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Review Article

Secondary Mitral Regurgitation: Cardiac Remodeling, Diagnosis, and Management

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ABSTRACT

Secondary mitral regurgitation (MR) refers to MR resulting from left ventricular or left atrial remodeling. In ischemic or nonischemic cardiomyopathy, left ventricular dilation (regional or global) leads to papillary muscle displacement, tethering, and leaflet malcoaptation. In atrial functional MR, MR occurs in patients with left atrial dilation and altered mitral annular geometry due to atrial fibrillation. In addition to cardiac remodeling, leaflet remodeling is increasingly recognized. Mitral leaflet tissue actively adapts through leaflet growth to ensure adequate coaptation. Leaflets, however, can also undergo maladaptive thickening and fibrosis, leading to increased stiffness. The balance of cardiac and leaflet remodeling is a key determinant in the development of secondary MR. Clinical management starts with detection, severity grading, and identification of the underlying mechanism, which relies heavily on echocardiography. Treatment of secondary MR consists of guideline-directed medical therapy, surgical repair or replacement, and transcatheter edge-to-edge repair. Based on a better understanding of pathophysiology, novel percutaneous mitral repair and replacement devices have been developed and clinical trials are underway.

ABBREVIATIONS

AF, atrial fibrillation; AFMR, atrial functional mitral regurgitation; ARB, angiotensin receptor blocker; CI, confidence interval; COAPT, Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation; CRT, cardiac resynchronization therapy; EROA, effective regurgitant orifice area; GDMT, guideline-directed medial therapy; LA, left atrium; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; MI, myocardial infarction; MITRA-FR, Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation; MR, mitral regurgitation; MV, mitral valve; PISA, proximal isovelocity surface area; PM, papillary muscle; TEER, transcatheter mitral edge-to-edge repair.

Introduction

Mitral regurgitation (MR) is the most common form of moderate or severe valvular heart disease in the United States, affecting 6% of adults >65 years old.[1] It is a cause of significant mortality and morbidity, and with an aging population, its prevalence is expected to rise. MR can be classified into primary (degenerative) MR and secondary (functional) MR: primary MR is characterized by leaflet prolapse or flail leading to loss of leaflet tip/edge coaptation. Secondary MR, on the other hand, is the consequence of left ventricular (LV) or left atrial (LA) remodeling and dysfunction leading to coaptation loss due to leaflet tethering, preventing adequate leaflet tip/edge approximation. Insufficient and maladaptive leaflet tissue growth and remodeling have been more recently recognized to compound secondary MR. Secondary MR is more common, accounting for 65% of all MR cases, and it conveys a worse prognosis (5-year survival, secondary MR vs. primary MR, 46%-50% vs. 66%).[2] In this review, we outline the anatomy of the mitral valve (MV) and the clinical and imaging features of secondary MR, summarize recent advances in our

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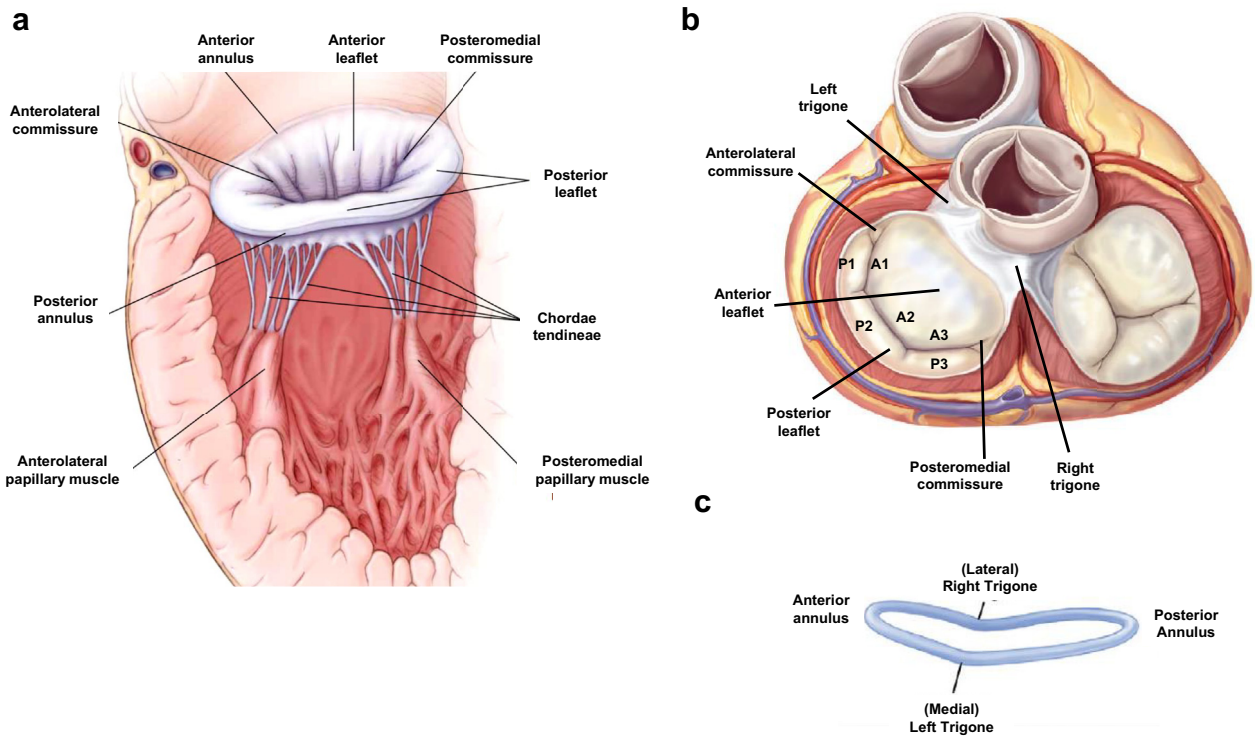


Figure 1. Mitral valve anatomy in (a) long axis view and (b) short axis view. (c) Schematic diagram showing the saddle-shape mitral annulus. The mitral apparatus is a complex structure consisting of the annulus, leaflets, chordae tendineae, and the papillary muscles. The annulus is bound by the fibrous trigones and in continuity with the noncoronary cusps and left coronary cusps of the aortic valve. The mitral annulus has a saddle shape with high points anteriorly and posteriorly, and low (=ventricular) points lateral-medially. Modified from Otto CM[7] and Carpentier A.[6]

understanding of its pathogenesis and discuss current and future treatment options.

Mitral Valve Anatomy

The MV apparatus consists of the annulus, leaflets, chordae tendineae, and papillary muscles (PMs). Normal function requires an intricate and dynamic interplay between all its components and the LV and LA to ensure brisk diastolic anterograde blood flow and effective leaflets closure and coaptation to prevent retrograde systolic MR flow. Readers are referred to thorough reviews for details,[3-6] here we provide a summary of functional anatomy pertinent to MR (Figure 1).

