondary MR.[7,8] Stress echocardiography has an important role in the evaluation of fluctuating MR by providing new prognostic insights and risk stratification parameters, which can help to define the optimal timing of intervention.[9–12] In this Review, we discuss the characteristics of dynamic MR and the potential mechanisms underlying its development, as well as the optimal strategies to treat the condition.

Factors that influence MR

Ischaemia-induced acute MR

Acute MR is a potentially life-threatening complication of acute myocardial ischaemia and infarction.[13] Acute MR commonly occurs as a secondary complication of acute left ventricular (LV) remodelling and dysfunction without structural valvular abnormalities, resulting from increased leaflet tethering and reduced mitral closing forces.[14] However, the severity of secondary MR varies widely, and even a mild form of MR in the acute setting of myocardial infarction is associated with poor prognosis.[15] Patients might also present with acute dyspnoea or flash pulmonary oedema.[16] Medical therapy for patients with acute ischaemic MR with or without myocardial necrosis is dependent on the underlying pathophysiology. In patients with myocardial ischaemia or infarction, restoration of blood flow to the affected territory, often the right or circumflex coronary artery, might be sufficient to reduce regurgitation. Early thrombolysis, when limited to the inferior wall, might also reduce localized LV remodelling and MR.[17] Furthermore, early revascularization also reduces mortality in patients with acute ischaemic MR presenting with shock.[18]

Chronic dynamic secondary MR

Chronic secondary MR is present in more than half of patients with symptomatic systolic heart failure due to ischaemic or nonischaemic cardiomyopathy.[19] Secondary MR results from the geometrical distortion of the subvalvular apparatus, which occurs secondary to LV enlargement and impaired contractility.[3,4,20,21] Secondary MR is a disease of the ventricles rather than of the valves *per se,* and is classified as type IIIb in Carpentier's surgical classification of mitral valve pathology.[11,22] The incidence and clinical importance of secondary MR is largely underestimated, in part owing to the insensitive nature of the physical examination. The presence of secondary MR in patients with LV dysfunction conveys an adverse prognosis, with a graded relationship between the severity

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Competing interests
The authors declare no competing interests.

Key points

- Mitral regurgitation (MR) often varies dynamically with changes in loading conditions
- Dynamic fluctuation of MR can precipitate symptoms and induce left ventricular remodelling, and might have prognostic value
- An intermittent increase in MR is often accompanied by dynamic pulmonary hypertension
- The optimal treatment strategy for fluctuating MR is uncertain, but can include a combination of surgery, cardiac resynchronization therapy, and new mitral valve approaches

