

REVIEW

Chronic Ischemic Mitral Regurgitation

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Ischemia-induced mitral insufficiency (IMI) can occur when a papillary muscle ruptures in the acute phase of myocardial infarction (MI) or, more commonly, when ischemic heart disease reaches the chronic stage, with or without infarction. In the latter case it can be distinguished from organic mitral regurgitation because the structure of the valve and the subvalvular apparatus are not affected. Many factors contribute to the complex mechanism of IMI: incomplete closure of the valve is mainly a result of changes in the geometry of the left ventricle, the mitral annulus, papillary muscles and to hemodynamic conditions rather than to muscular dysfunction

Chronic ischemic mitral insufficiency (IMI) results from left ventricular dysfunction caused by coronary heart disease. The condition occurs without any alteration of the structure of the mitral valve or the subvalvular apparatus and is a true myocardial disorder secondary to coronary heart disease. The pathophysiology of IMI differs from that of organic mitral insufficiency, and it has its own specific mechanisms, prognostic value and therapeutic implications.

Over the past 10 years, many investigations have been carried out on the pathophysiology and clinical manifestations of IMI. Herein, the pathophysiological mechanisms, diagnosis and assessment, prognostics and treatment of the condition are reviewed.

The mechanisms

Dislocation of the papillary muscles

When the left ventricle becomes distended, the papillary muscles are dislocated towards the apex and thus apply traction to the chordae tendineae (1). As the

tion of the papillary muscles. IMI is assessed mainly by Doppler echocardiography. The adverse prognostic value of chronic IMI following an infarction has recently been described. Regurgitant orifice area (ROA) >20 mm² and a resting regurgitated volume >30 ml or an increase in ROA >13 mm² on the treadmill-exercise echocardiogram were identified as relevant predictors of death. The therapeutic implications, both surgical and interventional, are currently under development using annuloplasty coupled, perhaps, to new strategies.

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chordae tendineae lack elasticity, the mitral valve no longer closes properly in systole. The mitral regurgitation that subsequently occurs in ischemic heart disease (in the acute phase) is known as restrictive regurgitation, classified type III on Carpentier's classification, as it is in dilated cardiomyopathy (Fig. 1). Many experimental studies have examined the mechanisms of the functional mitral regurgitation in ischemic models created by ligating the circumflex artery, thus producing posterior infarction (including the posteromedian mitral papillary muscle) (2,3). From these models it has been seen that, without dilatation, akinesia in the posteromedial area of the papillary muscle does not result in any significant mitral regurgitation. However, ventricular dilatation can change the geometry of the mitral valve and thus cause regurgitation. A classification with two types of tethering has been proposed, taking into consideration the following points: (i) displacement of the two papillary muscles in the left ventricular global enlargement, for example after a myocardial infarction in the anterior region; and (ii) displacement of the posteromedian papillary muscle responsible for an asymmetric tethering (4). The 'tethering effect' is associated with incomplete closure of the mitral valve caused by an apical dislocation of the point of coaptation. This produces a tent-shaped triangular space between the plane of the mitral annulus

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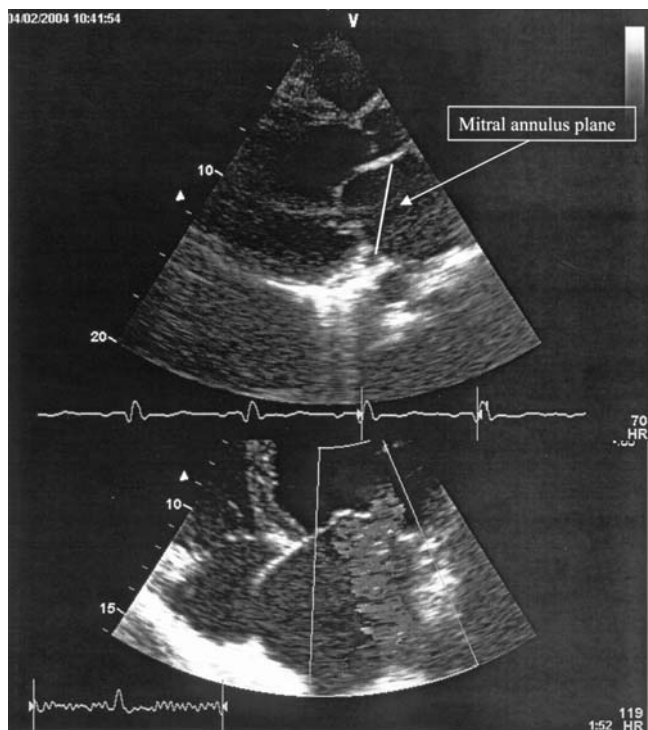


