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Exercise Dynamics in Secondary Mitral Regurgitation: Pathophysiology and Therapeutic Implications

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Abstract

Secondary mitral valve regurgitation (MR) remains a challenging problem in the diagnostic work-up and treatment of heart failure patients. Although secondary MR is characteristically dynamic in nature and sensitive to changes in ventricular geometry and loading, current therapy is mainly focused on resting conditions. Exercise-induced increase in secondary MR, however, is associated with impaired exercise capacity and increased mortality. In an era where a multitude of percutaneous solutions are emerging for the treatment of HF patients it becomes important to address the dynamic component of secondary MR during exercise as well. A critical reappraisal of the underlying disease mechanisms, and in particular of the dynamic component during exercise is of timely importance. This review summarizes the pathophysiologic mechanisms involved in the dynamic deterioration of secondary MR during exercise, its functional and prognostic impact, and the way current treatment options affect the dynamic lesion and exercise hemodynamics in general.

Keywords

secondary mitral valve regurgitation; exercise testing; heart failure; mitral valve surgery; exercise capacity

Introduction

Secondary mitral valve regurgitation (MR) is a challenging problem in the diagnostic work-up and treatment of heart failure (HF). It occurs in 11 to 59% of patients after a myocardial infarction[1, 2] and is present in more than half of patients with dilated cardiomyopathy[3–5].

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None.

Despite this high prevalence, the optimal approach to secondary MR remains a matter of debate, and the level of evidence for guideline recommendations is disappointingly low[6, 7]. Particularly controversial remains the question whether moderate and mild-moderate MR should be regarded as treatment targets: It is well known that outcomes and exercise capacity are impaired in secondary MR, even when only mild[8, 9]. This association may simply reflect the fact that the occurrence of MR, even if only mild, is a marker of more advanced disease. However, it could also be rooted in the characteristically dynamic behavior of secondary MR, often becoming more severe during exercise (Figure 1; Movie Clips 1–4) or with changing loading conditions[10]. To date, our knowledge of exercise dynamics in secondary MR is insufficient: Does relief of the dynamic lesion result in better outcome? Is the prognosis of severe exercise-induced MR (resting mild MR) comparable to resting severe MR? Should such patients be referred for surgical treatment? Do we even know the potential impact of the available therapies for secondary MR on the respective exercise hemodynamics? In an era where a multitude of percutaneous solutions are emerging for the treatment of HF patients it becomes important to understand who may benefit from a specific therapy and who not. A critical reappraisal of our knowledge of the underlying disease mechanisms, and in particular of the dynamic component of secondary MR during exercise, is therefore of timely importance.

This review summarizes pathophysiological mechanisms involved in the dynamic deterioration of secondary MR, its functional and prognostic impact, and the manner in which current treatment options affect dynamic MR and exercise hemodynamics in general. Finally, potential targets for future research are highlighted.

Pathophysiology

The mitral valvular apparatus

More than just a pair of leaflets, the mitral valve is an intricate apparatus comprised of multiple components (i.e., the mitral annulus, anterior and posterior leaflets, chordae tendineae, anterolateral and posteromedial papillary muscles and adjacent left ventricular wall) finely tuned to work together in ‘sealing’ the passage of blood from the left ventricle to the left atrium in systole, while at the same time enabling unrestricted inflow during diastole. Several mechanisms interplay during systole: (1) annular contraction and (2) left ventricular wall motion causing inward displacement of the papillary muscles, to facilitate leaflet coaptation while minimizing leaflet stress, and (3) measured contraction of the papillary muscles to avoid leaflet prolapse. A delicate balance is maintained between tethering forces (transmitted via the left ventricular wall, papillary muscles and chordae tendineae system influenced by annular/leaflet dimensions) and valve closing forces (left ventricular contractility and synchrony, mitral annular systolic contraction). Disruption in any of these mechanisms may unsettle the force balance and result in MR[11].

A mechanistic insight into secondary MR

Secondary MR results from a *functional* imbalance between increased tethering forces (annular and/or left ventricular dilation, segmental or global left ventricular dysfunction with papillary muscle displacement/dysfunction) and decreased closing forces (reduced left

ventricular contractility or synchrony) in the presence of a structurally normal valve. As a result, increased traction of the mitral valve leaflets – tethering – occurs during systole, resulting in incomplete coaptation and MR (Figure 2). This balance of forces creates a lesion that is evidently dynamic even within one cardiac cycle (Movie Clip 3): Schwammenthal et al[12] demonstrated a typical decrease in MR during ventricular contraction with a minimum in mid-systole (at the time of peak orifice velocity and peak systolic pressure), and an increase again during ventricular relaxation, suggesting a decisive impact of the instantaneous left ventricular-to-atrial pressure difference on leaflet coaptation. While a mid-systolic decrease in annular area could also contribute to this phenomenon it was subsequently shown that variation in annular area in patients with left ventricular dysfunction is minor and insufficient to explain the degree of observed orifice area variation[13]. In addition, it was shown that an acute rise in closing force due to acute activation of cardiac resynchronization therapy (CRT) in patients with dilated hearts and secondary MR also reduces the degree of MR significantly (Figure 3)[14]. However, an impaired closing force is not the primary cause of secondary MR in HF. Numerous studies, both in vitro[15] and in vivo[16, 17], have demonstrated that increased tethering is a prerequisite for occurrence of secondary MR, and geometric disturbances of the left ventricle are key in the dynamic imbalance between closing and tethering forces. In an animal model of left ventricular systolic dysfunction without ventricular dilation, only trace MR was observed and tenting depth was the only predictor of MR, in contrast to ejection fraction or dP/dt[16]. Hence tethering (i.e. geometry) sets the stage for secondary MR, while the closing force merely modulates its severity. More recent studies have confirmed that not left ventricular dimensions per se, but rather the position and dynamics of the papillary muscles are major determinants of secondary MR[18–20]. In a normal-sized left ventricle with regional wall motion abnormalities causing one or both papillary muscles to be displaced, to move asymmetrically[18, 19] or dyssynchronous[20, 21], tethering forces increase, disrupting the force balance and causing secondary MR.

A dilated mitral annulus further augments these effects and increases MR[18], although concomitant subvalvular tethering is usually needed to cause more than moderate MR[22]. Isolated annular dilation in patients with normal left ventricular dimensions and function, however, is an increasingly important cause of moderate (or more) secondary MR, particularly in patients with (long-standing) persistent or permanent atrial fibrillation[23, 24]. Such “atrial” functional MR has shown to be potentially reversible with rhythm control strategies (e.g. atrial fibrillation ablation)[23], and typically responds well to annular reduction strategies[25].

Of note, unlike the classic belief, the mitral valve leaflets are not innocent ‘healthy’ bystanders, but play an active role in the pathophysiology of secondary MR by undergoing significant leaflet tissue changes and adaptation[26, 27]. In reaction to the mechanical stretch, active leaflet growth and leaflet enlargement have been demonstrated[28–30], sometimes (e.g. in chronic aortic regurgitation) even matching the severe chamber dilation, hence preventing secondary MR[31]. Conversely, in case of insufficient leaflet adaptation and/or adverse fibrotic leaflet changes, the leaflets’ maladaptive response might even contribute to the development and severity of secondary MR[32].

Finally, inter-individual differences in mitral valve geometry, such as the inborn relative position of basal chordae tendineae insertion sites, modulate the individual susceptibility to development of (severe) secondary MR[33].

The normal cardiovascular response to exercise

During exercise, the cardiovascular system adapts to meet increased oxygen demands of peripheral muscles[34]. Stimulation of the sympathetic system and withdrawal of the vagal tone result in increasing heart rate and myocardial contractility, and a decrease in systemic vascular resistance, thus increasing cardiac output[35]. The dynamic response of the left ventricle depends on the type of exercise performed, which can be either dynamic (isotonic), static (isometric), or a combination of both. In dynamic exercises (e.g. running, cycling, swimming), multiple muscle groups contract in order to achieve joint movement. Such activity is associated with profound vasodilation in the muscular vasculature causing a significant reduction in systemic vascular resistance to almost half its value at rest[34], and a substantial increase in venous return due to the skeletal muscle pump. The decreased afterload, increased contractility, and increased venous return result in a significant increase in stroke volume. The rise in cardiac output is therefore mediated by an increase in stroke volume, with heart rate becoming the dominant determinant as stroke volume reaches its plateau[35]. In static exercise on the other hand (e.g. weightlifting, handgrip), systemic vascular resistance is not decreased and might even be increased. In the absence of afterload reduction, the stroke volume remains largely unchanged and the rise in cardiac output is determined mainly by the increase in heart rate. Hence, static exercise imposes a pressure load on the left ventricle, whereas dynamic exercise constitutes a volume load[35]. These differential loading conditions translate into different left ventricular geometric changes during exercise, as has been studied with radionuclide angiography[36, 37], echocardiography[38, 39] and cardiac magnetic resonance imaging[40]. In healthy subjects, dynamic exercise is associated with no increase (or a transient increase at mild-to-moderate exercise[38]) of the end-diastolic volume (EDV), while a concomitant decrease in end-systolic volume (ESV) is observed. This results in a substantially increased stroke volume and ejection fraction. In contrast, during static exercise, no significant changes in either ESV or EDV occur[41, 42].