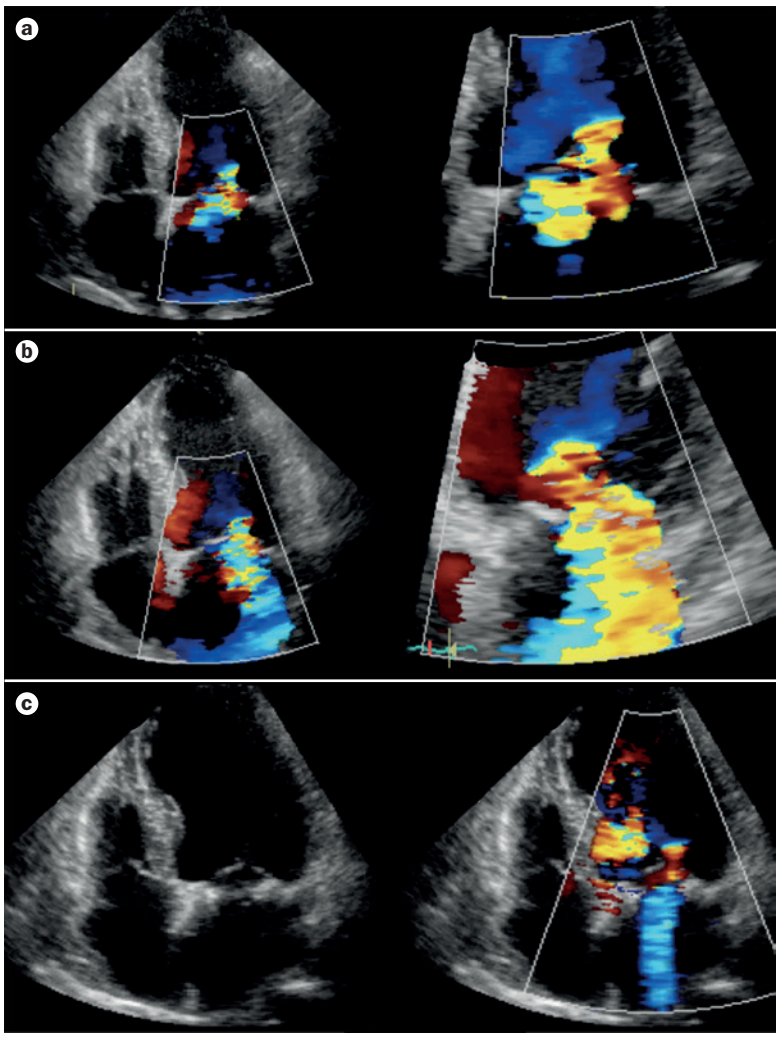

Figure 1 | Transthoracic Doppler echocardiogram of a patient with symptomatic ischaemic cardiomyopathy, severe left ventricular dysfunction, and moderate secondary mitral regurgitation at rest. **a** | Patient at rest. **b** | During exercise, a clinically significant increase in mitral regurgitation combined with dyspnoea and pulmonary hypertension was observed. **c** | After CABG surgery and mitral valve repair, the patient improved clinically and no substantial increase in mitral regurgitation was observed during exercise.

of regurgitation and reduced survival.[23] Based on previous outcome studies, secondary MR is defined as severe when the effective regurgitant orifice area (EROA) is ≥20 mm.[2,24] Chronic secondary MR is dynamic, and its severity can vary over time, depending on the dynamic interplay between tethering and closing forces, and on the physiological and pharmacological factors that can alter this balance.[14] Symptoms can, therefore, often seem to be out of proportion to the degree of MR at rest.[25]

Exercise-induced changes in MR

The dynamic behaviour of secondary MR can be reliably examined during exercise echocardiography.[5–8] More than 30% of patients with secondary MR have a clinically significant dynamic increase in MR during exercise; EROA at rest, therefore, does not predict EROA during exercise (Figure 1).[26,27] Patients who have an exercise-induced increase in the severity of secondary MR experience reduced stroke volume adaptation during testing, and often develop pulmonary hypertension and dynamic LV dyssynchrony; all these changes contribute to the limitation in exercise capacity.[28] In patients with previous inferior myocardial infarcts, a lack of contractile reserve can lead to increased annular size and leaflet tethering of the mitral valve during exercise, thereby expanding mitral valve tenting area and increasing the EROA.[5] Similarly, in patients with anterior myocardial infarcts, apical displacement of the mitral leaflet can lead to increased leaflet tenting. In both infarct territories, systolic bulging of the mitral leaflets is the major determinant of dynamic MR. An exercise-induced increase in the severity of MR, as indicated by an EROA ≥13 mm^2, confers a high risk of morbidity (such as acute pulmonary oedema and worsening heart failure) and mortality.[7,11]

Effect of anaesthetics and dobutamine on MR

Secondary MR also varies dynamically with loading conditions that modulate LV volume.[14] Regurgitant volume decreases substantially in response to unloading drugs, which is achieved through a reduction in EROA, but not through a change in the gradient across the mitral valve. Reduction of orifice area is likely to be related to a decrease in LV volume.[29] Such a dramatic variation in MR is observed most commonly in the operating room, where anaesthetic induction can reduce moderate MR to trace levels, confounding decisions regarding the need for mitral valve repair.[30] Inotropic agents can also reduce the severity of MR (Figure 2).[31] The underestimation of intraoperative MR might contribute to an inaccurate diagnosis of recurrent MR after isolated CABG surgery.[32] Dobutamine infusion causes a marked rise in mean forward stroke volume with a decrease in regurgitant volume. Such a reduction is partially related to an increase in contractility, as suggested by the rise in the ratio of peak systolic pressure over end-systolic volume. Dobutamine reduces the severity of MR, mainly as a result of a reduction in EROA. However, dobutamine infusion can also induce severe and extensive ischaemia, which results in worsening of MR.[14]