Figure 1: Diagram showing the impact of ventricular dilatation on the mitral valve and its infra-valvular apparatus. An overall or localized dilatation of the ventricle will result in the chordae tendineae tethering the mitral valve leaflets; since the chordae tendineae lack elasticity, the 'tethering effect' resulting from the above concept induces 'tenting'.

and the coaptation point that can easily be measured on echocardiographic imaging. Several authors have proposed that the tenting magnitude is a reflection of the 'tethering effect', that in turn reflects the degree of valvular restriction (Figs. 1 and 2). This is illustrated by the importance of the posterior ($P\alpha$) and anterior ($A\alpha$) angles between the valve and the mitral valve annular plane (see Fig. 2). These angles, as measured in control subjects by three-dimensional (3-D) echocardiography, are normally about 20 to 34°.

A different parameter, which may be more applicable for clinical practice, is the mitral valve tent height, which is <0.5 cm in controls compared to >1 cm in IMI. The area of this tent is also close to zero cm² in controls compared to 1.7 cm² in patients with IMI (3). Moreover, the only independent factor that correlated with the degree of mitral regurgitation was the distance between the posteromedial portion of the papillary muscle and the anterior portion of the mitral annulus seen on an echocardiographic apical two-chamber view, optimized by 3-D reconstruction imaging (5). Kwan et al. also concluded that IMI and dilated cardiomyopathy were associated with dilatation of the annulus and a 'tethering effect' (6). In the multivariate

analysis, the area of the tent is the best predictive factor of the severity of mitral regurgitation. Nevertheless, the roundness of the mitral orifice, the volume of the left ventricle and its index of sphericity (ratio of diameter over height of the left ventricular cavity) correlate with the degree of IMI.

Anteroposterior dilatation of the mitral annulus

A study performed on 30 patients with IMI and a left ventricular ejection fraction (LVEF) <30% showed that the surface area of the mitral annulus calculated on a two-dimensional (2-D) echocardiogram could be correlated with the presence of IMI. It was observed that anteroposterior dilatation of the mitral annulus is determinant in defining the degree of mitral regurgitation if no anomaly of the valvular leaflets exists (7-9). However, although this demonstration was convincing, it was performed in an animal model of rhythmic rather than ischemic cardiomyopathy.

New paradigms promoted by the progress of echocardiography and post-processing

As demonstrated by other groups, the importance of the mitral annulus must not be minimized in IMI, even if many published articles underscore the importance of 'tenting' (10-12). Progress in echocardiographic imaging - and in particular the development of software based on 3-D imaging matrices - now allows new assumptions to be tested, such as the possible importance of motion and the specific features of the kinetics of the mitral annulus during the cardiac cycle as an etiologic component of mitral regurgitation. The results of preliminary experiments have shown that the movements of the mitral annulus follow an extremely different pattern through the systole and the diastole, depending on whether the left ventricle is healthy, has suffered an infarction of its posterior wall, or is globally dilated.

Salgo et al. demonstrated, using mathematical models in animals, that the shape of mitral valve, and not only the size the annulus, is linked to the stress exerted on it (13). Further studies remain to be performed to explain the predominance of mitral valve calcification on the posterior leaflet instead of the anterior leaflet.

