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REVIEW

Frontiers in cardiovascular medicine

Ischaemic mitral regurgitation: pathophysiology, outcomes and the conundrum of treatment

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Ischaemic mitral regurgitation is a frequent complication of left ventricular global or regional pathological remodelling due to chronic coronary artery disease. It is not a valve disease but represents the valvular consequences of increased tethering forces (papillary muscles displacement leading to a more apical position of the leaflets and their coaptation point) and reduced closing forces (reduced contractility, dyssynchrony of the papillary muscles, intra-left ventricular dyssynchrony). Although mitral regurgitation has an unloading effect and reduces impedance, the volume overload begets further left ventricular dilatation, increases ventricular wall stress leading to worsened performance. Ischaemic mitral regurgitation is characteristically dynamic: its severity may vary with haemodynamic conditions. Both the severity of ischaemic mitral regurgitation and its dynamic component worsen prognosis. There are numerous possible treatment modalities, but the management of the individual patient remains difficult. Medical therapy is mandatory; revascularization procedures are frequently not sufficient to reduce mitral regurgitation; the role of combined surgical therapy by mitral valve repair is not yet defined in the absence of large randomized trial. Some patients are good candidates for cardiac resynchronization therapy that may reduce the amount of regurgitation. New therapeutic targets are under investigation.

Keywords Echocardiography • Cardiac resynchronization therapy • Mitral valve • Surgery

Introduction

Appropriate systolic coaptation of the anterior and posterior mitral leaflets depends on normal anatomy and function of the different components of the mitral valve apparatus: annulus, leaflets, chordae, papillary muscles, and the left ventricular (LV) wall. Mitral regurgitation (MR) consists in systolic retrograde flow from the LV to the left atrium (LA) because of the lack of adequate coaptation of the leaflets and a pressure gradient between the two cavities. It is important to distinguish between primary MR due to organic disease of one or more components of the mitral valve apparatus and secondary MR which is not a valve disease, but represents the valvular consequences of a LV disease. Secondary MR is defined as functional MR, due to LV remodelling by idiopathic cardiomyopathy or coronary artery disease. In the latter clinical setting, secondary functional MR is called ischaemic MR.

There are however limitations in both terms: functional and ischaemic. Indeed, recent studies have demonstrated evidence of structural changes in the mitral leaflets in response to tethering on them by LV pathological remodelling. The leaflet adaptation includes enlargement but increased stiffness.[1] On the other hand, the term ischaemic MR does not necessarily imply the presence of true myocardial ischaemia. It is in fact an abridgment, characterizing a clinical situation corresponding to chronic coronary artery disease with frequently a prior history of one or more myocardial infarctions which induced progressive LV global or regional pathological remodelling, usually in the absence of reversible ischaemia.[2]

Ischaemic MR is a frequent complication of chronic coronary artery disease; it worsens prognosis.[3,4] The poor prognosis mainly depends on the severity of LV dysfunction and the specific prognostic importance of the LV volume overload because the MR remains controversial. Although there are numerous possible treatment modalities, the management of this condition remains difficult in the individual patient.

Mechanisms of ischaemic mitral regurgitation

Reduced closing forces

Ischaemic MR results from an unbalance between increased tethering forces and reduced closing forces,[5] the latter including

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reduction in LV contractility, altered systolic annular contraction, reduced synchronicity between the two papillary muscles and global LV dyssynchrony, especially in basal segments.

Tethering forces

Inadequate closure of the mitral leaflets is the consequence of increased tethering forces.[6] The most frequent pattern corresponds to a posterior infarction, usually transmural, leading to local LV pathological remodelling and distortion contributing to apical, posterior, and lateral displacement of the posterior papillary muscle. The papillary muscle contributes non-extensible chordae to both leaflets; its displacement results in a more apical position of the leaflets and their coaptation point, and a characteristic deformity of the anterior leaflet described as 'seagull sign'.[7] The tethering process produces the shape of a tent between the annular plane and the displaced leaflets. The tenting volume relates closely to the regurgitant orifice area.[8] In the case of posterior infarction and regional remodelling, the tenting area is asymmetric, predominates on the posterior leaflet close to the medial commissure, accompanied by reduced mobility of the posterior leaflet. In other patients, LV dilatation is more global; LV is more spherical; both papillary muscles are displaced; the tenting area is symmetric; the regurgitant jet is central; the contribution of annular dilatation and flattening is more important (*Figure 1*). This situation occurs in patients with previous anterior or both anterior and posterior infarctions.

The previously held notion that ischaemic MR is caused by papillary muscle dysfunction is not true. Isolated papillary muscle infarction does not produce MR and may reduce the amount of MR.[9] Fibrotic elongation of papillary muscle after myocardial infarction is an unusual lesion. In this situation, there is an association of some degree of leaflet tethering and leaflet prolapse.[10]

Pathophysiology

Pathophysiology of ischaemic MR is much more complex than that of primary MR, since myocardial damage and LV dysfunction are the causes that precede MR. The consequences of MR depend on the severity of regurgitation, the driving force and the acuteness of the lesion and in turn of LA compliance. There are two relatively rare clinical entities in which MR occurs acutely with the energy generated by the regurgitation, transformed into potential energy: rupture of a papillary muscle in acute myocardial infarction and true ischaemic MR secondary to a transient active ischaemic episode. The rupture of a papillary muscle, usually a head of the postero-medial muscle, is a dramatic mechanical complication of acute myocardial infarction with a high mortality rate if surgery is not immediately performed.[11] Acute ischaemic episodes linked to a severe stenosis of the left circumflex and/or the right coronary artery can induce 'flash pulmonary oedema'.[2]

In the vast majority of patients in whom ischaemic MR is chronic and complicates LV dysfunction and most often heart failure, LA is