Effect of loading challenges on MR

In the operating theatre, a preload and afterload challenge test is sometimes used to minimize the effects of anaesthetic induction on secondary MR.[33] A rapid fluid filling test is performed until mean capillary wedge pressure reaches 15–18 mmHg. If the intensity of MR does not increase, phenylephrine is administered until the mean

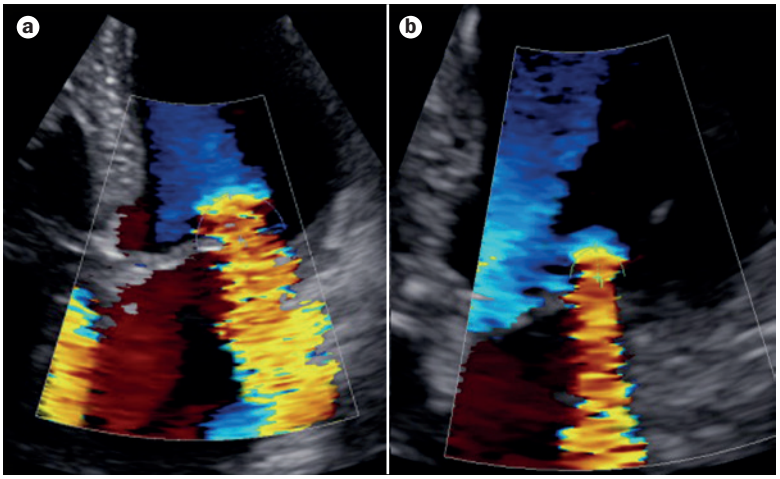

Figure 2 | Transthoracic Doppler echocardiogram showing a substantial decrease in secondary mitral regurgitation severity observed after dobutamine administration. **a** | Effective regurgitant orifice area = 33 mm^2. **b** | Effective regurgitant orifice area = 18 mm^2.

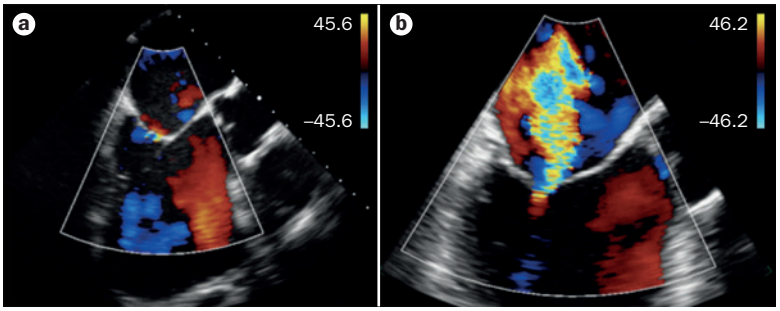

Figure 3 | Transoesophageal Doppler echocardiogram in a patient with a clinical history of flash pulmonary oedmea and fluctuating mitral regurgitation. **a** | Baseline measurement and **b** | during the Trendelenburg manoeuver.

arterial blood pressure rises to 100 mmHg. However, careful attention should be paid to avoid errors in MR estimation during phenylephrine infusion. The ultimate effect of the phenylephrine on MR severity can be challenged by the interplay between the recruitment of LV coaptation forces and the increase in systemic arterial pressure, which can reduce and increase MR, respectively. Alternatively, manoeuvring the patient into the Trendelenburg position using a specialized bed with a 40° inclination can induce fast LV volume loading without substantial arterial pressure changes, and can be used to elicit tethering LV forces and a related increase in MR. The manoeuver can be carried out in conscious patients to induce MR, and subsequently in the operating theatre to reproduce the site of valve regurgitation, especially to guide beating-heart percutaneous therapy (also known as the edge-to-edge Alfieri technique) in patients with fluctuating MR (Figure 3).