Atrial and intraventricular contraction time

Heart failure and cardiomyopathy, particularly in the setting of ischemic heart disease, are often associated with intraventricular conduction disorders that cause asynchronism and participate in the impairment of left ventricular systolic function, thus inducing functional mitral regurgitation. Erlebacher and Barbarash found a correlation between the width of the QRS and the degree of functional mitral regurgitation (14). The observational data on resynchronization

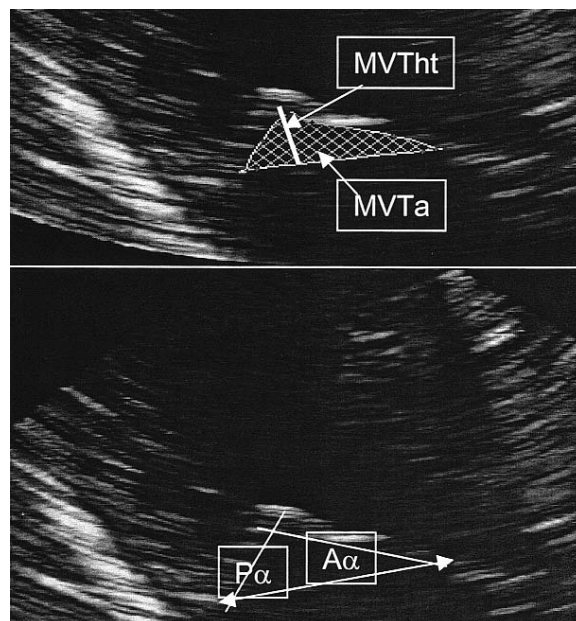
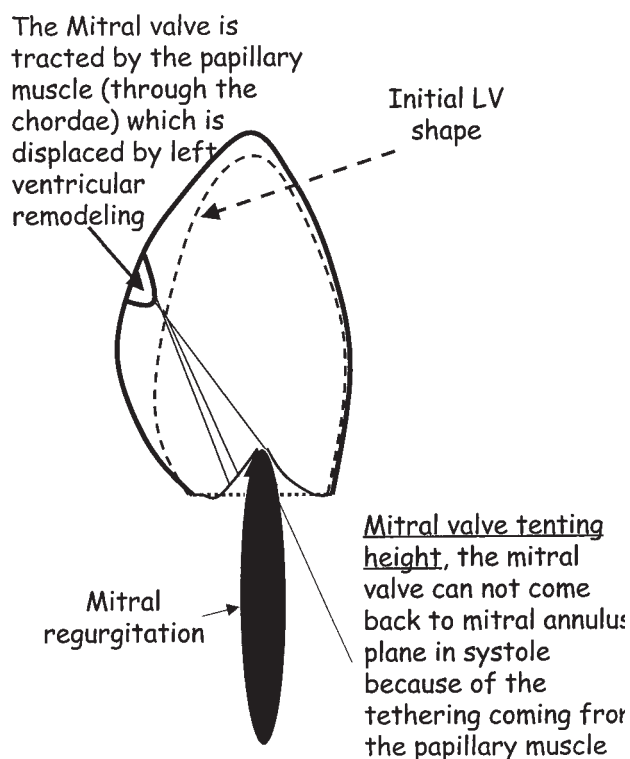


Figure 2: Three-dimensional measurements of 'tenting' on the echocardiogram (mitral valve 3-D geometry assessment by echocardiography). The figure shows: (i) the height of the tent formed by the mitral valve leaflets and the plane of the annulus on the systole (MVTht); (ii) the surface area of the tent (MVTa); (iii) the tenting or tethering angle of the anterior mitral valve ($A\alpha$); and (iv) the tenting or tethering angle of the posterior mitral valve (Pa).

by pacing is also consistent with results from the MUS-TIC and PATH-CHF studies, and others have all demonstrated that pacing can improve functional IMI (15,16). To explain the regression of IMI, Breithardt or Hung et al. suggested that when contractility improves, the left intraventricular systolic pressure increases, thereby enhancing closure of the valve leaflets (relationship between left ventricular $+dP/dt$ and the degree of regression of regurgitation in the acute stage under CRT) (2,17,18).