The Mitral Annulus

The mitral annulus refers to a tissue junction that separates the LA from the LV at the site of basal MV leaflet insertion. The anterior annulus is bounded mediolaterally by the left and the right trigones and extends superiorly and inserts into the noncoronary aortic valve cusps and left coronary aortic valve cusps, forming the aortomitral curtain. It is densely packed with collagen fibers which confers tensile strength. The posterior annulus has a semicircular shape. It is made of muscular tissue with looser leaflet anchorage, making it prone to dilation and remodeling. The mitral annulus has a saddle-shape, with its anatomical highpoints located anteriorly and posteriorly, and the lowest, ventricular points mediolaterally.[8] The mitral annulus changes its shape and size dynamically throughout the cardiac cycle, becoming overall larger and flatter during diastole and smaller and more folded during systole.[9] These shape and dynamic changes allow optimal LV diastolic inflow and increased coaptation area during systole while reducing leaflet tissue stress. MV annular function and size are often affected in disease states leading to an adynamic annulus with a larger annular area relative to the MV leaflet area, predisposing to insufficient coaptation and MR.[10] Effective closure requires sufficient leaflet apposition, that is, ~10 mm overlap.[11]

The Leaflets

The MV has an anterior and a posterior leaflet, separated by the anterolateral and the posteromedial commissures. The posterior leaflet takes up the posterior two-thirds of the mitral annulus and is divided by the 2 indentations into 3 scallops: the lateral (P1), middle (P2), and medial (P3) scallops. The thicker, circumferentially shorter anterior leaflet is similarly divided into 3 corresponding segments, A1, A2, and A3. Radially, the leaflets have basal, clear, and rough zones. The basal zone refers to where the leaflet joins the annulus. The clear zone is the central body of the leaflet, and it consists of a dense collagen network. The rough zone is at the distal leaflet end and has abundant hydrophilic glycoaminoglycans which ensures a tight sealing coaptation.[12]

Chordae Tendineae and Papillary Muscles

The chordae tendineae are dense, fibrous structures that originate from the PMs heads and insert into the leaflets in a fanlike fashion. There are 3 types of chordae: the marginal chordae are attached to leaflet margins and prevent leaflet edge eversion. The thicker secondary chords (also strut chords) are attached to the leaflet body and provide mechanical support. There are basal chordae that are attached to the base of the posterior leaflet.[6,13] The 2 PMs are named with reference to the mitral commissures and they provide chordae to both leaflets. The anterolateral PM usually has a single head and is supplied by the left anterior descending or left circumflex artery. The posteromedial PM most commonly has multiple heads and is vascularized by the right coronary or left circumflex artery.[6]

MR Secondary to LV Remodeling

Secondary MR is common in patients with heart failure or coronary artery disease. It is present in ~50% of patients after myocardial infarction (MI) and more than doubles the mortality risk.[14,15] Further,

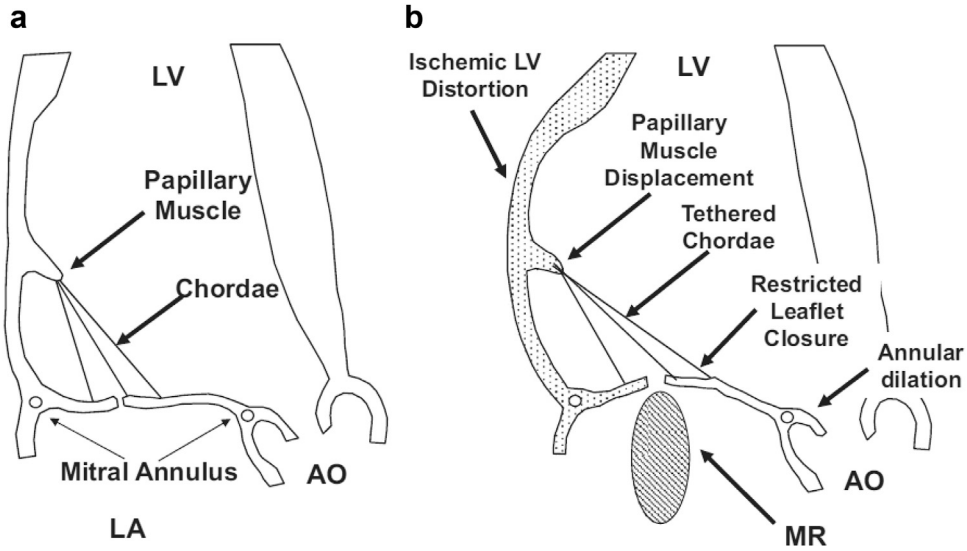


Figure 2. Mechanism of ischemic mitral regurgitation. (a) Normal left ventricular and mitral valve geometry. (b) In ischemic MR, LV remodeling leads to LV apical displacement of papillary muscles, mitral leaflet tethering, and restricted leaflet closure. Adopted from Hung JW.[24]
Abbreviations: AO, aorta; LA, left atrium; LV, left ventricle; MR, mitral regurgitation.

even mild secondary MR is prognostically significant.[16] Despite advances in cardiovascular therapeutics, secondary MR continues to be associated with worse patient outcome,[17] highlighting a clinical priority.

Mechanistically, secondary MR results from an imbalance between leaflet tethering and LV closing force (Figure 2). In addition to apical displacement of the PMs, mitral annular dilation and a loss of the dynamic saddle shape are present.[18] Closing force is provided by LV contraction. In patients with heart failure, reduced closing force occurs due to a combination of regional or global systolic impairment and LV or PM displacement. Of these 2 contributing processes, experimental evidence suggests that altered PM position is the predominant mechanism of secondary MR.[18] In a sheep model of beta-blockade induced cardiomyopathy, Otsuji et al.[19] showed that global LV dysfunction, in the absence of LV remodeling (which was prevented using a LV restraining device), does not cause significant MR. Similarly, investigators also demonstrated in a dog model of MI where the left circumflex artery was ligated that despite severe segmental LV dysfunction involving the PM, MR does not occur without LV dilation.[20] This notion is also supported by clinical studies. In a series of 128 patients, investigators found apical and posterior displacement of the PM to be an important determinant of MV tethering, which in turn, strongly correlates to MR severity ($R = 0.74$, $R < 0.001$), even after multivariate adjustment.[21] Interestingly, isolated PM dysfunction induced experimentally through ligation of corresponding arteries does not lead to secondary MR.[22] Indeed, in a series of 40 patients with prior inferior MI, reduction in PM longitudinal contraction is associated with lesser MR, suggesting it may even be protective against secondary MR.[23]