Fluctuating degenerative primary MR

In asymptomatic patients with moderate-to-severe primary MR (such as that caused by mitral prolapse or rheumatic disease), exercise stress echocardiography can induce a marked increase in MR severity (indicative of dynamic MR), which occurs in approximately one-third of all patients.[8,12] Of note, MR severity increases by one grade (from moderate to severe, by measuring the proximal isovelocity surface area) in 30% of all patients during exercise.[8,34] This phenomenon is often associated with exercise-induced pulmonary hypertension.[10] Patients with a marked increase in regurgitant volume or who develop pulmonary hypertension (defined as systolic pulmonary artery pressure >60 mmHg) during exercise have lower symptom-free survival than those who do not experience significant changes in MR and systolic pulmonary artery pressure during exercise. When combined with pulmonary hypertension, exercise-induced right ventricular dysfunction is an independent predictor of surgery-free survival in primary MR.[35] The absence of contractile reserve during exercise, defined as no or limited increase in LV ejection fraction and global longitudinal function, predicts postoperative LV dysfunction and impaired outcome, even in patients with apparently preserved LV ejection fraction (>60%).[12]

Management of dynamic MR

Medical therapy for the treatment of dynamic MR is limited in its efficacy. A combination of angiotensin-converting-enzyme inhibitors and β-blockers can limit the adverse LV remodelling process, but a decrease in the incidence or severity of dynamic MR has not been demonstrated by this approach.[32] In patients with heart failure and secondary MR, medical treatment should follow current ESC and AHA/ACC guidelines,[1,2] which recommend the use of β-blockers and angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers. The use of vasodilators such as nitrates before exercise can mitigate the worsening of dynamic MR.[31]

The advantages of surgical mitral valve repair over surgical mitral valve replacement are well-documented and the trend towards increased surgical repair procedures will continue.[36] The treatment for primary MR is straightforward, with a primary aim of timely intervention to prevent adverse LV remodelling and dysfunction.[1,2] The management of secondary MR is more challenging, because the mitral valve is not the primary cause of the disease. Furthermore, correcting MR without changing LV geometry is not guaranteed to be beneficial.[14] The ability to identify patients who have dynamic aggravation of MR, together with knowledge of the underlying mechanism, can influence revascularization strategies and concomitant mitral valve interventional procedures (Box 1).

Indications for treatment

Secondary MR

The management of patients with chronic secondary MR remains challenging (Figure 4). Current guidelines advocate mitral valve surgery in severe secondary MR at the time of CABG surgery.[1,2] The ESC guidelines consider combined surgery (CABG surgery plus mitral valve surgery) as a class IIa, level of evidence B indication, when LV ejection fraction is <30%, there is evidence of viability, and an option exists for revascularization. Surgery can also be considered in patients with severe MR, who remain

symptomatic despite optimal medical management or cardiac resynchronization therapy (CRT) and have few comorbidities, when revascularization is not indicated.[1,2]

Mitral valve repair is not unanimously recommended as a therapeutic option for chronic moderate secondary MR at the time of CABG surgery. The AHA/ACC guidelines give combined surgery in patients undergoing CABG surgery a class IIb, level of evidence C indication, whereas the ESC guidelines give combined surgery a class IIa, level of evidence C indication in patients with shortness of breath and exercise pulmonary hypertension in the setting of dynamic worsening of secondary MR.[1,2] Previous studies have provided some insight into the benefit of performing mitral annuloplasty together with CABG surgery in patients with exercise-induced elevations in MR.[37,38] Patients with either no clinically relevant changes or exercise-induced reductions in secondary ischaemic MR as a result of recruitable function in the inferobasal wall, which is an improvement in regional myocardial motion, might be referred for CABG surgery only.[32] However, larger outcome studies to examine the benefit of combined surgery in relation to results from exercise echocardiography are needed. Moreover, the additional risk of mitral valve surgery is not negligible, particularly in patients with comorbidities and poor LV function. Very ill patients or elderly individuals with a history of atrial fibrillation might be treated conservatively with revascularization alone or with a percutaneous approach,[39] although the treatment strategy also depends on the individual's risk profile.