The pulmonary circulation adapts to the increased cardiac output and (mildly) increased left atrial pressures during exercise by recruiting and distending pulmonary arterial vessels, hence decreasing the pulmonary vascular resistance and blunting the rise in pulmonary pressures in response to a significant increase in flow and volume[43, 44]. In healthy individuals, the increase in mean pulmonary pressure with respect to cardiac output is not expected to surpass 3.0mmHg/L/min[43]. As a rule of thumb, a mean pulmonary pressure during exercise >30mmHg at cardiac output <10L/min is considered abnormal (however in trained athletes values up to a mean pulmonary pressure of 50 mmHg have been reported)[45].

Secondary MR during exercise

Left ventricular geometry—In patients with ischemic or idiopathic cardiomyopathy the left ventricular volumetric response to dynamic or static exercise may differ significantly from that observed in normal subjects[37, 46, 47]. In general, both volume loading in dynamic

exercise and pressure loading in static exercise result in exercise-induced ventricular dilation (EDV and ESV both tend to increase), while ejection fraction typically remains unchanged. The increase in left ventricular EDV during exercise is reported to be greater in ischemic (than in idiopathic dilated) cardiomyopathy[46], which may be directly related to the extent of myocardial scar[48], a finding of particular importance for the exercise dynamics of secondary MR. In addition, exercise may result in dyssynchronous contraction of the left ventricle in HF with (rate-dependent) conduction delay[49]. While the acute rise in blood pressure during static exercise increases the mitral closing force, this is completely outweighed by increased mitral tethering resulting from the impact of the rise in afterload on left ventricular geometry. Consequently, significant increases in secondary MR have been observed during static exercise[47]. Significant increases in systemic venous resistance are generally not observed during dynamic exercise in patients with cardiomyopathy. However, failure of adequate arterial dilatation during exercise occurs[50] and, in the presence of an increased volume load, contributes to exercise-induced ventricular dilatation. Dynamic exercise studies therefore demonstrate increases in secondary MR in >75% of HF patients, both with ischemic[51–55] and non-ischemic etiology[54–59]. Table 1 summarizes the current literature on determinants of increasing secondary MR during exercise in HF. Interestingly, neither left ventricular volume nor ejection fraction at rest or during exercise are reliable predictors of exercise-induced MR deterioration. In fact, with respect to exercise-induced left ventricular dilatation, changes in shape (local remodeling) may count more than changes in the actual volume[51]. An increase in left ventricular sphericity, which correlates with greater papillary muscle distance, may have a pronounced effect on mitral geometry even without a significant change in volume. On the other hand, an increase in left ventricular volume caused by apical dilatation of the cavity (which does not involve the mitral valve apparatus) will have no effect on mitral valve geometry. It is therefore not surprising that, when looking at variables at rest that can predict worsening of MR during exercise, left ventricular sphericity and papillary muscle dyssynchrony are more useful along with mitral valve tenting, which reveals an already strained balance between closing and tethering forces. In addition, progressive annular dilation during exercise may be a contributor to exercise-induced MR in a majority of cases and is most predictive in non-ischemic cardiomyopathy[55].

Left ventricular scar—Especially in ischemic cardiomyopathy, the extent and localization of scar plays an important mechanistic role in dynamic MR deterioration (Figure 4)[48]. Following an anterior wall myocardial infarction extending to the apical segments of the inferior wall, patients show more apically tethered mitral leaflets, with coaptation depth being a determinant of exercise-induced MR deterioration[51, 52]. In patients with inferior wall infarction on the other hand, regional wall motion abnormalities during exercise tether the mitral valve more posteriorly, frequently restricting in particular the posterior leaflet, and increasing the annular dimension (in particular around P2–P3), thereby aggravating MR in a somewhat different way. Interestingly, significant contractile reserve of the inferoposterior wall in the latter group is related to an exercise-induced *decrease* in secondary MR, as tethering forces are reduced and the mitral annulus less distorted[51]. Large infarctions (which are frequently more anterior) or multiple infarctions leading to severe

remodeling lead to more spherical ventricles with greater papillary muscle separation exerting traction on the mitral valve from opposing ends.

Closing versus tethering forces during exercise—Intriguingly, predictors of increasing MR during exercise (Table 1) are all related to left ventricular geometry[51, 52], indicating that in the failing ventricle increases in tethering during exercise outweigh by far increases in closing force. This is supported by the observation that although onset of CRT causes an early decrease in secondary MR at rest (due to an immediate increase in closing forces[14]), this effect is not maintained during exercise. Indeed, early after CRT, secondary MR often deteriorates to pre-CRT severity during dynamic exercise, despite an acute reduction in resting MR[60]. Only after reverse left ventricular remodeling has taken place (resulting in reduced tethering forces), significant reductions in exercise-induced MR are observed (Figure 5)[60].

Of note, induction of myocardial ischemia during exercise in coronary artery disease associated with reversible wall motion abnormalities and a decrease in ejection fraction can also result in a subsequent increase in MR[61]. This type of MR, however, is not discussed here, since the underlying mechanisms (inducible reversible ischemia) and treatment approaches (revascularization) are different from the topic of this review. The term ‘ischemic MR’ in this review refers exclusively to post-myocardial infarction MR in patients with stable coronary heart disease. In these patients, it is the scar tissue and ventricular remodeling that truly determine the dynamic deterioration of MR during exercise[62].

Prognostic and functional impact of the dynamic lesion of mitral valve regurgitation

Exercise-induced increase in secondary MR is associated with poor exercise capacity[54, 59, 63] and outcomes[9, 64–67] (Figure 6). In a mixed cohort of ischemic and non-ischemic cardiomyopathy, Lapu-Bula et al[54] were the first to demonstrate a significant negative impact of exercise-induced MR deterioration on exercise capacity, even though MR was only mild-to-moderate at rest. The mechanism by which dynamic MR impairs exercise capacity is (1) an inhibition of the expected increase in exercise forward stroke volume, and (2) an exaggerated increase in exercise left atrial and pulmonary pressure[54]. The backward hemodynamic cascade of increased left atrial pressures and decreased left atrial compliance causes backward pulmonary venous congestion, gradually initiating pathologic changes in the pulmonary vasculature, thus increasing pulmonary vascular resistance and pulmonary arterial pressure[68]. Moreover, systolic pulmonary artery pressure during exercise is associated with dynamic increase in effective regurgitant orifice area (EROA)[64, 69, 70], and is a particularly relevant hemodynamic (echocardiographic) parameter to assess during exercise in the evaluation and prognostication of secondary MR[69, 71].

Piérard and Lancellotti[72] further showed that exercise-induced MR deterioration, by augmenting backward flow and pulmonary vascular congestion may contribute to the development of acute pulmonary edema. Importantly, a significant increase in EROA during exercise (defined as an increase >13mm^2) is observed in 30% of HF patients and associated with increased mortality as well as readmissions[9, 64]. Furthermore, all-cause mortality in HF

patients with secondary MR follows a graded relationship with respect to MR severity, with EROA >20mm^2 already implying poor outcome[8, 66]. This contrasts to the 40mm^2 cut-off that is traditionally used in primary MR. Although occurrence of secondary MR is also a marker of underlying heart disease, the lower EROA threshold in secondary MR could also be rooted in the typically dynamic nature of secondary MR, which is frequently underestimated at rest. Therapies for secondary MR aiming at improved exercise capacity and outcomes should therefore not only focus on resting status, but also reduce the dynamic component of MR.

Impact of treatment approaches for secondary MR on exercise dynamics

A complete and detailed overview of the evidence for the various therapeutic approaches for secondary MR, comprising guideline-directed HF medication, CRT, revascularization when appropriate, as well as mitral valve surgery and transcatheter interventions[67], is beyond the scope of this review. Instead, a critical evaluation of the (potential) impact of these therapies on the dynamic lesion in secondary MR is made based on the underlying determinants causing exercise-induced MR aggravation (Figure 7).

Medical therapy

Medical therapy remains a cornerstone in the treatment of chronic HF and secondary MR. Adequate decongestion should be pursued at all times and patients should take the maximally tolerated guideline-recommended[73] target doses of neurohumoral blocker therapies. Adherence to neurohumoral blocker therapy reverses adverse left ventricular remodeling[74, 75], although a reduction in secondary MR has only been reported in non-randomized small-sample series[76].

In order to understand the potential effect of a drug on the severity of secondary MR it is helpful to view it in terms of the underlying lesion mechanism: the tug of war between mitral closing and tethering forces. Table 2 summarizes the effects of the most frequently used HF medications[4]. Preload-reducing medications, such as diuretics and nitrates, may significantly decrease the tethering forces, thus reducing EROA. These medications may also enhance mitral closing forces, as they tend to decrease left atrial pressure (reduce the size of V-waves) more than systolic left ventricular pressure, in particular in the presence of high left ventricular end-diastolic pressures. Since the failing heart operates on the flat portion of the cardiac function curve a significant reduction in left ventricular end-diastolic pressure will not affect cardiac output and systolic blood pressure significantly. Afterload-reducing drugs can also relieve tethering significantly in left ventricular dysfunction by decreasing left ventricular size and improving its shape.