Based on etiology, secondary MR can be classified as ischemic or nonischemic. Ischemic MR occurs after MI (often inferior), which leads to posterior and outward remodeling of the infarcted myocardial segment underlying the PM. This in turn retracts the PM apically and outward which pulls the chordae and mitral leaflets, resulting in incomplete leaflet closure and impaired coaptation.[24] On echocardiography, the cardinal feature of tethering is convex LV leaflet tenting. In nonischemic MR, due to diffuse LV dysfunction and/or global LV remodeling, the LV becomes progressively dilated and spherical. This exerts similar effects on the PMs, causing apical displacement and leaflet tethering. In contrast to the often asymmetric leaflet tethering and posterior MR jet of ischemic MR, nonischemic MR usually has symmetrical tethering and a central regurgitant jet.[18]

Atrial Functional MR (AFMR)

Longstanding atrial fibrillation (AF) without LV pathology is known to cause mitral annular dilation and LA enlargement. An early study did not support a causal AF and secondary MR association,[25] however, Gertz et al. reported in a cohort of patients undergoing AF ablation, that persistent AF and annular size were independently predictive of significant (at least moderate) MR. Importantly, restoration and successful maintenance of sinus rhythm were associated with lower rates of significant MR (24% vs. 82%, $p = 0.005$) and a reduction in LA and mitral annular measurements.[26] This seminal observation implicates a causative role of AF in MR, and the authors coined the term atrial functional MR (AFMR) to describe this disease entity. AFMR, usually defined as significant MR with normal LV size and function, is estimated to be present in 13% to 19% of AF patients enrolled in randomized trials comparing warfarin to novel oral anticoagulants and affects a similar proportion of AF patients in a community setting.[27,28] Compared to functional MR due to LV remodeling, patients with AFMR are older, more likely to be female, and to have a history of hypertension.[2] Heart failure with preserved ejection fraction is increasingly recognized to be associated with AFMR.[29] Prognostically, patients with AFMR have a 5-year survival of 50 $\pm$ 4%, a mortality almost twice as high as age- and sex-matched controls (risk ratio, 1.88; 95% CI, 1.52-2.25).[2]

On echocardiography, AFMR is characterized by LA dilation, and normal LV size and systolic function without regional wall motion abnormalities. The MR jet is typically centrally directed. There may be concomitant tricuspid regurgitation or pulmonary regurgitation, which are prognostically significant.[28,30] Distinctive changes in the mitral annulus include (1) mitral annular dilatation with increase in annular area and/or perimeter, (2) flattening of the annulus (i.e., loss of saddle shape), and (3) a reduction in dynamic annular fractional area change between systole and diastole.[30-34] Due to the cross-sectional nature of these investigations, it remains unclear if these changes are the cause or consequence of AFMR. The mechanism of how annular changes compound AFMR is also poorly understood. Available data suggest that annular dilation alone is insufficient to cause AFMR,[25] and that atrial myopathy likely contributes to AFMR pathogenesis. It has been proposed that the posterior mitral annulus is pulled posteriorly as the LA dilates (Figure 3)[35]. Consequently, part of the posterior mitral leaflet is dragged along and rests on the crest of the LV inlet, causing a reduction in the

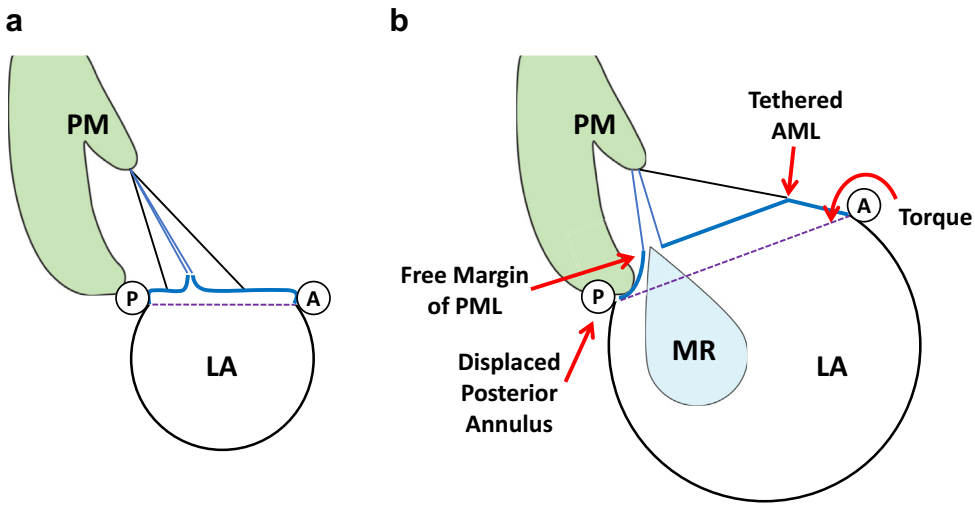


Figure 3. Proposed mechanism of atrial functional mitral regurgitation (AML). (a) Normal left atrial and mitral annulus geometry. (b) In atrial mitral regurgitation, left atrial dilation pulls the mitral annulus posteriorly onto the crest of the LV inlet. This reduces the free edge/area of the posterior leaflet. The annulus displaces superiorly and "flattens" the anterior leaflet. This results in an increased distance between the annulus and papillary muscles, leading to restricted leaflet motion during systole. Modified from Silbiger JJ.[35]
Abbreviations: AML, anterior mitral leaflet; LA, left atrium; LV, left ventricle; MR, mitral regurgitation; PM, papillary muscle; PML, posterior mitral leaflet.

leaflet area available for coaptation. This also restricts posterior leaflet movement and results in "atriogenic tethering" due to an increase in papillary-annulus distance.[35] This is supported by the clinical observation that the posterior leaflet is tethered toward the apex (as evidenced by an increase in the posterior leaflet angle) in patients with AFMR.[32] In addition, LA dilation and posterior movement of the posterior annulus will lead to superior annular displacement (away from the apex), which increases the distance between PM and annulus, and in turn, leads to more tethering.[35] Consistent with this, investigators have shown that the anterior leaflet flattens in AFMR.[36] Overall, despite the rising epidemic of AF and the well-recognized clinical significance, AFMR remains incompletely understood and thus further research is warranted.

Leaflet Adaptation and Maladaptation

Traditionally, secondary MR has been considered a disease of the LV, resulting from alteration in LV geometry or contraction. The MV leaflets have been seen as inert and passive. However, recent clinical and experimental studies have challenged this notion. Using 3-dimensional echocardiography, Chaput et al.[37] demonstrated a 35% increase in MV leaflet area in patients with LV dysfunction when compared to normal subjects, suggesting increased MV leaflet area in these patients. The increase in leaflet area, however, often remains insufficient to compensate for the increase in mitral annular closure area, resulting in inadequate leaflet coaptation and thus MR (Figure 4). Indeed, the investigators demonstrated that a leaflet to mitral annular closure area ratio of <1.7 is the threshold when significant secondary MR develops. This clinical observation prompted experimental studies exploring if MV leaflet area increase is due to passive stretch or active adaptation and how adaptation, if active, can be therapeutically modulated. In a sheep model with PM retraction causing MV leaflet tethering without causing significant MR, Dal-Bianco et al. found that over 2 months, tethered leaflet area increased by 17%.[41] Histological examination of the tethered leaflets provided compelling evidence of active MV leaflet growth through endothelial-mesenchymal transdifferentiation, an embryonic valve developmental pathway[41]. On the other hand, these experimentally tethered leaflets were also found to be thickened due to increased leaflet collagen, which may have detrimental long-term consequences. Clinical studies have shown that mitral leaflets progressively thicken in post-MI patients, which was independently associated with significant MR[42] (Figure 5). In advanced heart failure, thickened mitral leaflets have altered biochemical (15% more collagen and 58% more glucoaminoglycan) and biomechanical properties (50% stiffer and 35% less extensible).[43,44]