Degenerative MR

Degenerative MR involves mitral valve prolapse (type II) and covers a large spectrum of lesions, from an isolated scallop prolapse to multisegment prolapse. The location of the prolapse, the presence of valvular or annular calcifications, and the severity of annulus dilatation can affect the feasibility and choice of surgical or percutaneous repair techniques.[3] Chronic severe primary MR can lead to LV volume overload. Surgery is the recommended therapeutic option for patients who are symptomatic at rest or during exercise testing.[1,2] The major determinants of surgical outcome and mortality in asymptomatic patients include preoperative resting LV ejection fraction <60%, end-systolic diameter >40 mm, recurrent atrial fibrillation, and pulmonary artery systolic pressure >50 mmHg.[1,2] These factors are common indications for mitral valve surgical repair. Surgery can also be considered in asymptomatic patients with preserved LV function, high likelihood of durable repair, low surgical risk, and systolic pulmonary artery pressure ≥60 mmHg during exercise.[1,2] Currently, neither the ESC nor the AHA/ACC guidelines recommend intervention based on exercise-induced changes in the severity of degenerative MR. However, in patients with substantial LV remodelling and moderate MR at rest who develop severe MR during exercise, mitral valve repair might be considered. Similarly, patients with limited contractile reserve during exercise (possibly an indication of subclinical LV dysfunction) might benefit from early elective surgery.

Box 1 | Evaluation of patients with MR to guide treatment

Clinical and echocardiographic evaluation[31]

Signs and symptoms of heart failure, dyspnoea, flash pulmonary oedema, angina, and systemic venous congestion

Optimal medical therapy

Identification of modifiable factors

- Atrial fibrillation
- Arterial hypertension
- Anaemia
- Water and sodium intake (diet, drug-mediated)
- Ischaemic myocardial dysfunction
- Viable myocardium
- Left ventricular asynchrony
- Papillary muscle asynchrony

Evaluation of mitral valve configuration[4]

Substantial regurgitation at rest or during changes in loading conditions (for example, exercise and loading manipulation)

Anatomofunctional mechanisms

- Severity of mitral valve deformation (symmetrical malapposition [tenting area], systolic coaptation depth, posterior–lateral angle, presence and longitudinal extension of coaptation [manipulation at baseline and after loading])
- Central origin and intercommissural width of regurgitant jet
- Presence and extent of mitral valve calcification
- Presence and extent of mitral valve prolapse

Mitral valve area

Abbreviation: MR, mitral regurgitation.

Treatment strategies for MR

Surgical options

Therapeutic options for the treatment of primary or secondary MR include coronary artery revascularization alone, mitral valve replacement, and mitral valve repair with or without CABG surgery. Repair techniques for primary MR are well described; the success of the intervention depends upon the surgeon's skill and the severity of valve lesions.[36] At present, the efficacy of surgery in patients with exercise test results that favour mitral valve repair for the treatment of degenerative MR is unknown.

In secondary MR, CABG surgery alone does not result in a clinically significant change in MR grade, and a substantial percentage of patients with mild-to-moderate MR have an increase in severity or recurrence of MR during follow-up.[30,40] Although CABG surgery alone seems to produce long-term survival rates similar to those for combined surgery, patients with untreated secondary MR at the time of isolated CABG surgery have an increased risk of hospitalization for heart failure during follow-up.[41,42] The main aim of combined surgery is to improve long-term functional status and quality of life.[1,2] In the RIME trial,[38] mitral annuloplasty at the time of CABG surgery in patients with moderate ischaemic MR, present either at rest or developed upon physical exertion, was associated with improved functional capacity, reversal of adverse LV remodelling, reduced severity of MR, and decreased B-type natriuretic peptide levels. In a further randomized study, combined stringent restrictive annuloplasty with CABG surgery in patients