Whether such potential effects of medical therapy translate into attenuated exercise dynamics in secondary MR remains largely unknown. Most of the literature on this topic predates the era of neurohumoral blocker treatment in HF. Nevertheless, some interesting observations deserve attention: (1) nitrates (nitroglycerin, isosorbide dinitrate), mainly by reducing cardiac preload, offer a consistent and sustained reduction in left ventricular EDV as well as ESV at rest and during exercise in healthy subjects and patients with coronary artery disease[77]. Because they unload the heart, significant benefits on left ventricular

performance (i.e., increased stroke volume and decreased pulmonary arterial wedge pressure) are observed during exercise in HF patients treated with digoxin and diuretics[78]. In this context, a significant reduction in dynamic secondary MR was also observed[79]; (2) combined pre- and afterload reduction with nitroprusside and diuretics significantly reduces left ventricular EDV during upright bicycle exercise, thereby significantly decreasing secondary MR and increasing forward stroke volume in advanced HF[80]; (3) arteriolar vasodilation (hydralazine) and venodilation (nitroglycerin) offer a synergistic reduction in pulmonary arterial wedge pressure and V-wave amplitude during static exercise in patients with chronic MR[81]; (4) intensive medical unloading of the heart in acute decompensation results in a significant decrease in intraventricular dyssynchrony, even in the absence of CRT[82].

Cardiac Resynchronization Therapy

CRT reduces secondary MR[83] and improves outcomes in patients with symptomatic HF with reduced ejection fraction and intraventricular conduction delay[84]. The mechanism by which CRT reduces secondary MR is three-fold, comprising both acute and chronic effects that optimize the force balance[85]: (1) an acute rise in - and longer duration of – the systolic closing force (dP/dt) immediately after onset of CRT[14]; (2) an immediately improved coordinated mechanical contraction of the papillary muscles, which reduces tethering[86]; and (3) long-term reverse left ventricular remodeling with significant reductions in EDV and ESV, which further lessens tethering forces[83, 86, 87], and is probably the clinically most important effect.

The dynamic component of secondary MR during exercise is attenuated by CRT as well[88, 89], resulting in increased forward stroke volume during exercise[90] and improved exercise capacity[91]. However, dynamic worsening of MR during exercise is not entirely prevented by CRT[88]. The mechanism of MR reduction during exercise does not seem to be related to the acute effects, but probably relies on longer term reverse left ventricular remodeling and reduced dyssynchrony (Figure 5)[60]. Of note, the extent of reverse remodeling after CRT is most favorable in non-ischemic etiologies of HF[83]. The acute effects of CRT on the force-balance relationship are reversible, as cessation of biventricular pacing for 72h immediately causes a drop in dP/dt and an increase in secondary MR[92]. Furthermore, acute withdrawal of biventricular pacing after 6 months in patients with papillary muscle dyssynchrony results in recurrent dyssynchrony and abrupt reappearance of secondary MR[93].

CRT is considered a valid and less invasive alternative to surgery in eligible patients with moderate-to-severe secondary MR and reduced ejection fraction as well as broad QRS complex, based on a long-term survival benefit in this particular population[94]. Currently, CRT is not indicated in HF patients with narrow QRS complex and it has been shown that worsening of left ventricular dyssynchrony may be associated with exercise-induced MR deterioration and worse outcomes[56]. Finally, even after CRT, 37–50% of patients show less than 1 grade improvement in MR[86, 94]. In such patients, additional interventions should be considered.

Revascularization

In patients with ischemic cardiomyopathy and (moderate) secondary MR, revascularization can recruit viable myocardial segments and enhance reverse left ventricular remodeling, thereby reducing the degree of secondary MR in a majority of patients[95]. Whether this strategy is effective in reducing the dynamic component of MR during exercise is unknown. Secondary MR improvement at 1 year after isolated coronary artery bypass grafting (CABG) was predicted by ≥5 viable segments of myocardium (16 segment model) and absence of papillary muscle dyssynchrony in the prospective study of Penicka et al[96]. This observation has important implications with respect to exercise: (1) viability post-infarction; i.e. preserved contractile reserve during exercise, has been shown to decrease exercise-induced MR[51, 52], especially when inferior (basal) segments are involved; (2) papillary muscle dyssynchrony is implicated as an independent determinant of exercise-increased MR (Figure 7). Hence, the patients most likely to show improvement of secondary MR at rest after isolated revascularization (myocardial viability and/or papillary muscle synchronicity) are also the patients least likely to exhibit worsening of secondary MR during exercise preoperatively. Hypothetically, based on these findings, coronary artery disease patients with worsening of secondary MR during exercise (not associated with evidence of inducible ischemia) are less likely to show improvement of MR following isolated revascularization, and may therefore benefit from adjunctive therapy or intervention. This should certainly be subject to further study and exploration.

In the only prospectively randomized study to date that employed postoperative exercise echocardiography when comparing CABG versus CABG with mitral valve annuloplasty for moderate secondary MR, the dynamic (exercise-induced) MR component remained highly prevalent in the isolated CABG arm, but not after adjunctive mitral valve annuloplasty (Figure 8)[97]. Furthermore, in the Randomized Ischemic Mitral Evaluation (RIME) trial a better improvement in exercise capacity after 1 year was observed in the combined CABG with mitral valve annuloplasty arm than in the isolated CABG group, possibly due to improved dynamic MR during exercise[98]. In contrast, the moderate ischemic MR trial of the CardioThoracic Surgical trials Network (CTSN), comparing 151 patients with moderate ischemic MR undergoing CABG alone with 150 receiving concomitant mitral valve annuloplasty, did not demonstrate a difference in left ventricular remodeling (primary endpoint), functional capacity, or clinical outcome after 1 year[95]. However, in contrast to the RIME trial[98] and the randomized trial by Fattouch et al[97], exercise dynamics were not taken into account.

Mitral valve surgery

The surgical management of secondary MR remains challenging and controversial[67]. Not only the optimal surgical strategy but also indications for surgery remain highly debated, especially in case of moderate (possibly dynamic) secondary MR. Prospective randomized data to help decision-making are scarce, and the definition of moderate and severe secondary MR in the guidelines (severe = EROA ≥20mm^2 instead of ≥40mm^2) has been challenged[99, 100]. Inclusion criteria of all prospectively randomized clinical trials on mitral valve surgery for secondary MR are provided in Supplementary Table 1. It is unclear where mild-to-moderate secondary MR at rest that significantly increases during exercise can be

situated, or whether alternative EROA thresholds for MR severity should apply for exercise-induced MR. Preoperative exercise echocardiography was performed only in the RIME trial. Based on the prognostic impact of exercise-induced secondary MR deterioration, the European (ESC) guidelines suggest mitral valve intervention in such patients when there is an indication for other cardiac surgery[6]. However, the impact of the available surgical approaches on the dynamic component of secondary MR and the respective exercise hemodynamics needs to be better understood.

Mitral valve annuloplasty—Mitral valve annuloplasty for secondary MR typically involves the insertion of an undersized prosthetic ring (‘restrictive’ annuloplasty), thereby reducing the anteroposterior dimensions of the mitral annulus, resulting in better apposition of the leaflets and increased coaptation (target coaptation length ≥8mm)[101]. The mechanism of action is two-fold: annular dimensions (typically dilated) are reduced, while the coaptation surface of the leaflets increases, thereby allowing more efficient use of closing forces during systole. At midterm follow-up, this procedure has shown to induce significant reverse left ventricular remodeling and improved systolic function, making it an effective strategy for patients with moderate to severe secondary MR[98, 101, 102].

Secondary MR did not recur during exercise in patients treated with restrictive mitral valve annuloplasty and CABG in the randomized study of Fattouch et al (Figure 8)[97]. In another cohort study of 43 secondary MR patients, exercise echocardiography at 33±17 months after restrictive annuloplasty showed absence of more than mild MR at rest and during exercise in all but 4 subjects[103]. Hypothetically, inhibition of annular dilation during exercise, along with reverse left ventricular remodeling and optimization of the force balance, should be able to reduce the dynamic component of secondary MR, but not to abolish it, as tethering might still increase during exercise (Figure 7).

In addition, there is some concern that increased transmitral gradients after restrictive annuloplasty are associated with exercise-induced pulmonary hypertension and worsening functional capacity[104]. Although this was initially attributed to the small ring size, it was demonstrated recently that not the size of the prosthetic ring but rather the degree of subvalvular diastolic leaflet tethering is responsible for this functional stenosis after surgery. The effective mitral valve area at peak exercise was the strongest predictor of impaired exercise capacity and directly associated with all-cause mortality (Figure 9)[103, 105]. This should certainly be taken into account in the decision-making of patients with dynamic secondary MR, and adjunctive approaches that relieve diastolic tethering after surgery should be further explored.