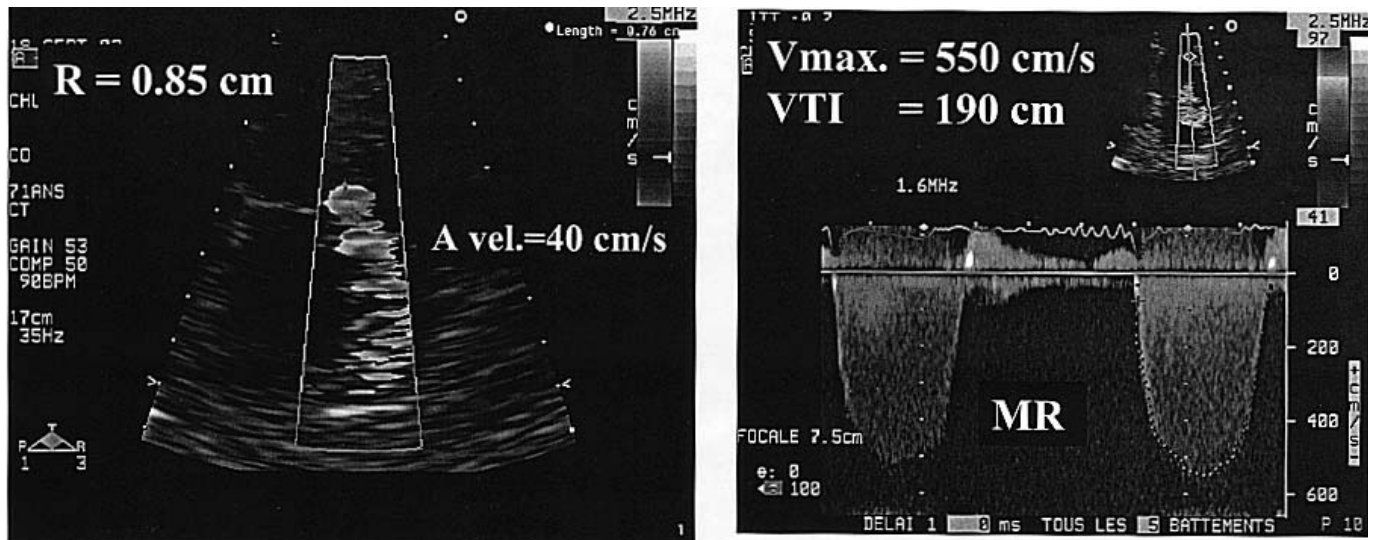
Key points of mitral insufficiency assessment

Evaluation is important, because the murmur is not usually very marked, even if the patient has a significant regurgitation. Doppler echocardiography is, little by little, replacing angiography in the assessment of mitral insufficiency. The assessment of IMI is based on a series of quantitative and semi-quantitative parameters, and the cornerstone of the method is based on studying the convergence area (Table I). This can be used to estimate the regurgitant orifice area (ROA) and the volume regurgitated per beat. In IMI, a ROA >20 mm^2 and a regurgitated volume >30 ml suffice to identify the high-risk patient group, independently of

ejection fraction (EF). This is consistent with the findings in non-ischemic, organic mitral insufficiency when regurgitation is only considered to be severe if the ROA is >40 mm^2 or the volume regurgitated is >60 ml (19,20). The evaluation must be repeated as the degree of severity may decrease when a suitable medical treatment is administered. Of great interest, some recent studies have demonstrated both the feasibility of a quantitative evaluation of mitral insufficiency by echocardiography during the treadmill-exercise test, and its prognostic value (21-23) (Fig. 3). Nevertheless, an expertise remains essential for the correct evaluation of an IMI over an exercise stress test (22). This approach allows evaluation of the behavior of the regurgitation under different hemodynamic conditions, and allows an assessment to be made of what might happen to the degree of regurgitation in the setting of routine clinical practice.