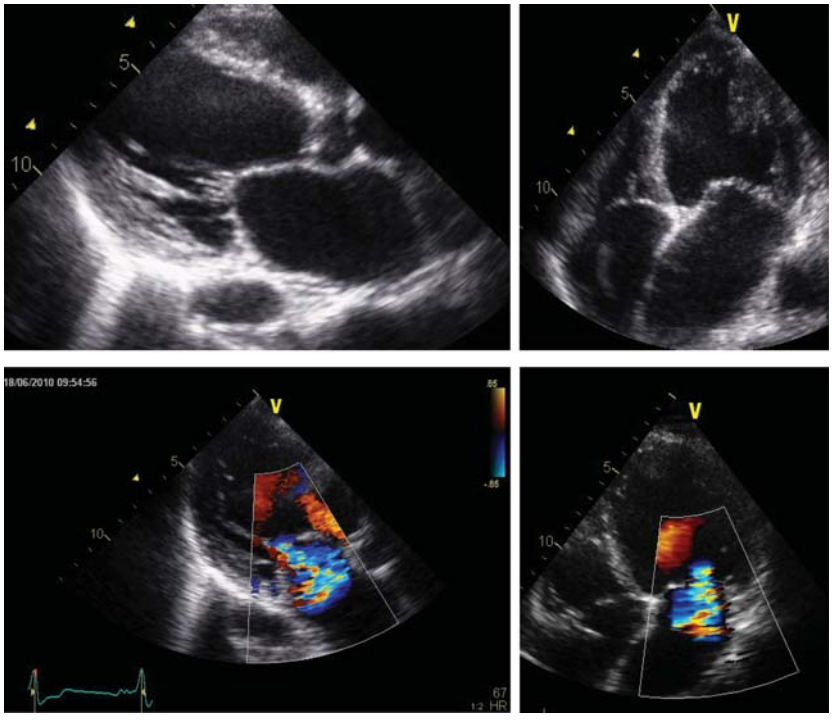

Figure 1 Symmetric mitral valvular distortion and central jet of ischaemic mitral regurgitation. Upper panel: parasternal long-axis view (left) apical four-chamber view (right). The left ventricle is dilated and spherical. Symmetric tethering of the leaflets is present, inducing large tented area and coaptation distance. Lower panel: corresponding images showing the colour jet, originating and directed centrally.

enlarged, more compliant and the driving force is relatively low. The volume overload due to MR contributes to a vicious circle: the more remodelled LV, the more severe MR which begets further LV dilatation and thus, further MR. This cycle has important effects on LV geometry, leading to a rather spherical LV. Although MR reduces impedance and has an unloading effect, the LV dilatation increases ventricular wall stress leading to worsened LV performance.[12] The upstream consequences are high LA pressure and pulmonary arterial hypertension.

An important characteristic of ischaemic MR is its dynamic component.[13] The degree of MR is best defined by the effective regurgitant orifice (ERO) area.[14] The regurgitation area can change during systole: it is less important in mid-systole when compared with early and late systole.[15] These changes are determined by dynamic changes of transmitral pressure contributing to valve closure.[16] Another aspect of the dynamic characteristics of ischaemic MR is a possible reduction in regurgitant volume related to a reverse LV remodelling obtained by appropriate medical treatment.[17] In patients with chronic ischaemic MR, the ERO area can also change dynamically in the daily life, in response to changes in loading conditions leading to transient episodes of increased regurgitant volume. The dynamic characteristics of MR can be appreciated during an exercise Doppler echocardiogram.[18] The degree of MR at rest is unrelated to exercise-induced changes in ERO area or regurgitant volume.[19] In some patients, exercise-induced changes are low. In other patients with moderate or even severe MR at rest, a decrease in ERO area can be observed with exercise and usually results from contractile reserve of the LV, in particular of the postero-basal segment and/or a reduction in intra-LV dyssynchrony.[20] In contrast, ~30% of patients develop a severe increase in MR and in systolic pulmonary artery pressure during exercise. The degree of exercise-induced increase or decrease in MR relates to changes in LV remodelling and valvular deformation and also to changes in LV and papillary muscles synchronicity.

Diagnosis and assessment of ischaemic mitral regurgitation

The regurgitant volume is usually much lower in ischaemic MR than in primary MR, because of reduced LV contractility and high atrial pressure in the former condition. Physical examination is rather insensitive; the regurgitant murmur is frequently mild; its intensity is unrelated to the severity of regurgitation; the auscultation may even be normal.[21] The diagnosis of ischaemic MR is usually obtained by an imaging technique; its frequency varies according to the method and is higher with Doppler echocardiography, when compared with contrast ventriculography. Doppler echocardiography is indeed the most useful imaging technique; several characteristics should be obtained: quantitation of MR, LV, and mitral distortion, functional abnormalities, and dynamic component.

Quantitation of ischaemic mitral regurgitation

Quantitation of MR is crucial. The semi-quantitative evaluation of regurgitant jet area should be abandoned.[22] This measurement is poorly reproducible and depends on numerous factors. The vena contracta width is more accurate.[23,24] The quantitative methods include the Doppler volumetric method (the regurgitant volume is calculated as the difference between mitral and aortic stroke volumes).[25] The flow-convergence method is the most practical and permits the measurement of ERO area and regurgitant volume.[26] There are several limitations of the proximal isovelocity surface area (PISA) approach.[27] First, the PISA radius changes during systole is larger in early and late systole, and smaller in mid-systole when the LV pressure is maximal.[16] Ideally, the PISA radius should not be measured at only one time point, but averaged through systole. Second, for an accurate measurement, the flow convergence should be hemispheric. Although the most appropriate aliasing velocity can be adjusted off-line on a dedicated workstation, the flow convergence—a three-dimensional structure—is frequently hemielliptic, implying an underestimated calculation of ERO and regurgitant volume.[28,29] Third, several jets may be present; the addition of several flow-convergence regions has not been validated.