Finally, in patients with severe secondary MR at rest, recurrence of moderate MR in up to 30% in the course of the first year after surgery is well recognized[106, 107], with pathophysiological mechanisms mainly related to ongoing adverse remodeling and subvalvular tethering, usually in patients with already severely dilated left ventricles[108]. Importantly, preoperative presence of basal inferior wall aneurysm or dyskinesia was most predictive for MR recurrence in the annuloplasty group of the randomized severe MR CTSN trial[109]. In such patients, either adjunctive subvalvular/ventricular procedures to relieve tethering or mitral valve replacement should be considered.

Mitral valve replacement—Exercise-induced MR is definitively abolished after successful mitral valve replacement. However, similar concerns of transmitral gradients and exercise-induced pulmonary hypertension apply, especially in patients with some degree of prosthesis-patient mismatch[110]. In patients with secondary MR treated with mitral valve replacement, effective orifice area was in fact an important independent predictor of exercise-induced pulmonary hypertension and functional capacity[111]. Therefore, when opting for mitral valve replacement for treating dynamic secondary MR, careful selection of prosthesis type and size is warranted to maximize postoperative effective orifice area and avoid abnormally high transprosthetic gradients during exercise.

Ventricular and/or subvalvular approaches—Since tethering is the primary mechanism causing secondary MR and its exercise-induced deterioration, targeted ventricular or subvalvular procedures reducing the degree of mitral leaflet traction is a particularly promising approach (Figure 7). Furthermore, successful relief of tethering may also reduce the risk of functional mitral stenosis and thus improve exercise hemodynamics after restrictive annuloplasty[103]. However, ventricular reshaping strategies (aneurysmectomy, external constraint devices) have not been shown to be more effective in reducing MR than conventional mitral repair techniques (although they may be associated with independent survival benefits)[112–114], and data regarding impact on exercise dynamics are lacking. A number of subvalvular approaches have been developed in animal studies and applied in small observational clinical series, with mixed levels of success[115]. Mitral leaflet augmentation, surgical papillary muscle relocation and/or approximation, or secondary chordal cutting have been proposed, as well as attempts to locally remodel the left ventricle e.g. by injecting a polymer in the ventricular wall, acting as a tissue-bulking agent reversing the ischemic distortion and limiting the outward displacement of the papillary muscle(s)[116, 117]. Despite promising results in small sample series or animal studies, none of these subvalvular or ventricular techniques have gained widespread clinical use or acceptance. Nevertheless, such lack of widespread use should not be seen as a refutation of the concept; it rather reflects the fact that some of the techniques are technically demanding. In fact, off-pump papillary muscle repositioning under echocardiographic guidance using a transventricular suture, combined with less restrictive annuloplasty using a partial ring (RING plus STRING technique), has been shown to produce an effective and lasting relief of tethering in the most challenging group patients: those with a tethering distance of ≥10 mm[118].

Because the specific mechanisms of subvalvular tethering and secondary MR are heterogeneous and show large interindividual variations, the optimal subvalvular approach may require a personalized approach: targeting the individual patient’s geometry, including individually observed exercise-induced aggravation in tethering and MR

Transcatheter mitral valve interventions

Transcatheter edge-to-edge mitral valve repair using the MitraClip® device (Abbott Vascular, Menlo Park, California) involves a percutaneous transseptal left atrial approach emulating the Alfieri stitch by clipping the mitral valve leaflets together. Although randomized data from the Endovascular Valve Edge-to-Edge Repair Study (EVEREST II)

mainly support MitraClip therapy in primary organic MR[119] (for which the Alfieri stitch was originally intended) real-world registries show that it is predominantly used for secondary MR in clinical practice[120]. The rationale for MitraClip in secondary MR arises from the uncertain risk-benefit ratio of mitral valve surgery in patients with left ventricular dysfunction, in particular if there is no other indication for cardiac surgery[67]. The mechanism of action by which MitraClip may reduce secondary MR is (1) an acute increase in coaptation area improving closing force efficiency[121]; and (2) a slight decrease in annular (antero-posterior) dimensions[122] relieving tethering. Tenting area is generally not reduced in the acute phase[121], but may reduce over time in patients with significant reverse left ventricular remodeling post-procedure[123].

To investigate whether these beneficial effects on remodeling translate into reduction of dynamic secondary MR a prospective multicenter study was performed in three Belgian centers (substudy of the Belgian MitraClip Registry, NCT02506387) comparing exercise echocardiography before and 6 months after MitraClip. In 31 secondary MR patients a significant reduction in secondary MR at peak exercise after 6 months, along with increased cardiac output and decreased pulmonary arterial pressures (Figure 10)[124]. However, a potential downside of the therapy is the reduction in mitral valve area caused by clipping the large mitral orifice into a double orifice of smaller size, causing increased transmitral pressure gradients at rest and during exercise[125]. The prospective Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial is currently recruiting secondary MR patients to compare MitraClip therapy with standard medical care. In a subset of patients, exercise testing will be performed (NCT01626079)[126]. These data may provide important insight into the impact of MitraClip therapy on exercise hemodynamics and outcomes.

Numerous other percutaneous devices for mitral replacement and/or repair are currently under development in preclinical or phase I/II studies. Targets for repair include the mitral leaflets, chordae, annulus or left ventricle[127].

Future research

Due to the paucity of data on exercise MR the approach to exercise-induced MR must, for the time being, rely heavily on pathophysiological insights gained from resting studies. At this point, we cannot offer definitive answers, only more precise questions, the most important of which may be: Can reduction of the dynamic component of secondary MR independently improve outcome? Is there an EROA threshold for secondary MR at peak exercise beyond which intervention is warranted even if resting MR is relatively mild? Is there a place for more aggressive ‘unloading’ of the heart using arterial and venous vasodilators on top of current guideline-recommended neurohormonal blockade in these patients?

Phenotyping secondary MR patients using exercise echocardiography should be incorporated in the protocol of prospective randomized studies assessing mitral interventions to help answer these questions. Finally, a patient-specific analysis of the three-dimensional geometry and dynamics causing mitral valve dysfunction is likely to improve our insights

and therapeutic efficiency for secondary MR. Current advances in three-dimensional cardiac imaging and computational models already provide the ability to simulate mitral valve dynamics during physiological loading conditions, and virtually perform a therapy while evaluating its impact on the patients-specific mitral valve function and dynamics[128]. Such innovative technology holds great potential to tailor treatments to the individual and unique patient.

Summary

The dynamics of secondary MR are governed by the balance between mitral closing and tethering forces. Exercise-induced changes mainly result from the impact of hemodynamics on left ventricular geometry, specifically global and local deformation, dyssynchrony, and annular dilatation – all of which critically affect tethering. Exercise-induced worsening of secondary MR through the final common pathway of more tethering is associated with impaired exercise capacity and increased mortality. Therapies for secondary MR should focus not only on resting status, but also aim at reducing the dynamic component of the valvular lesion. Individualized targeting of underlying geometric culprits, aiming at inhibiting increases in tethering by improving left ventricular size, shape and function during exercise are key elements for success.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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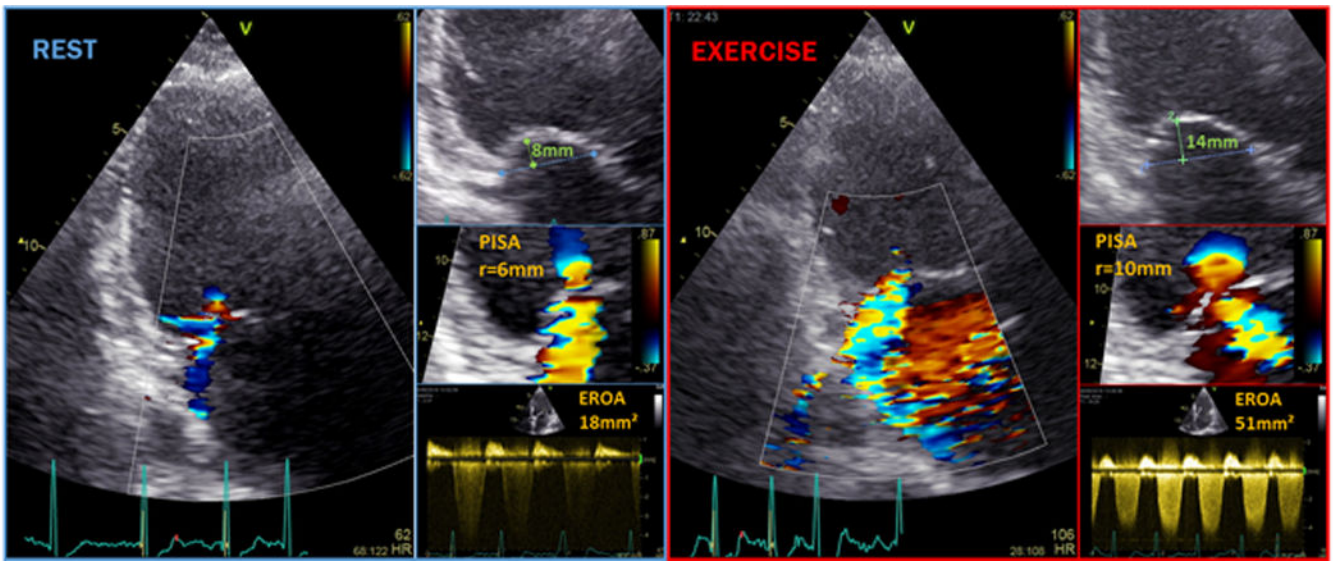


Figure 1. Secondary mitral regurgitation (MR) at rest and during exercise

Apical long axis view with color Doppler in a typical ischemic cardiomyopathy patient with (eccentric) moderate MR at rest that significantly increases to severe MR already at modest exercise (Movie Clips 1 and 2). Proximal isovelocity surface area (PISA) and coaptation distance (i.e. a measure of tenting severity) was substantially higher during exercise (Movie Clips 3 and 4 respectively).