The discovery of MV adaptation has prompted widespread interest in the cardiology community. Notwithstanding slight methodological differences, the initial clinical findings of Chaput et al.[37] were subsequently confirmed in 2 other patient cohorts.[38,39] Studies have also shown that leaflet enlargement similarly occurs in patients with AF but often fails to compensate for the increase in closure area due to annular dilation, resulting in AFMR (Figure 4).[31,40] Investigators have also shown that insufficient mitral leaflet enlargement is associated with significant MR following transcatheter mitral edge-to-edge repair (TEER).[45] In a clinical study that compared significant aortic regurgitation vs. secondary MR patients with similar degrees of LV dilatation and sphericity, Beaudoin et al.[46] showed significant MV area growth and rare MR in patients with significant aortic regurgitation despite similar leaflet tethering and mitral annular area. This suggests that nature has a way to modulate MV adaptation, a potential therapeutic target.

In a follow-up animal experiment, the Levine group at Massachusetts General Hospital found that a superimposed apical MI in a sheep model with controlled mitral tethering and LV remodeling augments endothelial-mesenchymal transdifferentiation, but also induces profibrotic responses.[47] This is also observed by Marsit et al.[48] in a sheep model of aortic regurgitation with MI. These profibrotic responses are signaled through transforming growth factor- β pathways, which can be selectively modulated using angiotensin receptor II blockers (ARB). Using the same sheep model, Bartko et al. showed that losartan, an ARB, was effective in preventing the MI-induced, transforming growth factor-β-mediated profibrotic changes without affecting leaflet enlargement, demonstrating for the first time that MV leaflet adaptation can be medically modulated[49]. Clinical studies showed that there is less leaflet thickening in patients tolerating maximal doses of renin-angiotensin blockade.[47,49,50] The benefits of ARB and angiotensin-converting enzyme inhibitor in preventing MR have also been observed in AFMR population,[31] suggesting that leaflet adaptation in AFMR may, at least in part, share similar profibrotic pathways as secondary MR due to LV remodeling.

The exploration of MV leaflet adaptation supports that there is a common compensatory biologic response that should be utilized and modulated to prevent MR. Whilst further clinical validation is needed, renin-angiotensin blockade appears to be a promising first step. Further elucidating the key MV leaflet adaptation molecular pathways will help to identify novel therapeutic targets.

Diagnosis and Echocardiographic Assessment

Echocardiography (Echo) is the primary imaging modality to diagnose and evaluate secondary MR. Careful examination of the mitral apparatus with 2-dimensional echocardiography can elucidate the mechanism of MR and help formulate appropriate management plans. In

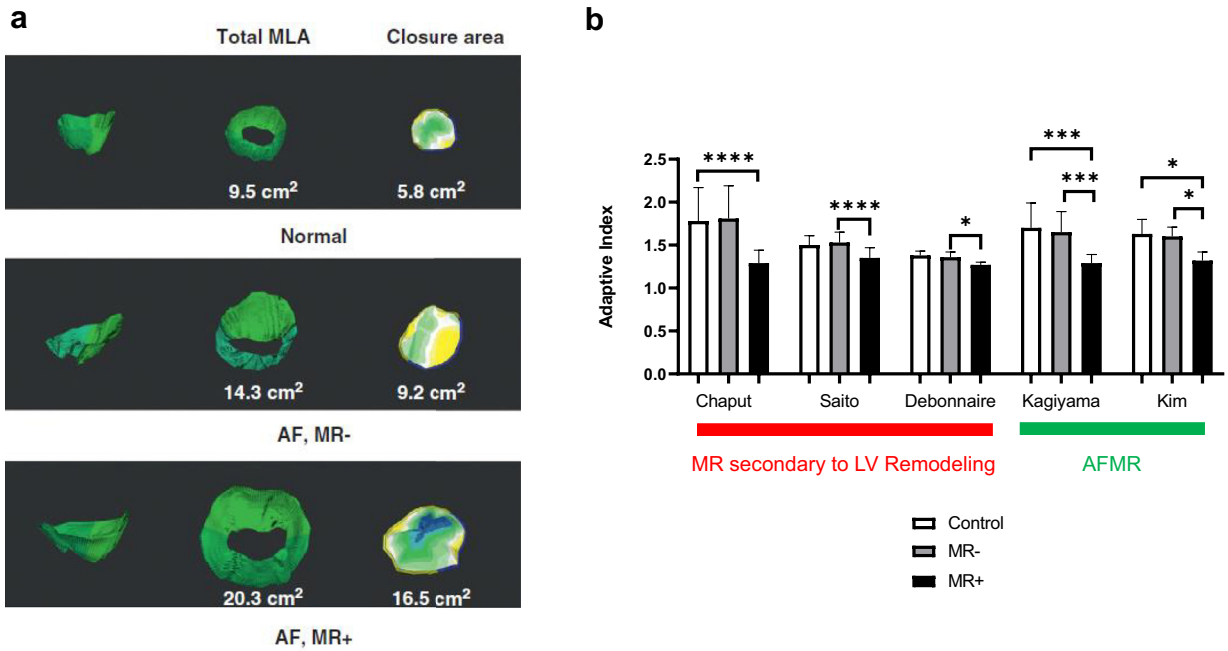


Figure 4. Leaflet adaptation. (a) Three-dimensional echocardiography can measure total MV leaflet and mitral annular closure area. Compared to control, patients with AF, even without mitral regurgitation (AF, MR−) have a bigger average leaflet area. However, those that develop atrial functional mitral regurgitation (AF, MR+) also have a bigger annular closure area. Thus, despite an increase in total leaflet area, there is a leaflet to annular area mismatch, resulting in mitral regurgitation. Figure adopted from Kim et al.[31] (b) Studies[31,37,38-40] on leaflet adaptation in MR. Adaptive index is the total leaflet/annular closure area ratio or total leaflet area/mitral annular area ratio. Patients with either left ventricular remodeling or atrial fibrillation but no significant MR (MR−) have similar adaptive index to the control. Patients with significant secondary MR (MR+) have lower adaptive index than MR- patients or control. *$p < 0.05$, ***$p < 0.001$ ****$p < 0.0001$.
Abbreviations: AF, atrial fibrillation; AF, MR−, patients with atrial fibrillation but no significant mitral regurgitation; AF, MR+, patients with atrial fibrillation and significant mitral regurgitation; AFMR, atrial functional mitral regurgitation; LV, left ventricle; MLA, mitral leaflet area; MV, mitral valve.