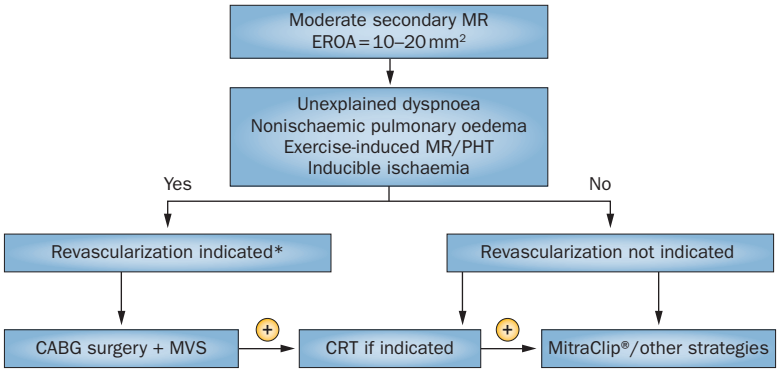

Figure 4 | Management of patients with moderate secondary MR and left ventricular dysfunction. *CABG surgery is an alternative option in patients with posterior–lateral wall viability and exercise-induced decrease in secondary MR. MitraClip® is manufactured by Abbott Vascular Inc., USA. Abbreviations: CRT, cardiac resynchronization therapy; EROA, effective regurgitant orifice area; MR, mitral regurgitation; MVS, mitral valve surgery; PHT, pulmonary hypertension.

with mild-to-moderate secondary MR improved functional status and inhibited the dynamic changes in MR observed during exercise at follow-up.[36] Conversely, CABG surgery alone did not prevent an increase in MR induced by physical exertion, which contributed to persistent exercise intolerance. Remodelling annuloplasty using a prosthetic undersized ring is the technique of choice for patients with Carpentier's type IIIb dysfunction MR, or MR that involves restricted mitral leaflet motion during the end-systolic phase. This technique provides good results in selected patients with minimal LV dilatation and little mitral valve tenting.[41,43,44] Although initially effective in most patients, persistent or recurrent MR, which occurs mid-term to long-term after the procedure (>3 months), is often observed in patients with severe mitral valve deformation and LV enlargement, contributing to the ongoing adverse LV remodelling process and worsened cardiovascular outcome.[45] In the presence of severe mitral leaflet tethering and LV dilatation, subvalvular approaches such as chordal cutting, papillary muscle repositioning, and edge-to-edge leaflet approximation have been proposed to enhance the effectiveness of mitral valve annuloplasty.[46,47] Mitral valve replacement using bioprosthetic heart valves that preserve the entire subvalvular apparatus might be a valid alternative to mitral valve repair in patients with comorbid diseases, complex regurgitant jets, and severe remodelling of the mitral valve apparatus.[48] This technique can be recommended in patients with severe mitral valve tethering (coaptation distance >1 cm) in secondary MR, where it is likely to produce similar survival rates and less recurrent MR than mitral valve repair.[49]

Cardiac resynchronization therapy

The development of CRT has substantially changed the treatment of patients with advanced heart failure. Currently, CRT is an adjunctive treatment indicated for the treatment of patients with LV systolic dysfunction and prolonged QRS duration, who remain symptomatic despite optimal drug therapy.[1,2] CRT improves exercise tolerance, in addition to providing symptomatic benefits and reducing mortality.[50] The potential mechanisms for the benefits associated with CRT are mainly related to optimized LV filling, synchronized LV electromechanical coupling resulting in an improvement in LV myocardial performance, and a reduction of MR both at rest and during exercise.[51] The beneficial effect of CRT on secondary MR occurs through the reversal of adverse LV remodelling, improved LV systolic function, increased closing force (indicated by a change in EROA, which was directly related to the increase in LV dP/dt) and improved coordinated timing of mechanical activation of the papillary muscles.[52,53] However, these benefits are reversible, and studies have demonstrated that CRT withdrawal after 6 months of implantation acutely results in MR recurrence.[54,55] In addition, owing to the smaller benefits in LV remodelling derived from CRT in patients with ischaemic cardiomyopathy, the regression of MR is subsequently less in this subset of patients. The beneficial effect of CRT on MR that worsens upon exercise occurs late after CRT implantation (>3 months), and parallels the timeframe of reversal of LV remodelling and reduction in LV dynamic dyssynchrony.[55] According to two studies, the expected rate of attenuation of exercise-induced secondary MR is approximately 30%.[56,57] However, CRT reduces the severity of secondary MR, but does not prevent the development of dynamic MR in most patients. In these individuals, combining CRT with a percutaneous mitral valve approach might be of benefit. The proposal that exercise worsens dyssynchrony, which consequently increases MR, warrants further study and might indicate the need for CRT in affected patients.[58,59]