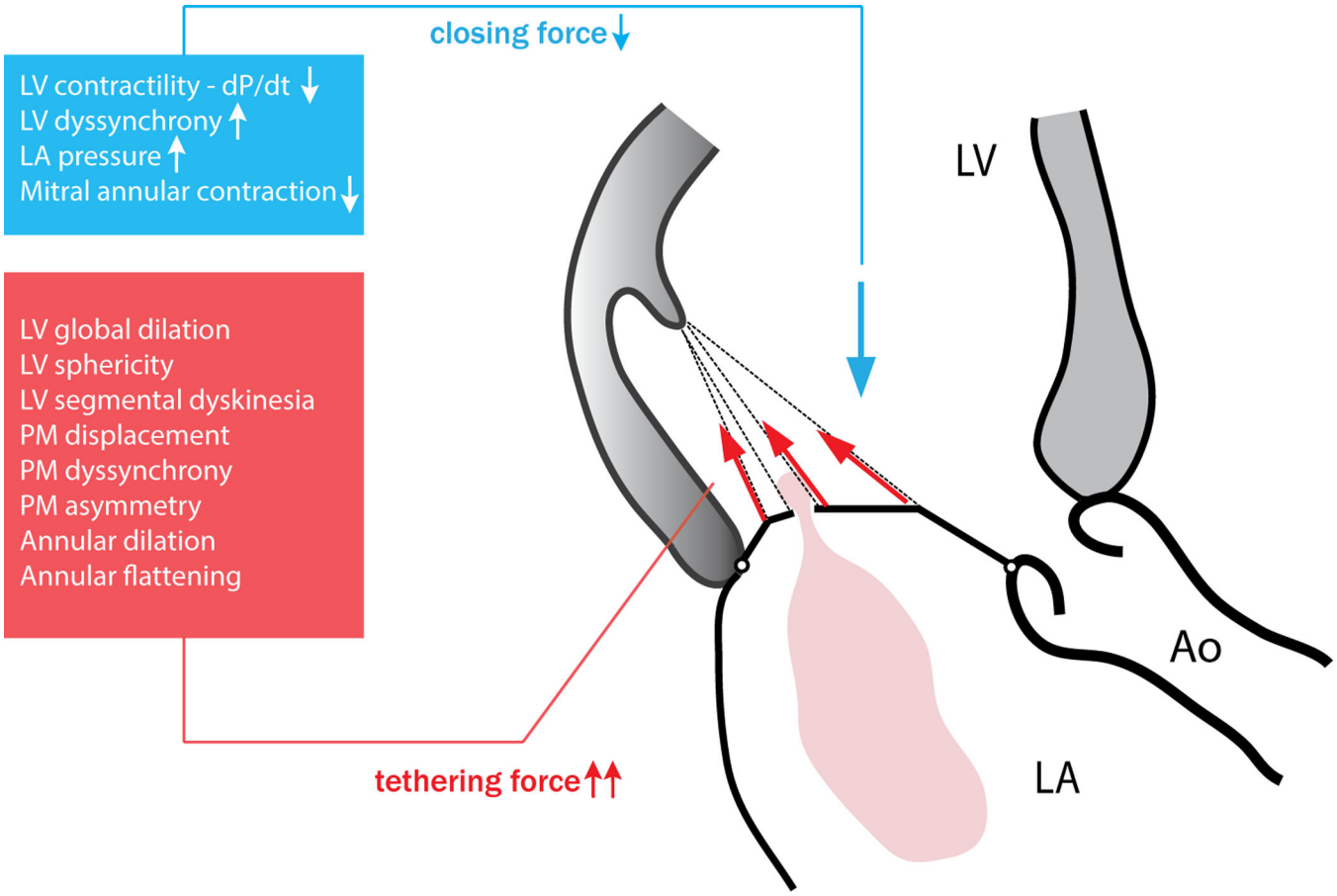


Figure 2. Secondary mitral regurgitation results from functional disruption in the force balance between tethering and closing forces, inhibiting normal mitral leaflet coaptation

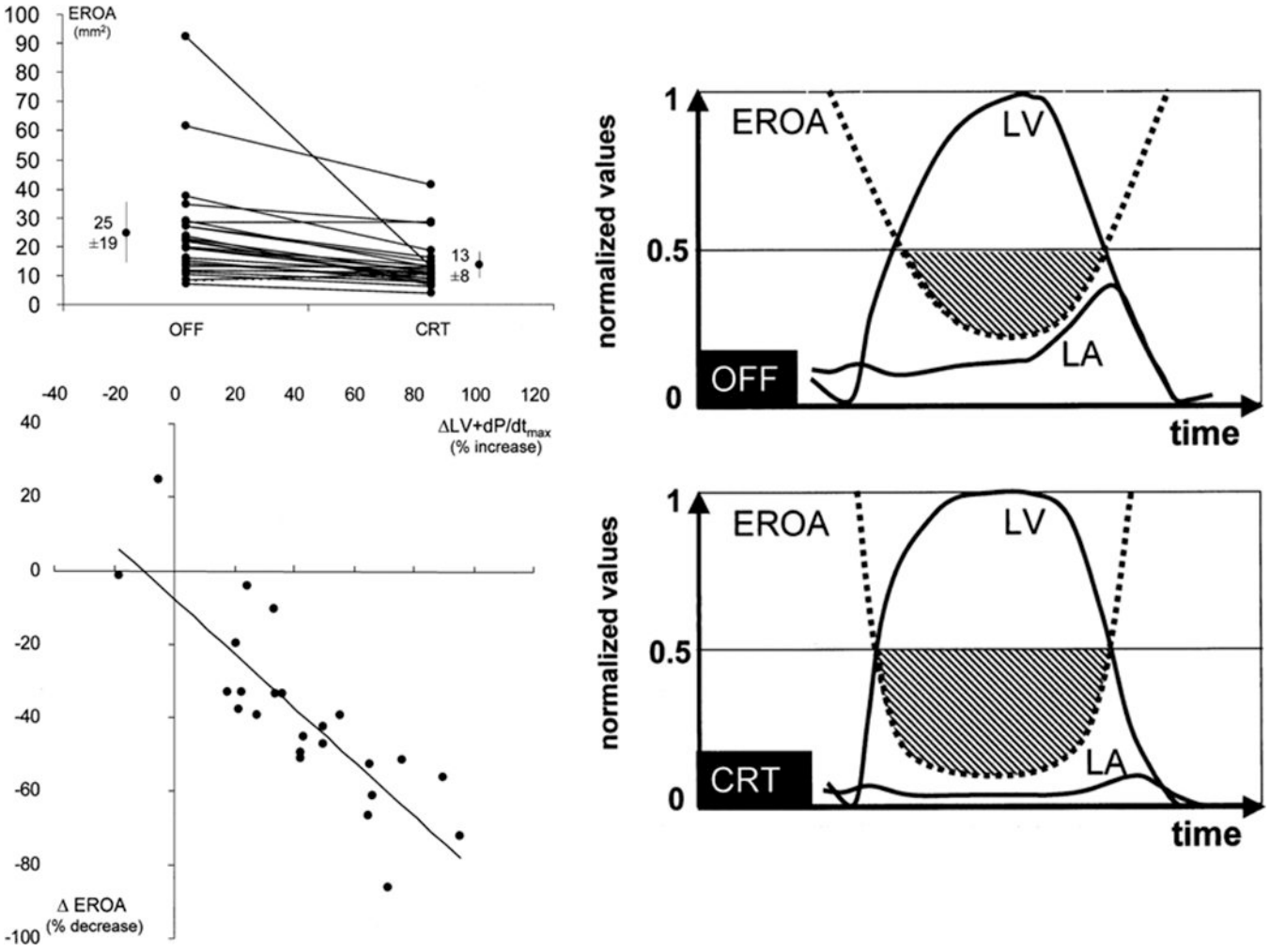


Figure 3. The acute impact of cardiac resynchronization therapy (CRT) on secondary mitral valve regurgitation (MR) at rest

An immediately decreased effective regurgitant orifice (EROA) relates to the increase in closing force (dP/dt) and longer relative duration of maximal closing force. Adapted from Breithart et al[14], with permission.