addition to the aforementioned classificational scheme (primary vs secondary MR), the Carpentier classification, which is based on leaflet motion (Figure 6) provides a useful conceptual framework[51]. In Carpentier type I MR, mitral leaflet motion is normal, and the pathology lies in the annulus (e.g., annular dilatation from atrial fibrillation, as in AFMR) or the leaflet integrity (e.g., leaflet perforation from infective endocarditis). Type II MR describes MR due to excessive leaflet motion, as occurs in leaflet prolapse or flail. In type III MR, leaflet motion is restricted in systole and diastole (type IIIa) or systole only (type IIIb), due to leaflet thickening/fusion or tethering, consequent to LV or LA remodeling, as in ischemia and nonischemic MR. MV tethering can be quantified by measuring the height, area, or volume from leaflet tips to the annular plane. Though these measurements typically correlate with MR severity, they are not sufficiently discriminative for clinical use.[52]

At the ventricular level, ischemic MR is associated with regional LV remodeling (typically the inferior wall), whereas nonischemic MR is characterized by global LV dilation and increased sphericity. Furthermore, geometry differences in these 2 types of LV remodeling lead to distinctive patterns of PM displacement. Ischemic MR is associated with increased distance between the PMs and the aortomitral fibrosa, whereas increased inter-papillary distance is seen in nonischemic MR. In AFMR, on the other hand, LV size, geometry, and function are usually within

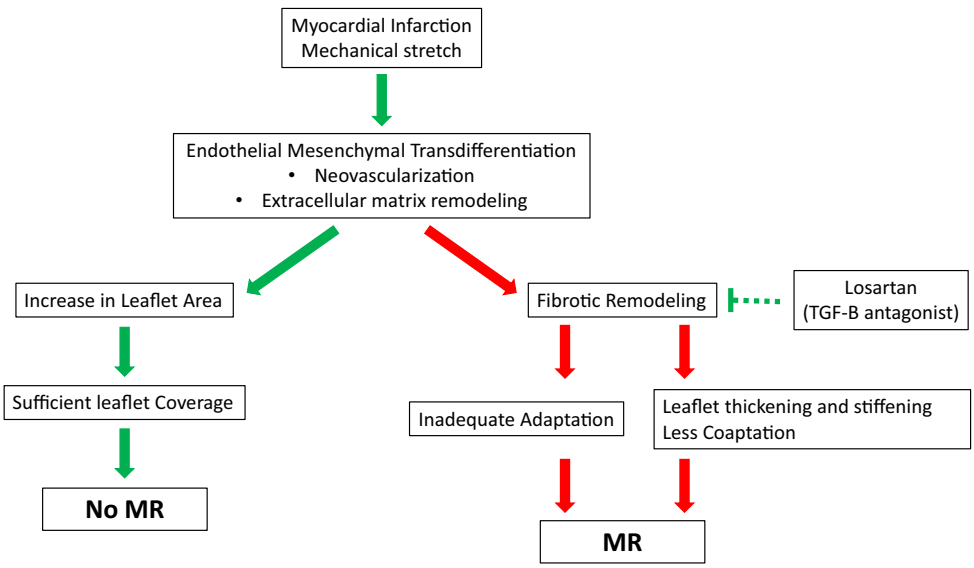


Figure 5. Leaflet remodeling. Leaflet remodeling is mediated by endothelial mesenchymal transdifferentiation. This adaptive response leads to leaflet area enlargement, but it also has a deleterious profibrotic effect that results in leaflet thickening. Transforming growth factor-β (TGF- β) is a main mediating molecule, and losartan, a TGF-β antagonist, may have therapeutic benefits in suppressing this profibrotic response. (Green arrow denotes adaptive response, red arrow denotes maladaptive response). MR, mitral regurgitation

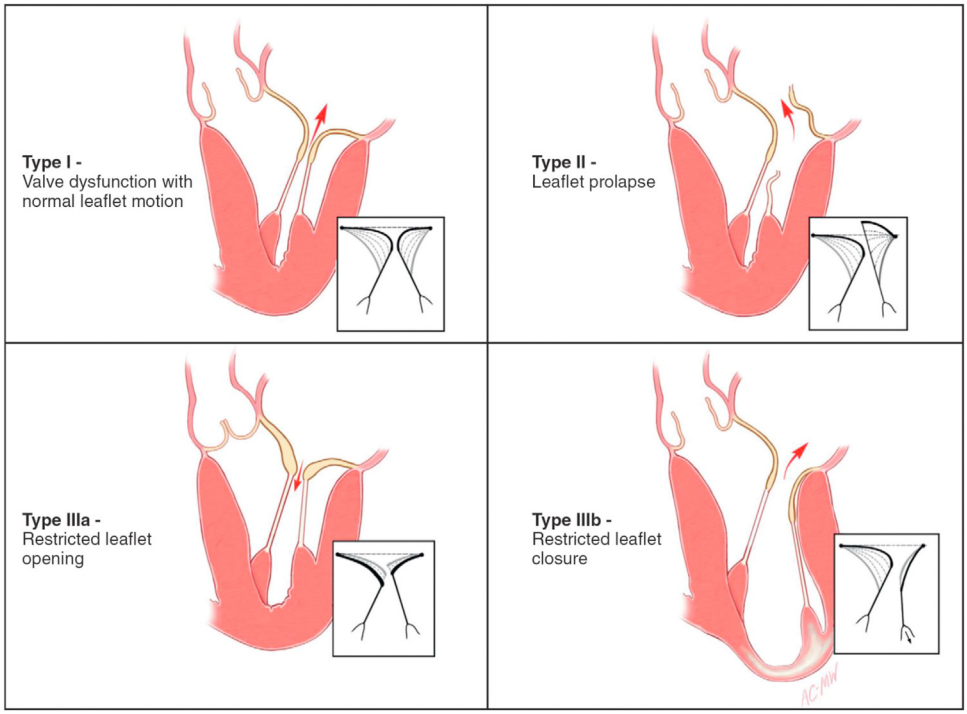


Figure 6. Carpentier classification. Mitral regurgitation is classified by leaflet motion. Type I refers to normal leaflet motion, type II refers to excessive leaflet motion and type III refers to restricted leaflet motion in systole and diastole (type IIIa) and systole only (type IIIb). Adapted from Carpentier A.[6]

normal limits. At the level above the annulus, LA and mitral annular dilation are often present in both ventricular and AFMR, and they are due to LV remodeling, atrial myopathy, or longstanding concomitant atrial fibrillation. The echocardiographic features of these 3 subtypes of secondary MR are summarized in Figure 7.