Thus, practically, the most reliable calculation of regurgitant volume and ERO area, although time-consuming, is the averaging of the quantitative Doppler and the PISA methods. Severe ischaemic MR has been defined as $>$ 30 mL regurgitant volume and $>$ 20 mm^2 ERO[22,30] although this definition has not had universal acceptance.

Mitral valve distortion

Several measurements should be obtained: leaflet length, tenting area, apical displacement of the coaptation point, distance between the posterior papillary muscle head and the intervalvular fibrosa, lateral and posterior displacement of the papillary muscles, leaflet angles (*Figure 2*). It is important to determine, usually from the direction of the regurgitant jet whether the valvular distortion is asymmetric (posterior jet) or symmetric (central jet) (*Figure 3*). Three-dimensional echocardiography permits the measurement of tenting volume and a better definition of annular geometry and dynamics.

Left ventricular function and pathological remodelling

Left ventricular abnormalities should be defined and quantified: LV end-diastolic and end-systolic volumes, assessment of sphericity, regional abnormalities, including location of necrotic segments, myocardial thickness of akinetic regions, and LV ejection fraction. This parameter if highly dependent of loading conditions and, when MR is significant, is overestimated as it represents the addition of forward LV ejection fraction and the regurgitant fraction.

The mitral closing force can be estimated by the measurement of intra LV dyssynchrony and/on the non-invasive calculation of LV maximal d*P*/d*t*, obtainable by the continuous-wave Doppler method, as the time interval between 1 and 3 ms^{-1} velocities of the regurgitation. Left ventricular d*P*/d*t* is calculated by the simplified Bernouilli equation as 32 mmHg/time interval in second. Thirty-two millimetres of mercury represents the difference between 36 mmHg (velocity of 3 ms^{-1}) and 4 mmHg (velocity of 1 ms^{-1}) (*Figure 4*). It is important to recognize that d*P*/d*t* is an

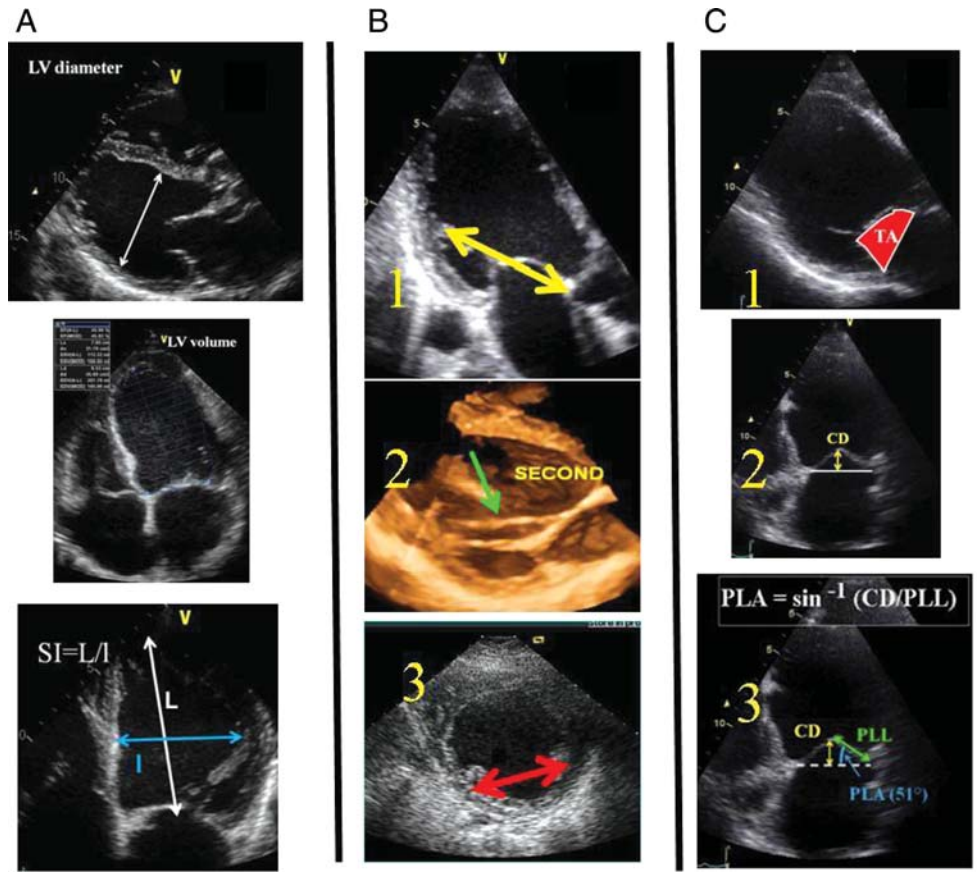

Figure 2 Echo morphologic parameters that are measured in ischaemic mitral regurgitation. (*A*) Global left ventricular remodelling [diameter, left ventricle volumes, sphericity index (sphericity index =L/1; L, major axis; 1, minor axis)]. (*B*) Local left ventricular remodelling (1, apical displacement of the posteromedial papillary muscle; 2, second order cords; 3, interpapillary muscle distance). (*C*) Mitral valve deformation (1, systolic tenting area; 2, coaptation distance; 3, posterolateral angle). Reproduced with permission from Lancellotti *et al.*[22]