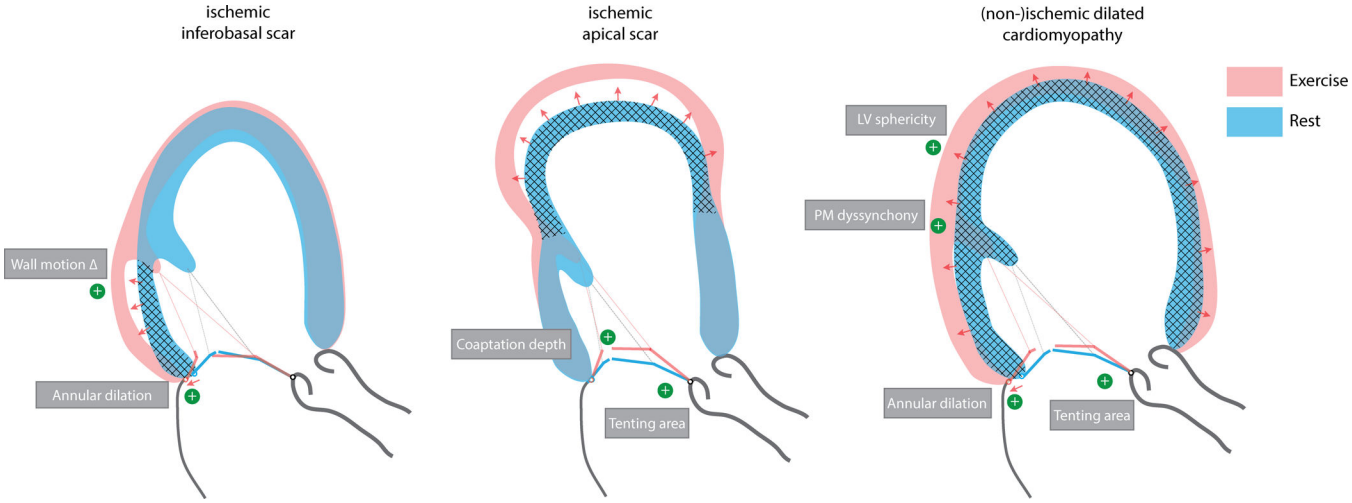


Figure 4. The differential left ventricular response to exercise in cardiomyopathy based on the underlying etiology and location of the scar

Dominant determinants of worsening secondary MR during exercise are highlighted for each situation.

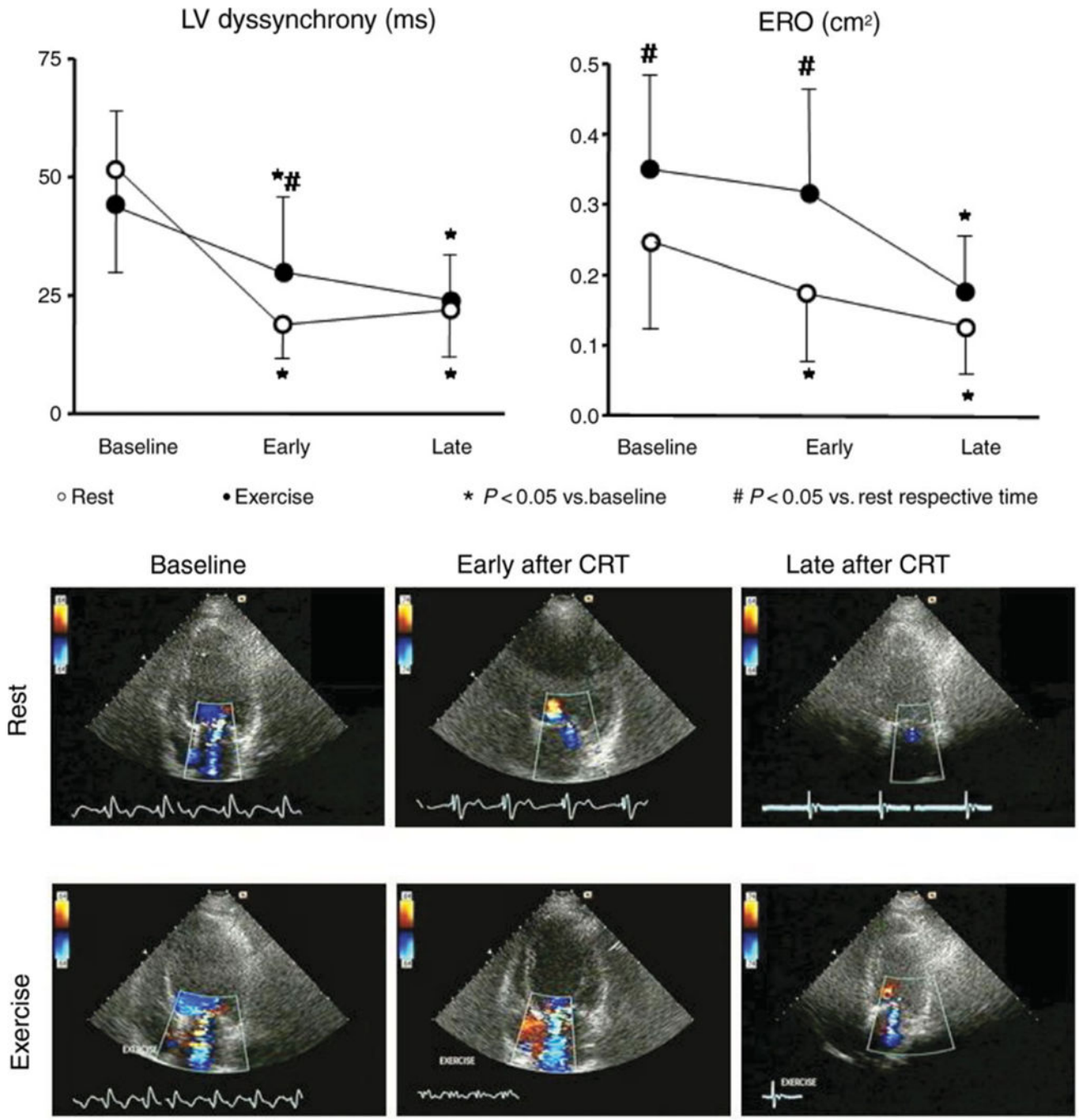


Figure 5. Impact of cardiac resynchronization therapy (CRT) on secondary mitral valve regurgitation (MR) during exercise

In contrast to the resting situation (Figure 4), during exercise immediately after CRT implantation, no decrease in EROA is observed. Only after 3 months when reverse remodeling has occurred, a significant reduction in exercise-induced MR is observed. Adapted with permission from Madaric et al[60].