MR can be readily detected using color Doppler. MR severity can be semiquantitatively graded based on the vena contracta diameter. The regurgitant proximal flow convergence on color Doppler (PISA, proximal isovelocity surface area) can be used to derive the effective regurgitant orifice area (EROA), the regurgitant volume and regurgitant fraction. PISA has been validated against LV angiography and has been shown to be prognostically meaningful.[16,53] PISA-derived parameters may, however, underestimate MR severity as this method assumes a circular regurgitant orifice and not the typically elliptical orifice in secondary MR.[54] The elliptical orifice can also lead to the "splay phenomenon" where MR is under-represented as a nonphysiological arc on color Doppler, which in turn can lead to underestimation of MR severity.

Therefore, an integrated, multi-parametric approach is warranted.[18] Supportive Doppler evidence of severe MR should be sought, including reversal of pulmonary systolic venous waveform, high mitral inflow E wave velocity, and dense regurgitant jet with lower jet velocity. Moreover, interpretation of these findings with consideration of patient factors (e.g., elevated LA pressure confounded from underlying cardiomyopathy rather than severe MR) and loading conditions (MR severity can be attenuated by hypotension and anesthetic agents,[55] and accentuated by exercise[56]) is critical.

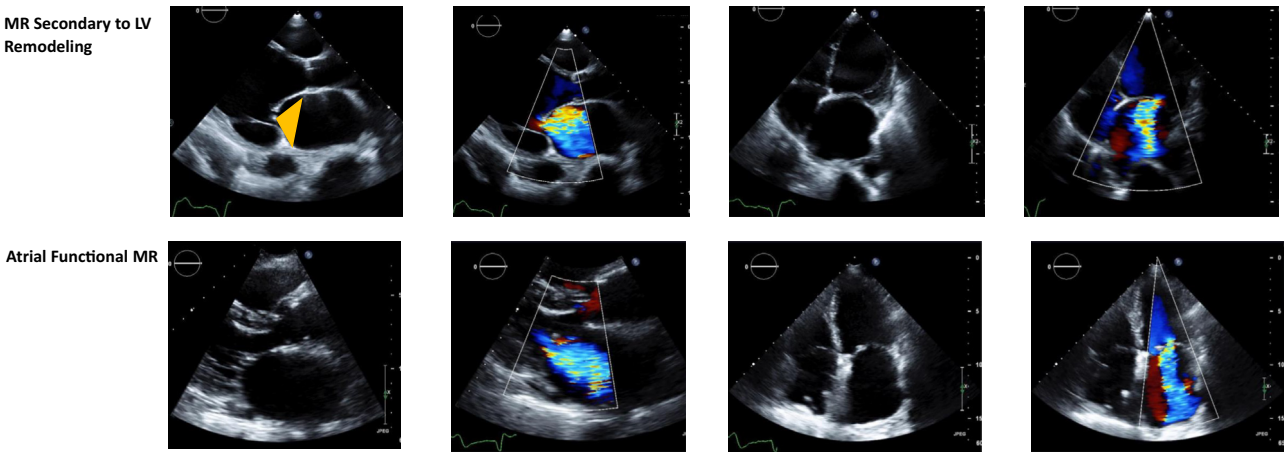
In addition to transthoracic echocardiography, transesophageal echocardiography provides anatomical information critical in determining suitability for percutaneous interventions, including leaflet pliability, the extent and location of leaflet calcium, and the dimensions of the coaptation defect. Three-dimensional echocardiography has proven particularly useful in precise localization of leaflet pathology and identification of clefts. It allows accurate MR quantification through direct planimetry of vena contracta area and anatomical regurgitant orifice, free of geometric assumption. Transesophageal echocardiography has provided novel insights in the geometric changes of mitral apparatus that accompany LV remodeling and MR progression and is indispensable in TEER procedural guidance.

Treatment

Medical Therapy

The goal of secondary MR therapy is to alleviate symptoms, improve functional status, and reduce morbidity and mortality. To achieve this, one needs to address reversible causes of LV dysfunction and underlying heart failure as well as the MR (Figure 8). Importantly, obstructive coronary artery disease needs to be revascularized to alleviate LV ischemia. Currently, there is a paucity of data and no guideline recommendation on the management of AFMR. Limited data suggest ablation of AF may reduce AFMR.[26]

In the 2020 American College of Cardiology/American Heart Association Guideline for Management of Valvular Heart Disease, guideline-directed medical therapy (GDMT) is strongly recommended for patients with chronic severe MR and reduced LV ejection fraction.[57] The guideline strongly recommends GDMT to be implemented and monitored by a cardiologist with expertise in heart failure.[57] GDMT consists of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, beta blockers, aldosterone antagonists, sangiotensin receptor neprilysin inhibitor, and if appropriate, cardiac resynchronization therapy (CRT).[57] GDMT has been shown to reduce MR, likely through reversal of LV remodeling and recovery of LV function. In a randomized trial of 169 patients with dilated cardiomyopathy, MR reduction was seen in approximately 42% in the metoprolol group and 20% in the control group.[58] In a randomized trial of 118 patients, Kang et al.[59] showed that angiotensin receptor neprilysin inhibitor can reduce MR to a greater extent than valsartan, an ARB, alone. In heart failure patients with persistent symptoms and evidence of LV dyssynchrony despite maximal medical therapy, CRT is recommended. Though there are divergent recommendations in the specific threshold for CRT implantation (e.g., duration of the QRS complex, bundle branch morphology, and device type), CRT has been consistently shown to reduce MR, which is associated with improved survival, by decreasing leaflet tethering and augmenting LV closing force.[60-65] Once GDMT has



	MR Secondary to LV Remodeling	AFMR
Left ventricular size	Dilated	Normal
Left ventricular global systolic function	Reduced	Normal
Left ventricle regional wall motion	Inferoposterior hypo/akinesis or global hypokinesis	Normal
Mitral leaflet motion	Restricted	Normal or restricted (posterior leaflet)
Papillary muscle position	Often inferoposteriorly displaced	Normal
Mitral annulus size	Normal or dilated	Dilated
Left atrial size	Normal or dilated	Dilated
Main mechanism	Tethering	Annular dilation

Figure 7. Echocardiographic features of mitral regurgitation secondary to left ventricular remodeling and atrial functional mitral regurgitation. The hallmark of mitral regurgitation secondary to left ventricular remodeling is left ventricular apical leaflet tethering, represented by the orange triangle. The left ventricle is usually dilated with regional or global systolic dysfunction, and the left atrium is dilated to variable degrees. In AFMR, left ventricular size and function are usually normal, but there is left atrial and mitral annular dilation.
Abbreviation: AFMR, atrial functional mitral regurgitation; LV, left ventricle.

been optimized, patients should be followed by echocardiography every 3 to 6 months to follow LV remodeling and MR severity over time. MR can improve significantly in up to 40% of patients.