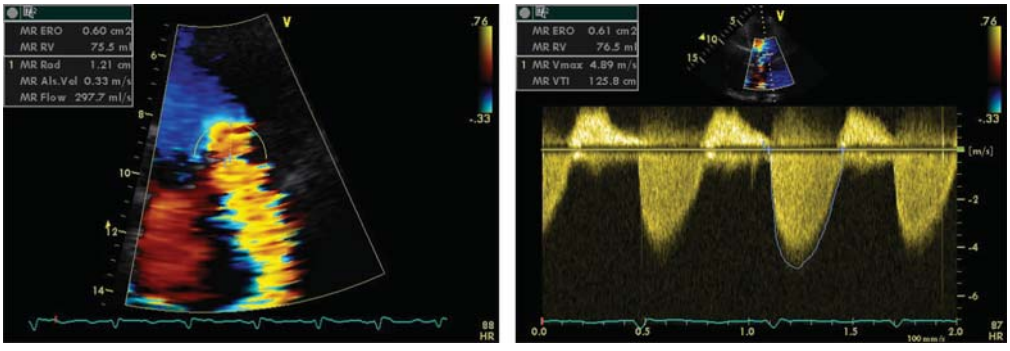

Figure 3 Left: severe asymmetric mitral regurgitation: the proximal isovelocity surface area radius is 12 mm with aliasing velocity of 33 cm s^{-1}. Right: continuous-wave Doppler recording. The effective regurgitant orifice is 60 mm^2 and the regurgitant volume is 76 mL.

isovolumetric measure of LV function. Because no true isovolumic phase exists in MR (ejection occurs into the LA well before the aortic valve opens) d*P*/d*t* not only varies directly with contractility but also inversely with the severity of the MR present.

Dynamic component

Ischaemic MR is characteristically dynamic.[2] The dynamic component can be assessed and quantified by exercise echocardiography. If the exercise test is performed on a dedicated table, in

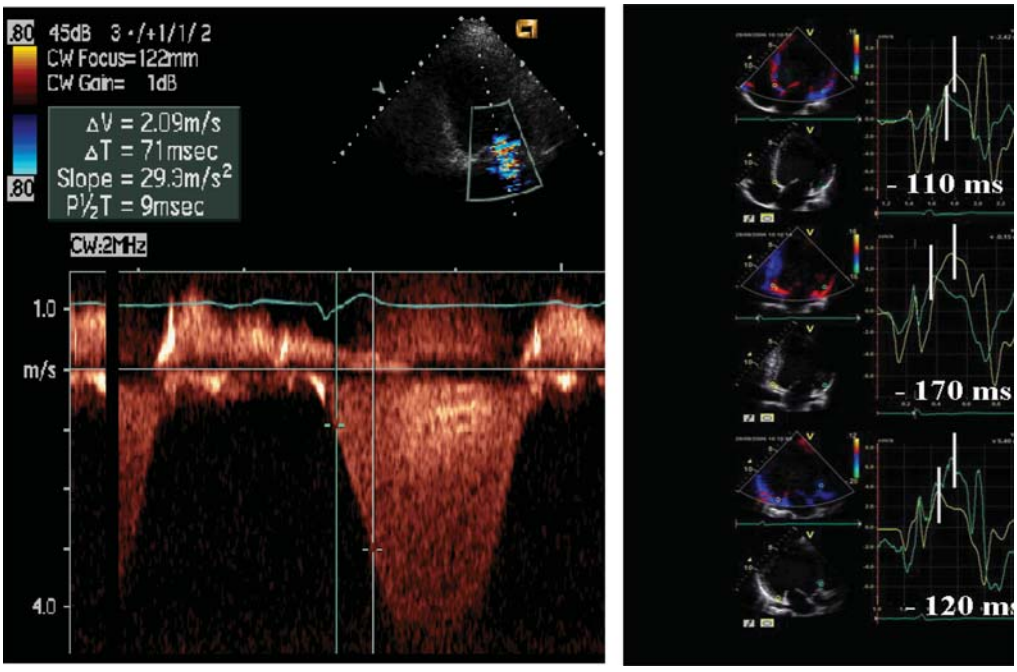

Figure 4 The assessment of mitral valve closing force. Left: estimation of left ventricular d*P*/d*t*. The time interval between 1 and 3 ms^{-1} velocity of the regurgitation is 71 ms. The estimation of left ventricular d*P*/d*t* is 32/71 = 451 mmHg s^{-1}. Right: important left ventricular dyssynchrony. The time intervals between peak velocities of the basal left ventricular segments vary from 110 to 170 ms.

semi-supine position, numerous parameters can be obtained during exercise and not only during the recovery period.[18] Effective regurgitant orifice area and regurgitant volume can be obtained with an excellent reproducibility. In the presence of at least a trivial tricuspid regurgitation, continuous-wave Doppler recording of its velocity permits the measurement of transtricuspid pressure gradient and an estimation of systolic pulmonary artery pressure.[31] Exercise-induced changes in the ERO area, the systolic pulmonary artery pressure and the LV ejection fraction can be obtained. Other interesting measurements can be obtained during exercise: the tenting area (its changes correlate well with changes in the severity of MR) and LV dyssynchrony (exercise-induced increase of dyssynchrony correlates with increased severity of MR and reduction in stroke volume during exercise).[19,32]

Outcomes

The presence of ischaemic MR is associated with increased morbidity and mortality. In acute myocardial infarction, MR may pre-exist or more frequently, results from the acute event through regional LV dilation and loss of contraction. When compared with patients without MR, the patients with acute infarction and MR are older, more frequently female, have more frequently a history of previous myocardial infarction and a more severe coronary artery disease. The size of dyssynergy is usually larger. Many studies have shown that ischaemic MR is an independent predictor of cardiovascular death.[3,4,33–35] The relative risk varies from 1.48 to 7.5. The worse long-term prognosis is also observed in patients with a first non-ST segment elevation acute coronary syndrome.[36]

Among one-month survivors of myocardial infarction, a community study has also confirmed the prognostic importance of ischaemic MR: its presence is associated with a three-fold increase in the risk of heart failure and a 1.6-fold increased risk of death at 5-year follow-up, independent of LV ejection fraction, Killip class, age and gender.[3] The increased mortality risk relates to the quantified degree of MR.[30] Survival curves are strikingly different between patients with no ischaemic MR, moderate MR (ERO area $< 20\ mm^2$) or severe MR (ERO area $> 20\ mm^2$). The prognosis is worse in the latter subgroup. However, the severity of ischaemic MR tends to follow the severity of the LV dysfunction causing the MR; the worse the MR, the worse the LV function. Currently there are no studies of outcome using sophisticated measures of LV function to determine whether ischaemic MR is a predictor of outcome independent of the amount of LV dysfunction present. Supporting this concept is the lack of evidence that correction of ischaemic MR prolongs life which would be expected to occur if MR were an independent risk factor for death beyond the LV dysfunction present.