Percutaneous mitral valve intervention

In the past 5 years, the introduction of percutaneous mitral valve intervention (PMVI) techniques has opened new frontiers in MR therapy, by eliminating the need for thoracotomy and extracorporeal circulation.[60] PMVI techniques can correct MR by means of direct or indirect reduction of mitral annular dilatation, or through treatment of the primary or secondary abnormalities of the mitral apparatus. The efficacy and feasibility of PMVI is dependent on careful selection of patients with a suitable clinical profile, and on an accurate evaluation of the mechanism and severity of their MR using integrated Doppler echocardiography.[61] Among PMVI techniques, the MitraClip® system (Abbott Vascular Inc., USA), which can reproduce the edge-to-edge surgical procedure, is the only percutaneous therapeutic approach that has been clinically validated.[62,63] Studies on numerous other PMVI techniques are still in the experimental phase.

The selection of patients suitable for PMVI therapy requires a different clinical–instrumental approach in those with secondary MR compared with those with primary degenerative MR. The selection of patients with secondary MR eligible for echocardiography is a challenging clinical issue, owing to the complex interplay between LV disease and associated dynamic valve regurgitation. Secondary MR is affected by loading

forces that might influence the degree of remodelling and LV contraction.[29] Echo–Doppler mapping and intercommissural extension of the regurgitant lesion is essential for predicting the site of clip implantation, to determine whether an additional clip is needed, and to predict the risk of postprocedural residual stenosis. The ideal indication for MitraClip® therapy in patients with secondary MR involves a mitral valve lesion with symmetrical systolic leaflet tenting and maintenance of systolic coaptation shape within a depth of 10 mm and ≤2 mm of longitudinal extension.[60] However, these echocardiographic criteria can be dynamically changed by LV load and functional conditions, which can have a substantial effect on the characteristics of target-valve lesion.

As such, the indication, strategic planning, and efficacy of repair of the MitraClip® procedure in patients with fluctuating MR remains a clinically relevant consideration. Several issues need to be addressed: the identification and possible treatment of underlying mechanisms subtending fluctuating MR before considering MitraClip® therapy; intraprocedural inducibility of MR to guide clip positioning and to establish the number of clips required; and re-evaluation of the inducibility of MR after clip implantation.

Percutaneous MitraClip® therapy can also be applied to central prolapsing lesions with poor intercommissural extension (width <12 mm) and a limited systolic coaptation gap (<10 mm) in the absence of annular dilatation. MitraClip® therapy for degenerative primary MR, in the absence of extensive clinical application and randomized studies, cannot be considered equivalent to surgical repair, and should be performed only in patients with adequate valve lesions and at high operative risk.[1,2] Mitral valve prolapse is a dynamic lesion resulting from excessive valve tissue, and leads to coaptation loss and related regurgitation. However, the prolapse threshold can be decreased by LV volume-related tethering and increased by contraction-based coaptation forces.[8] Consequently, evaluation of the targeted prolapsing lesion should take into account the potential fluctuation caused by LV load conditions, which can mask or unmask the prolapse; this assessment can have a substantial effect on MitraClip® feasibility and efficacy. This complex interplay between LV forces and the threshold of the prolapse is lost upon rupture of the chordae tendinae, simplifying the MR mechanism, which then becomes dependent solely on LV systolic pressure.[14] Therefore, MitraClip® therapy guidance might require different approaches in patients with isolated prolapse compared with those with ruptured chordae. Nonphysiological LV load (for example, as a result of administration of unloading drugs such as diuretics) should be carefully considered and optimized to avoid the opposite effects on MR. For example, low preload or afterload conditions might result in an overestimation of prolapse-related MR or an underestimation of flail-related MR, respectively. The Trendelenburg manoeuver might attenuate prolapse, while increasing flail-related MR; the opposite effect can be observed using an anti-Trendelenburg manoeuver.