Prognosis

In the acute phase of myocardial infarction, IMI can occur due to rupture of the papillary muscle, and this is a daunting surgical emergency in terms of its catastrophic prognosis (24). However, the prognosis for functional IMI immediately after infarction or in the



$$\text{Regurgitant Flow} = 6,28 \times 0,85^2 \times 40 = 181 \text{ ml/s}$$

$$\text{ROA} = \text{Regurgitant Flow} / V \text{ max. MR} = 181/550 = 33 \text{ mm}^2$$

$$\text{Regurgitant Volume} = \text{ROA} \times \text{VTI MR} = 0,33 \times 190 = 62 \text{ ml}$$

Figure 3: Example of the tethering effect on the parasternal long axis and its impact on the apical four-chamber view of severe mitral regurgitation in a patient with sequelae of anterosepto-apical infarction. MR: Mitral regurgitation; ROA: Regurgitant orifice area; VTI: Velocity time integral.

medium term is less well known; few articles have been published on the subject, and most of these are recent.

The SAVE study, which included patients who presented with recent myocardial infarction (≤ 16 days) studied the prognostic value of angiographically diagnosed moderate IMI. The cardiovascular mortality rate for patients with IMI was superior to that in patients without IMI during the follow up (29% versus 12%; $p = 0.001$). Multivariate analysis showed that moderate IMI (grade I to II) was a major predictive factor for cardiovascular mortality in the medium term (odds ratio 2.0, $p = 0.002$) (25).

The prognosis for IMI diagnosed at >15 days post myocardial infarction was studied recently by Grigioni et al. (26), in a group of 303 patients with a case-history of myocardial infarction and Q waves of more than 15 days. Among these patients, 194 had IMI while 109 were without IMI but paired and/or comparable in terms of age, gender and EF. IMI was assessed using transthoracic ultrasound. The total mortality and cardiac mortality rates at five years were higher among patients with IMI ($62 \pm 5\%$ and $50 \pm 6\%$, respectively) than for the patients without IMI ($39 \pm 6\%$ and $30 \pm 5\%$, respectively; $p < 0.001$). In the multivariate analysis, IMI was identified as being an independent predictive

Table I: Parameters used to assess the severity of the mitral regurgitation in case of IMI.

Parameter	Method for significance	Cut-off value
ROA	Color Doppler	$>20 \text{ mm}^2$
Regurgitant volume	Doppler	$>30 \text{ ml}$
Regurgitant fraction or continuity equation	ROA + continuous Doppler	$>40\%$
VTI	VTI of anterograde mitral flow / LVOT VTI (cm)	>1.3
Vena contracta	Color Doppler	$>5 \text{ mm}$
Venous pulmonary flows	Doppler S-wave	Blunted or reversed

LVOT: Left ventricular outflow tract; ROA: Regurgitant orifice area; VTI: Velocity time integral.

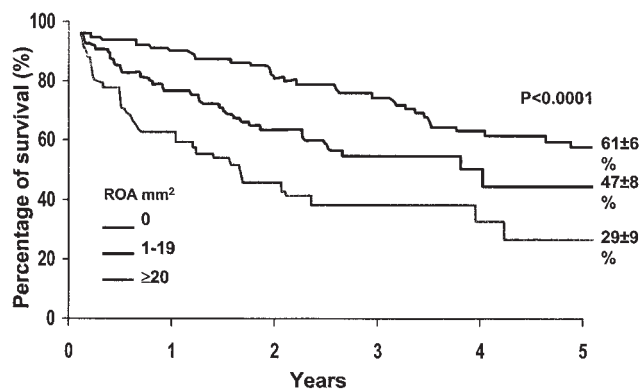


Figure 4: Survival curves in the ischemic mitral regurgitation population in relation to regurgitant orifice area (ROA).

marker of global mortality at five years (relative risk 1.88; $p = 0.003$) and of cardiac mortality (relative risk 1.83; $p = 0.014$). Even grade 2 severity has been shown to have a negative impact on the prognosis. A regurgitated volume >30 ml (relative risk 2.01; $p = 0.009$) and, above all, a ROA >20 mm² (relative risk 2.38; $p = 0.004$) were identified as powerful predictive factors of cardiac mortality. These severity criteria are, therefore, specific to IMI and differ from those of organic IMI (Fig. 4)(27).