The dynamic component of ischaemic MR has also prognostic implications. At 3-year follow-up, there is a five-fold increase in the relative risk of death in patients with an exercise-induced increase of $\geq 13\ mm^2$ of the ERO area.[37] The multivariate analysis shows that severe MR at rest ($\geq 20\ mm^2$) is also an independent predictor of death. The severity of MR at rest has, in contrast, no independent value to predict cardiovascular morbidity and in particular hospitalization for cardiac decompensation. The dynamic component is the best predictor of such complications (*Figure 5*). The deleterious effect of ischaemic MR is probably

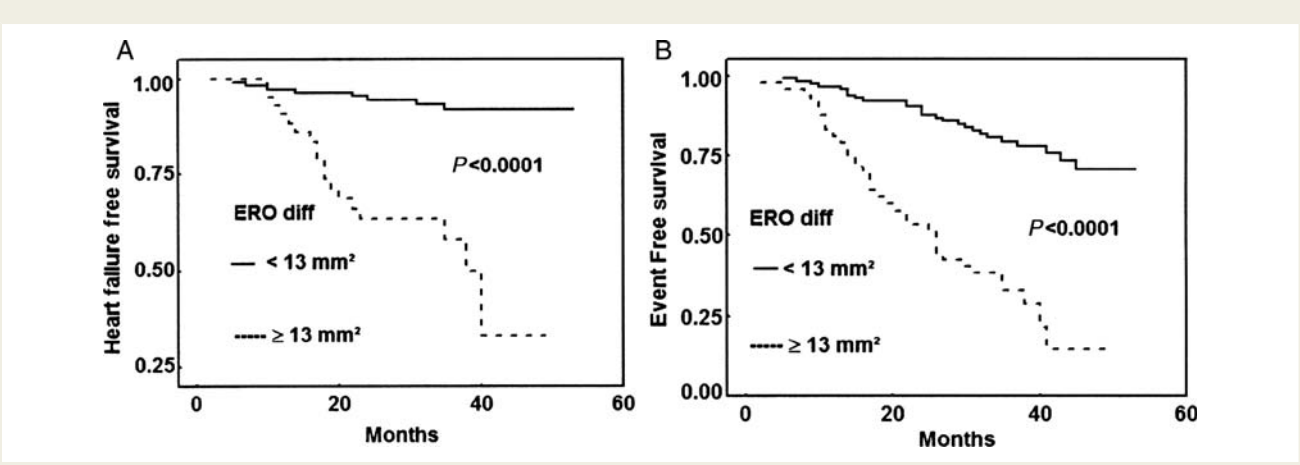

Figure 5 (*A*) Proportion of patients without admission for heart failure and (*B*) without major adverse cardiac events, according to exercise-induced differences in effective regurgitant orifice area of mitral regurgitation. Reproduced with permission from Lancellotti *et al.*[37]

related to different factors. The frequent acute increase in regurgitant volume raises the volume overload and contributes to further LV dilatation. In addition, frequent acute increases in ventricular wall stress are associated with rapid QRS widening and in turn, worsening in LV dyssynchrony.[38] The prognostic importance of dynamic ischaemic MR is not necessarily applicable to functional MR due to non-ischaemic dilated cardiomyopathy or in patients with mild MR at rest.[39]

In patients with LV systolic dysfunction, acute pulmonary oedema has been shown to be associated with dynamic changes in ischaemic MR and the resulting increase in pulmonary vascular pressure.[40] When mild or moderate ERO area and regurgitant volume suddenly increase, the acute raise in LA pressure can be transmitted back to the pulmonary circulation, generating pulmonary oedema. Exertional dyspnoea is also related with a large exercise-induced increase in MR and in systolic pulmonary arterial pressure[41] (*Figure 6*).

In 20% of patients, an improvement in the severity of ischaemic MR is observed during exercise. These patients have a better long-term prognosis.[37] Such a reduction is most frequently observed in patients with contractile reserve, especially of the posterior wall, resulting in a temporary reduced distortion of the mitral valve.[19]

The conundrum of treatment

Although the pathophysiology and the clinical consequences of ischaemic MR are well defined, this condition is still in search of its best treatment.[42] A potential explanation of the controversy in the management of ischaemic MR is that it is not known whether the MR is simply a marker of LV dilatation and dysfunction or whether MR is directly the cause of the poor prognosis as noted above. In brief, medical therapy is mandatory in all patients. Some patients are good candidates for cardiac resynchronization therapy (CRT) that may reduce the amount of MR. Percutaneous coronary intervention is usually not sufficient to reduce MR. In patients submitted to coronary artery bypass grafting (CABG), the role of combined therapy by mitral valve repair is not yet well defined. New therapeutic targets are currently under investigation but their role has yet to be validated.

The management of the individual patient should be selected according to a careful integration of clinical data and the results of cardiac imaging. The clinical parameters include age, functional NYHA class, episodes of acute heart failure, and comorbidities, such as diabetes and renal dysfunction. Parameters obtained with imaging techniques, especially Doppler echocardiography, include the severity of MR at rest, the dynamic component, the importance of LV pathological remodelling, the presence and extent of contractile reserve, myocardial viability and inducible ischaemia, the presence and extent of LV dyssynchrony, and the relative contribution of tethering and mitral valve closing forces.[43]

Medical therapy

Medical treatment should be given in line with the guidelines in the management of heart failure.[44] Medical treatment includes an angiotensin-converting enzyme (ACE) inhibitor (or an angiotensin receptor blocker if the ACE-inhibitor is not well tolerated). A beta-blocker should be prescribed and titrated appropriately, using carvedilol, bisoprolol, or metoprolol. An aldosterone antagonist is given in the presence of heart failure. A diuretic can be added in the presence of fluid overload. Several of these agents can progressively produce LV reverse remodelling and in turn reduce the tethering force and the severity of ischaemic MR.[45] In patients with a large dynamic component, episodes of acute dyspnoea can be treated by sublingual nitrate.