Surgery

A significant proportion of patients, however, do not respond to GDMT,[66] and therefore, MR reduction through surgery may be indicated, although the role of surgery in severe secondary MR is less clear. A randomized controlled trial in patients with moderate MR undergoing coronary artery bypass graft has shown that concomitant MV repair, despite durable reduction in MR, does not improve 2-year mortality or LV remodeling.[67,68] In a second trial where patients with severe secondary MR were randomized to either mitral repair or replacement, there was no difference in survival or LV reverse remodeling between the 2 groups at 2 years,[69] although there was >50% recurrence of significant MR in the MV repair group and increased heart failure events as well as hospitalizations. The current guidelines recommend that in patients with severe, symptomatic MR despite GDMT, surgical repair is reasonable if surgical revascularization is

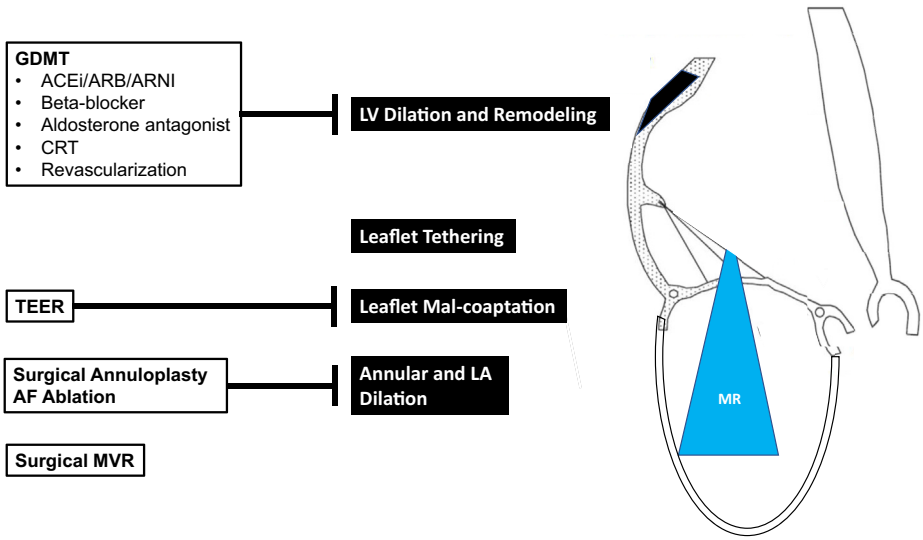


Figure 8. Evidence-based therapy to reduce mitral regurgitation includes guideline-directed medical therapy (GDMT), coronary revascularization or CRT to reverse LV remodeling, transcatheter edge-to-edge repair (TEER) that approximates leaflets and surgical MV repair or replacement (MVR). Ablation of atrial fibrillation may prevent atrial functional mitral regurgitation.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; AF, atrial fibrillation; CRT, cardiac resynchronization therapy; LV, left ventricle.

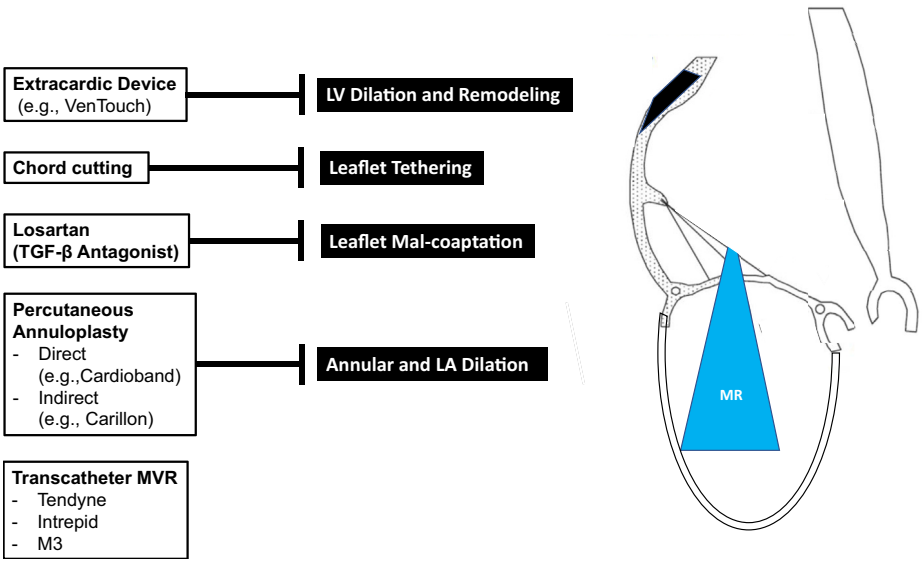


Figure 9. Potential therapies for secondary mitral regurgitation include extracardiac device that restrains LV dilation and remodeling, chordal cutting with surgery or percutaneous device, and medical therapies that favorably modify leaflet adaptation. Additionally, novel percutaneous mitral repair or replacement devices are being developed.
Abbreviations: LV, left ventricle; MVR, mitral valve replacement; TGF-β, transforming growth factor-β.

undertaken, and should be considered in patients with severe MR and LV ejection fraction >50%.[57]

Transcatheter Mitral Edge-to-Edge Repair (TEER)

There has been a growing interest in reducing secondary MR through transcatheter MV interventions[70]. The TEER technique uses a clip (e.g., MitraClip, Abbott Vascular) to approximate the anterior and posterior mitral leaflets and coaptation defect, thus creating a double-orifice valve.[71] Safety and efficacy of TEER in secondary MR was recently evaluated in 2 clinical trials.

The MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary MR) trial enrolled 304 patients with symptomatic heart failure and severe secondary MR. At 12 months, there was no difference in the composite primary endpoint of all-cause death and unplanned hospitalization for heart failure (intervention vs. control; 54.6 vs. 51.3%, $p = 0.53$).[72] The recently reported 2-year clinical outcome similarly showed no significant difference in outcomes between the intervention and the control groups (63.8 vs. 67.1%, hazard ratio 1.01, 95% CI, 0.77-1.34).[73] The COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional MR) trial enrolled 614 patients with at least moderate-to-severe secondary MR and symptomatic heart failure despite maximally-tolerated GDMT. In contrast to MITRA-FR, COAPT, reported significantly reduced hospitalization for heart failure (annualized rate of all hospitalization for heart failure at 24 months, device vs. medical group, 35.8 vs. 67.9%, $p < 0.001$) and all-cause mortality (29.1 vs. 46.1%, $p < 0.001$).[74] At 3-year follow-up, the investigators reported that MR reduction is durable[75] and that the between-group differences in clinical outcomes continued to diverge.

The discrepant results between these 2 trials have been a subject of vigorous debate and active research.[76-82] Despite comparable trial design, similar patient populations, and identical treatment strategies, there are important differences. Firstly, in the COAPT trial, patients were evaluated and managed by heart failure specialists to ensure optimal maximal tolerated dose of GDMT prior to and during study enrollment. On the other hand, MITRA-FR reflected a more "real-world" practice where medical therapy adjustment was variable and less supervised. Secondly, based on different guidelines,[18,83] MITRA-FR and COAPT used different EROA cutoffs to define significant MR. COAPT enrolled patients with more severe MR (average EROA for COAPT vs. MITRA-FR; 41 ± 15 vs. 31 ± 10 mm^2). Thirdly, in COAPT, patients with severe LV dilation (LV end-systolic dimension >7 cm) were excluded, so the average LV size was smaller than that of MITRA-FR patients. It is thus possible that COAPT patients had less advanced LV remodeling and higher likelihood for reverse remodeling. Lastly, COAPT had a higher procedural success rate (significant residual MR at 1 year, 5% vs. 17%) and a lower complication rate (8.5% vs. 14.6%).