More recently, Lancellotti et al. analyzed the prognostic value of variations in IMI induced by exercise (28). For this purpose, 98 patients with chronic ischemic heart disease and left ventricular impairment (EF $<45\%$) and IMI were submitted to echocardiography during an exercise stress test (21). With a mean follow up of 19 ± 8 months, two independent predictive factors of cardiac mortality were identified: (i) a resting ROA >20 mm², which confirmed the results of Grigioni et al.; and (ii) an increase of >13 mm² in the ROA during exercise, regardless of the severity of IMI at rest. These authors also demonstrated that the variation in ROA with exercise was not correlated with the severity of resting IMI (28).

Resting and exercising IMI therefore seem to be of major prognostic value, independently of the EF. This has led to a debate on the utility and benefit of surgical correction of regurgitation when a bypass is performed if the resting ROA is >20 mm² with optimized medical treatment. However, the benefit of this surgery remains to be proven, and this strategy cannot be recommended systematically.

New perspectives for treatment

IMI differs from other valve disorders in that it is the consequence of a myocardial pathology, but there is no organic anomaly of the valve tissue. The pathophysiol-

ogy, as discussed previously, is complex, involving the myocardium, the mitral subvalvular apparatus, and the mitral annulus.

Medical treatment

The treatment of myocardial ischemia and the impact of loading condition on the consequences of the mitral regurgitation must be considered. Echocardiographic studies demonstrated a decrease in the regurgitating volume in patients treated with vasodilators, ACE inhibitors and angiotensin receptor blockers (29). Beta-blockers may also reduce regurgitation through ventricular remodeling (30,31). Nevertheless, to the best of the present authors' knowledge, no pharmacological approach has been shown to improve clinical outcome.

Interventional treatment

The observational and randomized studies converge, both confirming that myocardial resynchronization by pacing permits a significant reduction in the degree of mitral regurgitation (14-16). Nevertheless, this strategy cannot be proposed in the absence of any cardiomyopathy. The mitral regurgitation was shown to decrease with resynchronization by pacing, but cardiac resynchronization is not a dedicated treatment for severe mitral regurgitation but rather a treatment for severe heart failure despite maximal pharmacological treatment.

In a few cases this might form the discussion for a joint medical and surgical decision process. A combined interventional and surgical attitude might also offer a solution to the problem for some patients.

Surgical treatment

Functional mitral regurgitation resulting from ischemic heart disease is associated with a poorer outcome than for other types of mitral regurgitation. The surgical mortality rate is reported to be about 11-13% (32). The short-term prognosis appears better if an annuloplasty is performed (if necessary, completed by a procedure on a papillary muscle) in comparison with the implantation of a prosthetic valve, even if the subvalvular apparatus is maintained. Recent data from Bolling and colleagues tended to demonstrate the absence of interest of mitral annuloplasty for IMI in a group of patients with an especially poor prognosis (33). This last observation was of interest, but no randomized trials comparing pharmacological surgical or interventional treatment have yet been conducted. It is only the present authors' point of view that in selected patients (after a surgical and medical discussion) advantage might be taken of a surgical approach associated with optimal medical treatment (34).