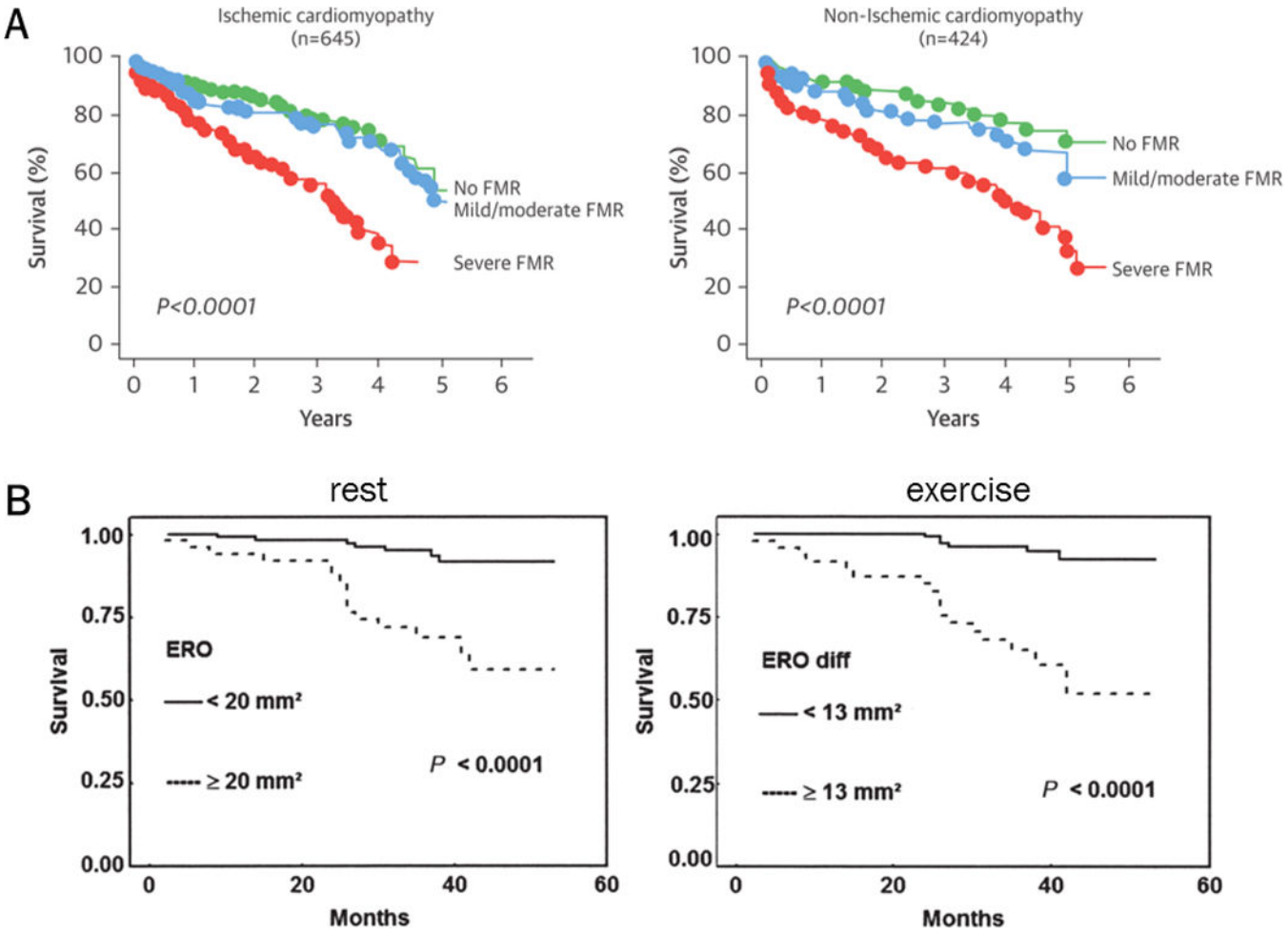
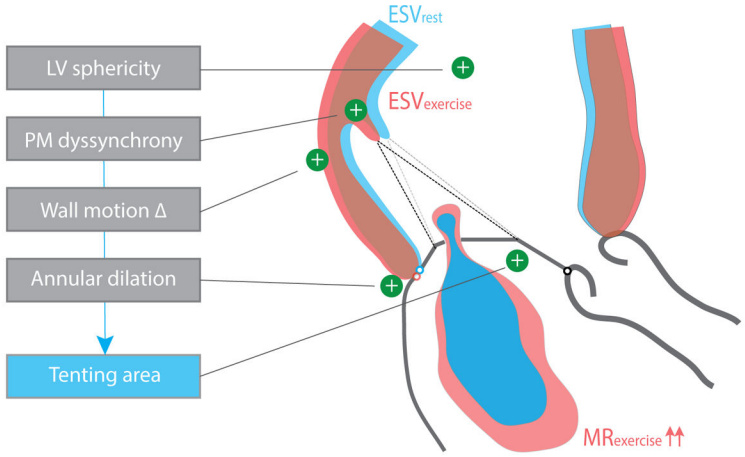


Figure 6. Prognostic impact of secondary mitral valve regurgitation (MR) at rest and during exercise

(A) Mortality in heart failure patients with secondary MR at rest follows a graded relationship with respect to MR severity. Severe MR (EROA>20mm^2) already implies worse outcome for both ischemic and non-ischemic cardiomyopathy. Adapted from Rossi et al[66] and Asgar et al[67], with permission. (B) Mortality in patients with deteriorating secondary MR during exercise (EROA increase >13mm^2), is increased and similar to patients with severe secondary MR at rest. Reproduced from Lancellotti et al[9], with permission.



	LV sphericity	PM dyssynchrony	Wall motion Δ	Annular dilation	Tenting area
Medical therapy	+	+/−		+	+
Cardiac Resynchronization Therapy	+	+	+	+	+
Revascularization	+		+	+	+
Restrictive annuloplasty	+			+	+
Ventricular approach	+			+	+
Subvalvular approach	?			?	+
MitraClip	+			+	+

Figure 7. Overview of geometric determinants of exercise-induced secondary mitral regurgitation and the respective impact of current treatment approaches

'+' indicates favorable impact on the determinant, i.e. inhibition of its exercise-aggravation.

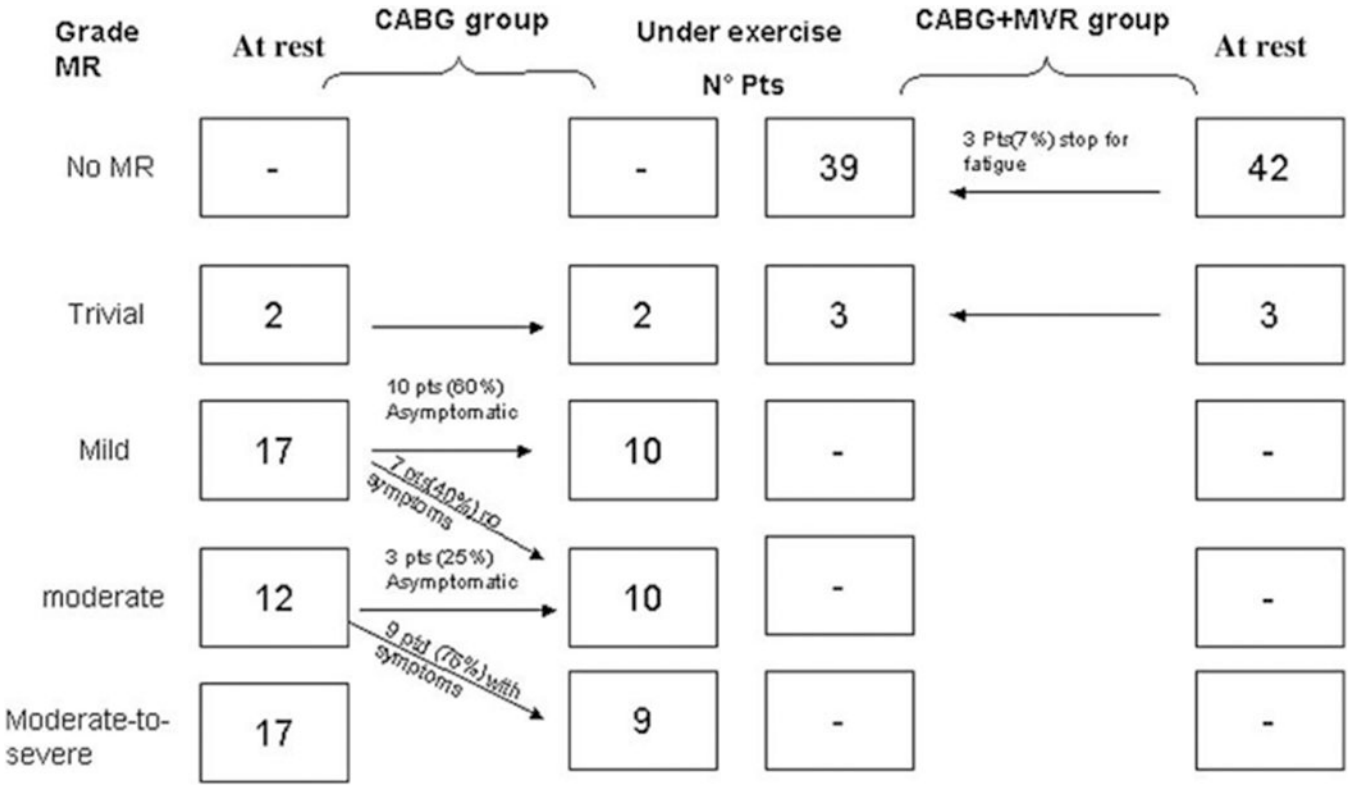


Figure 8. Impact of restrictive mitral valve annuloplasty (RMA) on the dynamic lesion in secondary mitral valve regurgitation (MR)

Sustained MR reduction during exercise in patients undergoing additional RMA for secondary MR is observed with exercise echocardiography, in contrast to the exercise-induced MR deterioration observed in coronary artery bypass grafting only patients. Reproduced from Fattouch et al[97], with permission.