Percutaneous mitral annuloplasty

Various percutaneous techniques that mimic surgical annuloplasty have been tested in both animal models and the clinical setting.[45,46,60,64–68] Percutaneous devices used to reshape the mitral annulus can be separated into indirect and direct types; the former are positioned in the coronary sinus, whereas the latter addresses the mitral annulus. Indirect annulopasty involves the placement of a device into the coronary sinus to promote favourable annulus remodelling, thereby optimizing leaflet coaptation. In direct annulopasty, a device is implanted into the annulus, using the retrograde (into the left ventricle via the aorta) or the transatrial (transeptal) approach.

Echocardiographic MR analysis for annuloplasty is crucial for patient selection. Similar to the criteria for surgical annuloplasty, the ideal lesion includes type I (incomplete copatation due to annular dilatation or deformation) or type IIIb (functional leaflet tethering) with symmetric leaflet malapposition and a coaptation depth <1 cm.[3] Structural abnormalities of the mitral valve (type II and type IIIa), or recognized tethering shapes that are typically associated with unsuccessful surgical annuloplasty (asymmetric or extreme tethering), should not be treated using the percutaneous approach. Fluoroscopy and transoesophageal echocardiography are used to determine the final position of the annuloplasty devices.[61] Transoesophageal echocardiography is performed to guide annulus reshaping and other related changes in MR. Successful reduction of MR requires careful attention to LV load conditions to avoid misleading procedural results. Given the close proximity of the circumflex artery to the coronary sinus, ischaemia-related MR worsening should be excluded before considering the transcoronary sinus procedure unsuccessful.[69]

Other strategies

Although they are currently unavailable for clinical use, some percutaneous devices have been considered for secondary MR treatment to promote favourable LV remodelling with a direct approach.[1] Some devices are designed to correct the distortion in LV shape and annular dilatation using a system of chordae release through the left ventricle between the two papillary muscles, with subsequent anteroposterior LV reduction, by shortening of the implanted chordae.[70] Another device utilizes a beating-heart implantation of a circular band with inflatable chambers at the base of the left ventricle.[71] Other percutaneous techniques consist of a direct beating-heart chordae implantation using a transapical approach to treat prolapse or ruptured chordae tendinae in selected patients with degenerative MR.[72] Transcatheter mitral valve replacement is another innovative approach.[63] Echocardiographic assessment of the dynamic changes in MR is crucial to guide these procedures and monitor the effects of device implantation on mitral valve target lesions. Careful attention is required to recognize MR fluctuation to establish the therapeutic benefit of the proposed new techniques, given the complex pathophysiology of mitral valve incompetence.

Conclusions

Transient worsening of MR can be the underlying cause of clinical destabilization with exertional dyspnoea, acute pulmonary oedema, and impaired clinical outcome. Loading-change stress echocardiography is an important clinical tool in the assessment and management of patients with fluctuating MR. Although further evidence is needed to determine the benefit of combined surgery in relation to loading changes on echocardiography, the technique has already entered the clinical arena and has contributed to defining the optimal timing of intervention in patients with MR. Current therapies used to treat fluctuating MR are customized according to its aetiology, and include mitral valve surgery associated with coronary revascularization, cardiac resynchronization therapy, and new mitral valve approaches.

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Author contributions

All the authors researched data for the article, discussed its content, and wrote, reviewed, and edited the manuscript before submission.