Nevertheless, the decision to perform a 'restrictive

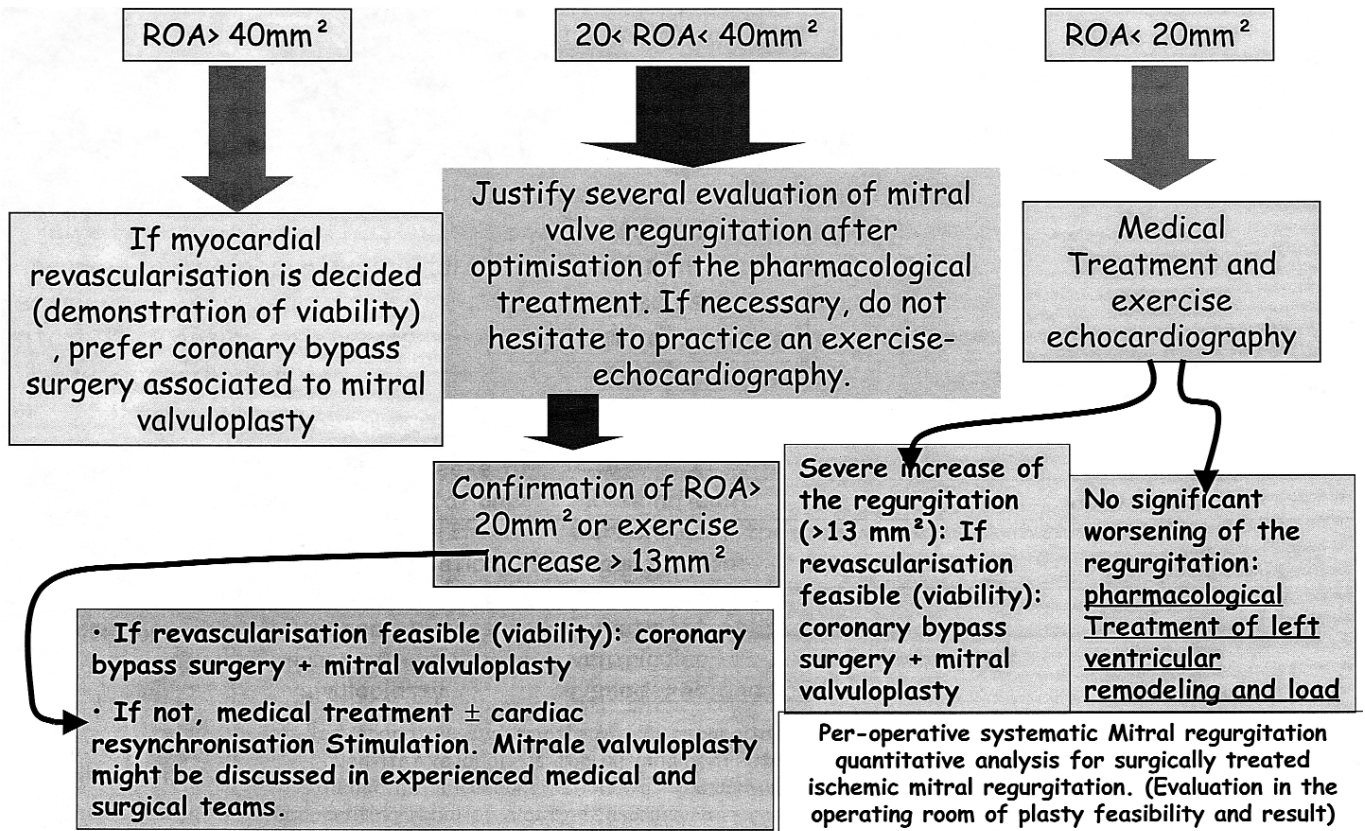


Figure 5: Proposed 'decision tree' for the management of ischemic mitral insufficiency.

annuloplasty' of the mitral valve is made on a case-by-case basis, involving parameters that depend on the patient, the valve, the ventricle, and the level of experience of the surgical team. It was shown that the risk of recurrence can be predicted by the left ventricle sphericity index at end-systole (35). Thus, annuloplasty should not be the dedicated therapy for a dilated left ventricle. Instead of that theoretical analysis, there are increasing data available that support corrective annuloplasty. The implantation of an undersized, semi-rigid ring (downsizing by two sizes) tightens the mitral annulus, slightly restricting the orifice, sufficient to counterbalance the persisting tenting effect on the valve leaflets (36). Initially, Bolling et al. reported good short-term functional results, although the mortality rate at one year was 18% (37). However, as just mentioned, the follow up at 1,000 days did not confirm this optimistic observation (33). Another series reported a mortality rate of 6.1% at 30 days when the annuloplasty involved the mitral and tricuspid valves, while Chen et al. reported a mortality rate of 11% (38,39). Prognosis at one and two years has been recently reported by at least four groups. In the study by Bax et al., with 51 patients, the early mortality was 5.9% with 84% survival at two years and minimal symptoms of heart failure (40).