Cardiac resynchronization therapy

The candidates for CRT have usually significant ischaemic MR. However, ischaemic MR *per se* is not an indication for biventricular pacing. This modality is indicated in patients in functional class III–IV despite optimal medical treatment, reduced LV ejection fraction and QRS duration >120 ms.[46] Cardiac resynchronization therapy produces an immediate reduction in MR through increased closing force, usually due to resynchronization of papillary muscles.[47,48] In responders, a further reduction in the severity of MR is observed after several weeks or months, through a reduction in tethering

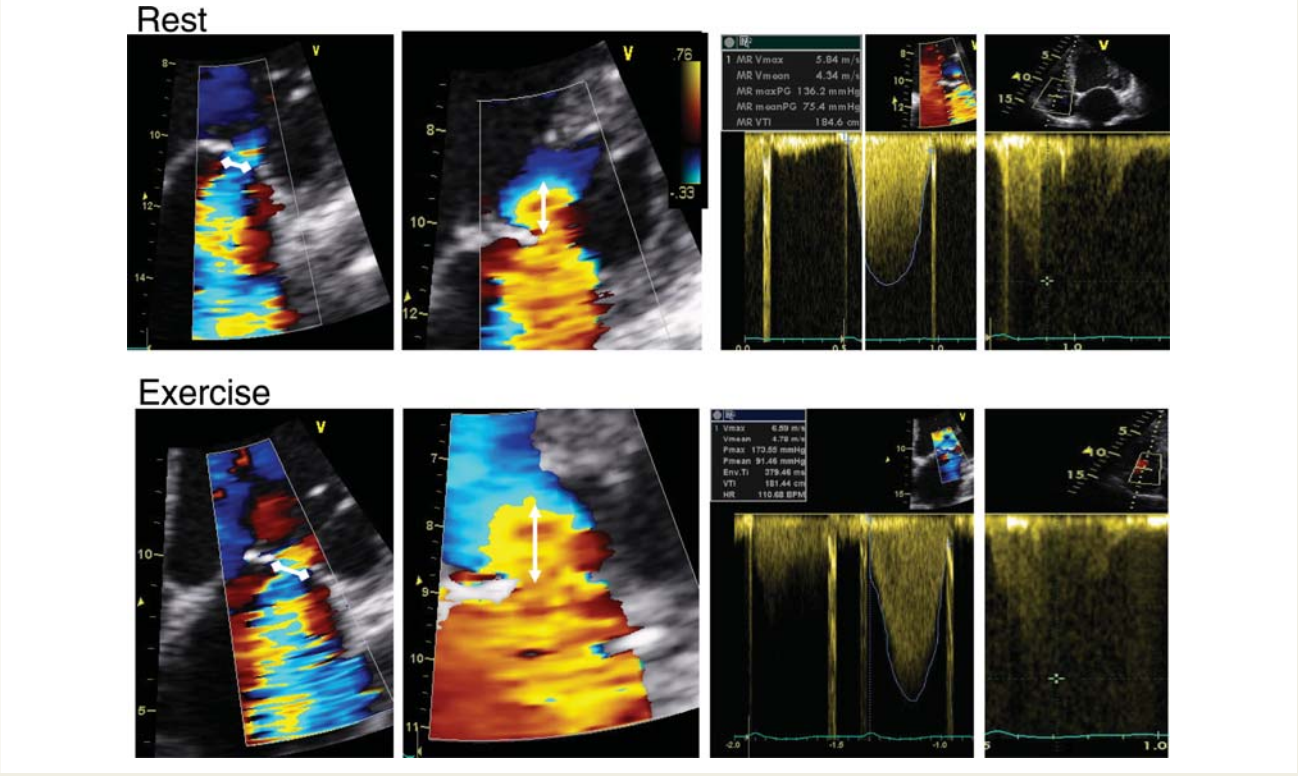

Figure 6 Large exercise-induced increase in ischaemic mitral regurgitation. Upper panel showing at rest, from left to right: vena contracta width (5 mm), the proximal isovelocity surface area radius, Doppler continuous-wave recording of regurgitant jet and functional tricuspid regurgitation. Effective regurgitant orifice $=22\ mm^2$; Regurgitant volume $=40$ mL; Transtricuspid pressure gradient $=36$ mmHg. Lower panel showed corresponding images obtained during exercise. Vena contracta width 7 mm; Effective regurgitant orifice $=38\ mm^2$ (exercise-induced increase of $16\ mm^2$); Regurgitant volume $=69$ mL, Transtricuspid pressure gradient $=77$ mmHg.

forces, in relation with LV reverse remodelling. Cardiac resynchronization therapy may also result in an improved contraction of the mitral annulus. Although the severity of MR is usually reduced, residual MR persists in most cases. In several studies evaluating the effects of withdrawal of CRT, the immediate dyssynchronization of the papillary muscles leads to immediate recurrence of MR.[49–51]

Cardiac resynchronization therapy can also reduce dynamic MR.[52] The time course of CRT on dynamic MR has been determined.[53] One week after implantation, CRT induced a decrease in LV dyssynchrony and in MR severity but not a reduction in the dynamic component of MR. Three months after implantation, the magnitude of exercise-induced MR was significantly attenuated in parallel to reverse LV remodelling and resulted in improved cardiopulmonary performance.

Percutaneous coronary intervention

In the minority of patients in whom MR is directly related to inducible myocardial ischaemia, percutaneous coronary intervention may lead to a reduction in MR at rest and exercise.