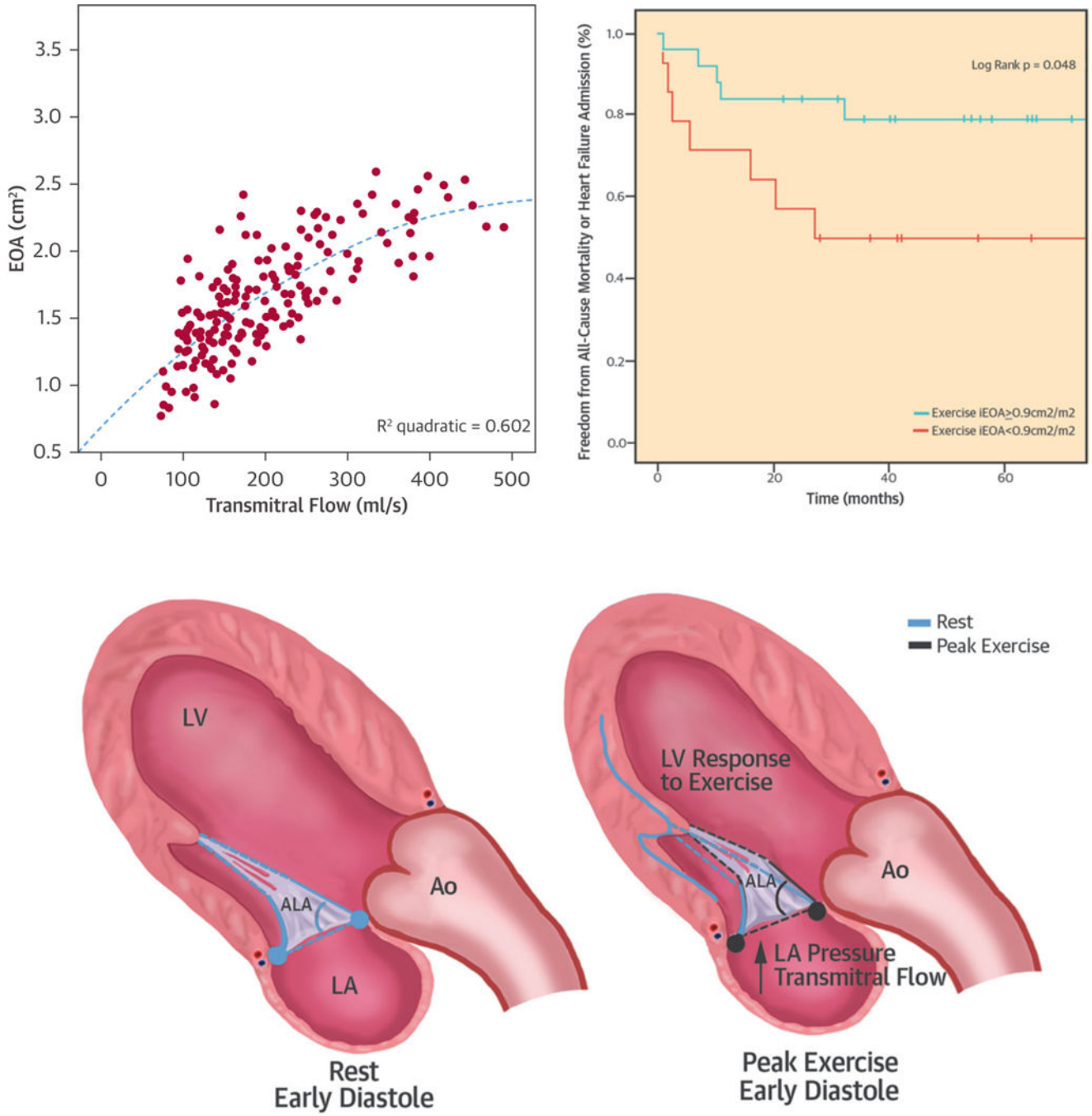


Figure 9. Impact of restrictive mitral valve annuloplasty (RMA) on exercise hemodynamics and transmitral gradients in secondary mitral valve regurgitation (MR)

The mitral valve area after RMA increases during exercise because of an increasing anterior leaflet opening angle. This suggests that the functional stenosis after RMA relates to impaired diastolic anterior leaflet opening (i.e., ongoing tethering). Impaired effective orifice area at peak exercise is associated with worse outcomes. Adapted from Bertrand et al[103] with permission.

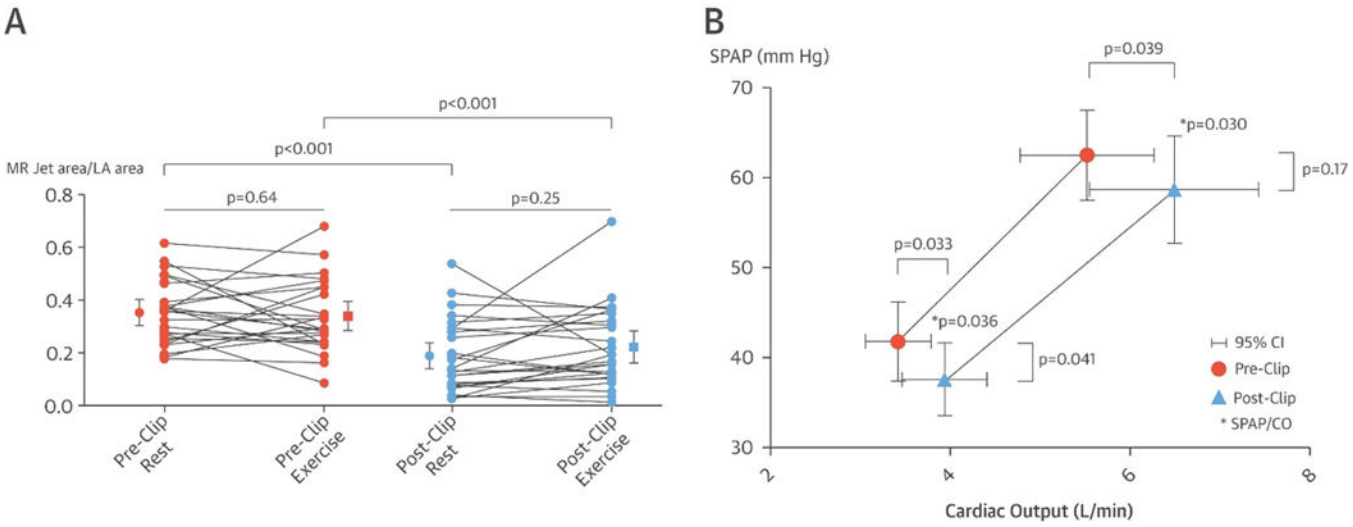


Figure 10. Impact of percutaneous mitral valve repair on mitral regurgitation (MR) severity and exercise hemodynamics in secondary MR patients

(A) Mitral regurgitation severity at rest and during peak exercise before and 6 months after percutaneous repair therapy. (B) Pulmonary pressures and cardiac output at rest and peak exercise are improved at 6 months after the therapy. CI, confidence interval; CO, cardiac output; LA, left atrial; MR, mitral regurgitation; SPAP, systolic pulmonary artery pressure. Reproduced from Van de Heyning et al[124] with permission.

Table 1

Geometric determinants of increasing secondary mitral valve regurgitation during exercise.

Author, Year, Ref.	n	IMR	Regression	LVEDD		LVEF		LV sphericity		LV dyssynchrony		Annular dilation		Tenting area		Coaptation depth		WMSI	
				Rest	Δ	rest	Δ	rest	Δ	rest	Δ	rest	Δ	rest	Δ	rest	Δ	rest	Δ
Keren et al., 1989[47]	17	50%	UV		-														
Lapu-Bula et al., 2002[54]	25	50%	UV		-				+				-				-		
Lancellotti et al., 2003[51]	70	100%	UV MV		-		-						+ +		+ +†		+ +*		+† +†
Giga et al., 2005[52]	40	100%	UV MV	-	-	-	-	-	+			-	+ -	-	+ +	-	+ +	-	+ -
Lancellotti et al., 2005[53]	35	100%	UV MV		-		-				+ +				+ +				
Ennezat et al., 2006[55]	70	50%	UV MV	+ -	- -				+ +			+ +							
Takano et al., 2006[57]	17	5/17	UV			-													
D'Andrea et al., 2007[56]	60	0%	UV MV		-		-				+ +				+ +				
Yamano et al., 2008[59]	32	0%	UV	-	-	-	-	+	-			-	-	+	+	-	+		
Izumo et al., 2009[58]	50	16/50	UV MV	-	-	-	-	+	+ +	-	+ +	-	+ -	-	+ -	-	+ +		

The symbol '+' indicates an association between the geometric determinant (or change in determinant) and the severity of secondary MR during exercise was found, in univariate (UV) and/or multivariate (MV) analysis. The symbol '–' indicates no correlation was found in UV and/or MV analysis. Only studies without inducible ischemia were included. Δ = changes during exercise; LV, left ventricle; LVEDD, left ventricular end diastolic dimension, LVEF, left ventricular ejection fraction; WMSI, wall motion score index; IMR, ischemic mitral regurgitation.

* anterior myocardial infarction only.

† inferior myocardial infarction only;

Table 2

Potential effects of common HF drugs on the balance of forces acting on the mitral valve lesion in secondary MR

Drug	Preload	Afterload	Closing Force (LV-LA Pressure)	Tethering Force (PM-Displacement)	Net Effect (EROA)
Diuretic	↓↓	↔	↑	↓	↓↓
Nitrate	↓↓	↓	↑	↓	↓↓
ACE-I/ARB	↓	↓↓	↑↔	↓	↓
Hydralazine	↔	↓↓↓	↑↔	↓	↓↓
Chronic BB	↓	↓	↑↔	↓	↓

ACE-I= ACE-inhibitor, ARB = Angiotensin Receptor Blocker, BB = Beta blocker.

Although arterial vasodilators reduce systolic ventricular pressure they may nevertheless increase closing force, if the reduction in MR they induce through a relief in tethering decreases left atrial pressure sufficiently. Please note that the assessment of the individual effects of hydralazine is theoretic insofar as the drug is typically administered together with diuretics and/or nitrates.