One recurrent problem in daily practice comes from

the difficulty in IMI quantification. The severity of regurgitation may well vary from one echocardiogram to another. Thus, it is necessary to have a good understanding of the mechanism of regurgitation (degree of tenting), with an exercise echocardiogram as an aid to research viability and the use of perioperative echocardiography (27,28,41,42). One group found that IMI with a ROA >20 mm² must be considered as severe in terms of its prognostic value. In such case of IMI, if myocardial revascularization is indicated, then IMI annuloplasty is considered. However, no stringent proof of the prognostic impact of the correction of IMI less than grade 3 or 4 (ROA ca. 40 mm²) exists (43). It is proposed that, in the absence of myocardial viability, mitral annuloplasty should not be considered (42).

The hypothesis of myocardial revascularization without any procedure correcting mitral regurgitation has been envisaged. When IMI is diagnosed during myocardial infarction, in 50% of the cases, the mitral regurgitation persists after six months of follow up, despite revascularization (44). Also, even when the viability of infarcted myocardial segments has been demonstrated, coronary bypass without correction of IMI has recently been reported as having only a minor effect on the degree of postoperative mitral regurgitation; the mean degree of regurgitation falls from 3 to 2.3 postoperatively, according to Aklog et al. (45).

Nevertheless, current data are insufficient to recommend the correction of chronic ischemic mitral regurgitation without revascularization. If this strategy is proposed, it should certainly be coupled with surgical reduction of the size of the ventricle and/or pacing to resynchronize the myocardium (46).

In future, new approaches to percutaneous annuloplasty currently being tested in animals and in clinical trials, may change this cautious, case-by-case approach to IMI (47-49). In this limited number of cases, an annuloplasty cannot be performed, and consequently the surgeon would implant a prosthetic valve. Based on these findings, the present authors propose the use of a decision tree (Fig. 5) that might help in a case-by-case decision process to decide on surgical intervention for IMI.

New perspectives

In ischemic mitral regurgitation of the posterior infarction area, surgical plication of the infarcted area has been attempted experimentally to restore the geometry of the left ventricle, resulting in significant regression of IMI (51). A gel-filled pad positioned against the infarcted area has also been used to correct deformities of the left ventricle consecutive to infarction (52). Based on the same pathophysiologic background of repositioning the posteromedial papillary muscle, in order to decrease the tension on the chordae tendineae, Messas and colleagues showed in animals that a specific cut performed on two of the chordae tendineae (referred to by the authors as the basal and central chordae tendineae) corrected the functional mitral insufficiency after posterior infarction (9,53). Recent enthusiasm for this type of approach must, however, be counterbalanced by a caveat: another experimental model without ischemia or left ventricular impairment showed that chordal cutting induces an acute regional impairment of the left ventricle, and is potentially capable of aggravating the patient's hemodynamic status (54). A few other recent strategies have not yet been validated, namely the use of a bag, a supporting device around the heart such as the Accorn system, or rings such as the 'Myosplint' system (55,56). The aim of these approaches is to reduce the stresses and change the geometry of the ventricle and, in the long term, to participate in positive 'remodeling' of the left ventricle. These procedures are major in nature, and their relevance has not yet been confirmed, although the Coapsy devices show promise (57).

Conclusion

The diagnosis of IMI has important prognostic value. It must be assessed in terms of mechanism and severi-

ty with great care once the patient's hemodynamic condition has been optimized and the medical treatment correctly adjusted. The current strategy remains largely centered on surgical annuloplasty if the patient has significant regurgitation, but new techniques based more on the pathophysiology of the regurgitation are now being investigated and will, perhaps, lead to an earlier, more specific management of this condition. A suggested decision tree for the clinical management of patients with IMI is illustrated in Figure 5

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