Surgical treatment

In contrast to primary MR which can usually be eliminated after surgical valve repair, surgical treatment of ischaemic MR can only reduce its severity. Persistence and recurrence of MR and the absence of evidence that surgery prolongs life may explain the current controversies. The indication of surgical correction of MR is usually discussed in patients who are candidates to bypass surgery. Coronary artery bypass grafting alone usually does not correct MR.[54] The persistence of even mild to moderate residual MR has been shown to be associated with increased mortality risk.[55] Although the use of a prosthetic undersized (preferably two-sizes) ring can be performed with a low operative mortality[56] and can lead to a reduction in LV volume and even a small increase in LV ejection fraction,[57] the long-term benefit remains questionable.[58,59] Several studies using propensity-matched groups analysis indicate that long-term functional status or survival is not improved by combined surgery.[58,60,61] A recent randomized trial showed that the addition of mitral valve repair to CABG was associated with improvement of the New York Heart Association functional class, percentage of LV ejection fraction, and with decrease in LV diameter, pulmonary artery presence and LA size.[62] The study was not powered to analyse the effect on survival. In summary, some valves probably should be fixed in certain patients who still remain difficult to identify.[63]

The ESC guidelines recommend that patients with severe ischaemic MR (ERO area $\geq 20\ mm^2$) submitted to CABG should be treated by combined surgery (class I, level of evidence

C).[64] The indications of mitral valve repair in symptomatic patients with severe MR who cannot be revascularized are more questionable. Surgery may be considered (class IIb, level of evidence C).[64] Patients with mild or trivial MR should not be operated. The most controversial issue is the role of combined therapy in patients with moderate MR (ERO $>10\ mm^2$ but $<20\ mm^2$). In the absence of clear evidence, the management could be individualized. The decision should integrate the presence of myocardial viability, inducible ischaemia and the dynamic component of MR. It is important to predict whether revascularization will be associated with sufficient functional recovery, especially at the level of the posterior basal wall and in turn, will decrease tethering forces, increase mitral valve closing force and thus, correct or at least sufficiently reduce MR. Regional contractile reserve or biphasic response during stress can help in such decisions. These patients usually have exercise-induced reduction in MR or no significant changes. Intuitively, patients with dynamic increase in MR during exercise (exercise-induced increase in ERO area $\geq 13\ mm^2$) could be submitted to combined surgery. However, such an approach has not yet been validated. Intra-operative transoesophageal echocardiography is frequently performed for selecting the candidates who should be submitted to combined surgery. However, the severity of MR is always underestimated because of the loading conditions associated with general anaesthesia. Several groups use a preload and/or afterload challenge: rapid fluid administration until the capillary wedge pressure is at least 15 mmHg and if necessary, intravenous bolus of phenylephrine to increase afterload and obtain during echocardiographic examination systolic blood pressure at or above the preoperative level.[65]

The specific contribution of annular dilatation in the development of ischaemic MR is usually mild. It is not surprising that even undersized ring annuloplasty fails to eliminate the subvalvular component of leaflet tethering. Undersized ring reduces the anterior–posterior annular dimension, frequently associated with a decrease in LV dimension at early follow-up but the incidence of persistence or recurrence of MR is relatively high.[66] Several factors can explain this treatment failure: persistence or even increase in tethering of both leaflets, progressive LV remodelling and progression of coronary artery disease.[67–69] The two latter causes can explain the absence of clinical long-term benefit. In addition, a restrictive mitral valve annuloplasty may create a functional mitral stenosis, associated with a higher systolic pulmonary arterial pressure and a worse functional capacity.[70]

To prevent such disappointment, it is useful to identify preoperatively the patients at risk of persistence or recurrence and/or use additional subvalvular repair techniques.

Echocardiographic predictors of unsuccessful mitral repair by annuloplasty alone have been identified: systolic sphericity index, end-systolic volume, wall motion score index, severe MR, large systolic tenting area ($>2.5\ cm^2$), large distance between the coaptation point and the mitral annulus plane (>1 cm), large angle ($\geq 45^\circ$) of the posterior leaflet, very enlarged LV or the presence of several regurgitant jets.[66,68,71]

Several surgical modalities have been performed in patients and other approaches have been investigated in experimental studies. These adjunctive techniques may consist in internal direct repositioning of the displaced papillary muscle, infarct plication using plaquating sutures, external repositioning of the displaced papillary muscle using an epicardial patch containing an inflatable balloon, or chordal cutting,[7] although this latter technique, useful in the experimental setting has not yet shown clinical benefit. Moreover, a retrospective analysis of outcome was obtained in patients with ischaemic MR who underwent mitral valve repair or mitral valve replacement. After adjusting for risk factors and propensity score, the type of procedure was not an independent predictor of operative and overall mortality.[72] However, a recent meta-analysis indicates that mitral valve repair for ischaemic MR is associated with better short-term and long-term survival compared with mitral valve replacement.[73]

Percutaneous techniques

Several percutaneous modalities are currently investigated. Percutaneous edge-to-edge Alfieri procedure has been proposed to reduce organic and also ischaemic MR, through the apposition of the centre of the two mitral leaflets, producing a double orifice.[74]

Several interventions take advantage of the close proximity of the posterior mitral annulus to the coronary sinus. Several devices can be inserted into the coronary sinus to remodel the posterior portion of the annulus, modify its shape and push the posterior leaflet forward, restoring mitral competence or at least, reducing the severity of MR[75,76] (*Figure 7*). Although most devices can be inserted successfully and can reduce MR in the short term, maintenance of these effects over time and long-term clinical benefit remains to be established.