In an attempt to reconcile these discrepant results, Grayburn et al.[84,85] put forward the concept of proportionate-disproportionate MR. The premise of this concept is that secondary MR in heart failure is a result of 2 processes: (1) progressive LV remodeling and (2) regional dyssynchrony due to tethering or left bundle branch block. The relative contribution between these 2 processes is different in each patient. When LV geometry is the sole contributor, one can expect the degree of MR to be proportionate to LV end-diastolic volume (LVEDV), and MR should improve with reverse LV remodeling when GDMT is instituted. On the other hand, if regional dyssynchrony is the predominant process, MR is disproportionately severe in relation to LVEDV. Disproportionate MR is unlikely to regress with GDMT, so CRT or TEER may be required. Applying this framework, Grayburn et al. reported that the COAPT population falls into the disproportionate category, where MR is excessive relative to LVEDV (large EROA, modest LV dilation). On the other hand, the MITRA-FR population had proportionate MR relative to LVEDV (modest EROA, severe LV dilation). To validate this concept, investigators performed a post hoc analysis and found that at 12 months, the only subgroup that did not benefit from TEER was a MITRA-FR-like group, with a EROA/LVEDV of 0.11 (EROA/LVEDV of MITRA-FR patients is 0.12).[86] In support of this concept, investigators found that patients with disproportionate MR, when managed medically, have worse outcomes, which may be corrected by TEER.[86] Similarly, in a large real-world registry of patients that underwent TEER, disproportionate MR (which, in theory, is corrected by TEER) is associated with better survival.[87]

Other studies, however, have challenged the applicability of the proportionate-disproportionate MR theory. In a post hoc analysis of the COAPT population, investigators found that the "MITRA-FR-like subgroup" still had significant improvement in their quality of life and functional status at 2 years.[88] Similarly, when the MITRA-FR investigators performed a post hoc analysis, dividing their study population according to MR severity, the extent of LV remodeling and a combination of these (including EROA/LVEDV), none of the subgroups derived benefits from TEER.[89] Similarly, a multi-center retrospective analysis also showed that echocardiographic parameters used to categorize patients into proportionate and disproportionate groups did not have independent prognostic value in patients undergoing TEER.[90]

Given the limitations of current studies (post hoc subgroup analysis, retrospective registry analysis, and small sample size), the proportionate-

disproportionate MR theory remains intriguing, and needs to be validated in prospective studies. In the absence of other proven patient selection strategies, clinicians should for now closely follow the COAPT trial inclusion and exclusion criteria, and in particular, take a heart team approach including active engagement of heart failure specialists.

Future Directions

Novel therapies are being developed with exciting results anticipated in the short, medium, and long term (Figures 8 and 9). In the short term, pooled analyses of COAPT and MITRA-FR trials may hopefully explain the conflicting result and help guide optimal patient selection. Current TEER devices are continuously being refined, allowing incremental improvement in safety and procedural success. The RESHAPE-HF2 trial (A Clinical Evaluation of the Safety and Effectiveness of the MitraClip System in the Treatment of Clinically Significant Functional Mitral Regurgitation, NCT02444338), enrolling patients with MR severity similar to COAPT, but LV function similar to MITRA-FR, is currently underway and could be a "tie-breaker" defining the optimal target population of TEER. On the other hand, the MATTERHORN trial (A Multicenter, Randomized, Controlled Study to Assess Mitral vAlve reconsTrucTion for advancEd Insufficiency of Functional or iscHemic ORigiN Left ventricular end diastolic volume, NCT02371512) will compare surgery to MitraClip in patients with secondary MR and high surgical risk.

In addition to currently available TEER, novel transcatheter technologies are at various stages of clinical trials. Based on the mechanism of action they fall into 2 broad categories: In the first category, transcatheter annuloplasty is achieved either directly by cinching the mitral annulus (e.g., Cardioband, Edward Lifesciences; Millipede, Boston Scientific) or indirectly through tightening of the coronary sinus (e.g., Carillon, Cardiac Dimensions). These devices have been shown to be safe and effective in early feasibility trials, and some have entered phase III trials (NCT03016975, NCT03142152).[91,92] The second broad category is transcatheter MV replacement, and examples include the Intrepid (Medtronic), Tendyne (Abbott Vascular), and the Sapien M3 (Edward Lifesciences). The Intrepid valve (Medtronic) consists of an outer ring that attaches and conforms to the mitral annulus and an inner stent that houses the bovine tissue valve. The Tendyne system (Abbott Vascular) has a dual frame valve and a tether that is connected to and secured by an LV apical pad placed over the apical access site. The Sapien M3 (Edwards Lifesciences) system uses a nitinol spiral which encircles the chordae and the MV leaflets to create a "dock" where a bioprosthetic valve (Sapien S3, Edwards Lifesciences) is implanted into. Transcatheter MV replacement holds the promise of consistent and durable elimination of MR across diverse leaflet pathologies, some of which are not amenable to TEER. However, challenges remain, including difficulties in achieving adequate annular seal, and the risk of neo-LV outflow tract obstruction. Following encouraging results from early feasibility studies,[93-95] these devices have entered phase III trials (NCT03242642, NCT03433274, NCT04153292).

Future additional treatment strategies are being developed and may come to fruition in the long-term. For example, LV shape may be remodelled by placing inflatable chambers external to the pericardium to reposition the PMs and decrease leaflet tethering. (VenTouch, Mardil). Alternatively, it may be possible to relieve leaflet tethering by selectively cutting chordae. Animal studies as outlined above and small-scale, retrospective studies have implicated the therapeutic potential of angiotensin II blockade.[49] Medical therapies that directly target the MV leaflets to promote favorable MV remodeling resulting in just large enough and pliable leaflets to ensure adequate coaptation would offer a potential ground-breaking secondary MR treatment approach, but much work remains to be done.

Conclusion

Significant progress has been made in understanding the mechanisms of secondary MR, and the diagnosis and treatment of this complex condition. Secondary MR assessment, especially severity grading, can be challenging and a thoughtful synthesis and integration of all available information is essential. The importance of recognizing and optimally treating underlying ischemic and nonischemic heart failure by GDMT and if indicated, revascularization and/or CRT, is paramount prior to considering MV surgery and especially TEER. Research in optimizing TEER patient selection and MV leaflet targeted medical therapies, as well as the ongoing development of transcatheter therapies will benefit patients with secondary MR in the coming years.

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