Future therapeutic targets

Autologous myoblast transplantation in the infarcted area has been used in an experimental model, showing the potential of decreasing ischaemic MR by a localized LV reverse remodelling.[77]

The recently observed mitral leaflet adaptation to LV remodelling could potentially be in the future a therapeutic target when the mechanisms that underly leaflet adaptation will be completely understood and if they can be potentially modified.[1]

Conclusion

Chronic ischaemic MR is a frequent and important complication after myocardial infarction and is associated with an increased risk of heart failure and cardiac mortality. It is the consequence of damaged pathologically remodelled LV inducing apical and posterior papillary muscle displacement and tethered leaflets. Mitral valve tenting is accompanied by an enlarged and flattened annulus and decreased mitral valve closing forces. The specific role of MR in the poor prognosis of patients with this condition remains controversial but is probable as the most severe the MR, the worse the outcome, independently of age and ejection fraction. Ischaemic MR is characteristically dynamic and can change substantially with changes in loading conditions, in mitral valve distortion and in LV dyssynchrony.

Although medical treatment is mandatory, is it usually insufficient. Cardiac resynchronization therapy may help the good candidates for this therapy. Surgical correction of MR can be performed with a low surgical mortality; however, it provides significant but

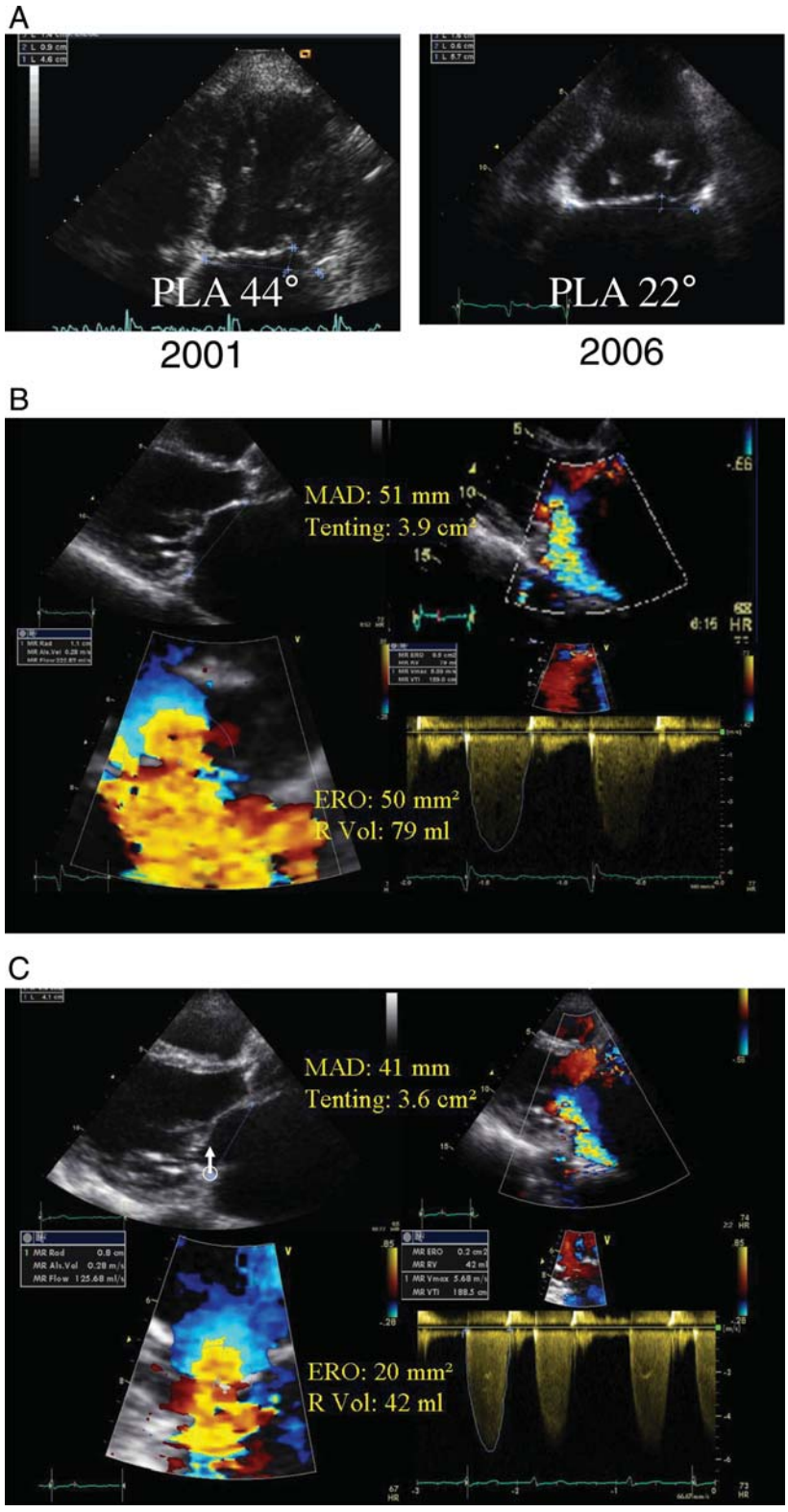

Figure 7 (*A*) Progressive dilatation of mitral annulus in a 5-year period with concomitant decrease in the posterolateral angle (in degrees). (*B*) Severe ischaemic mitral regurgitation: mitral annular diameter =51 mm; tenting area =3.9 cm^2; effective regurgitant orifice =50 mm^2; regurgitant volume =79 mL. (*C*) Early results of percutaneous remodelling of mitral annulus by straightening rods within a catheter positioned in the coronary sinus. Mitral annular diameter and tenting area decreased to 41 mm and 3.6 cm^2, respectively. The severity of mitral regurgitation is reduced: effective regurgitant orifice =20 mm^2; regurgitant volume =42 mL.

usually temporary reduction in MR without changing significantly the long-term prognosis. The future role of new adjunctive surgical techniques and of percutaneous interventions is not yet determined. Importantly, clinical randomized trials are mandatory to provide guidelines with improved level of evidence.

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