Ischaemic mitral regurgitation is a distinctive valve disease in that, unlike with organic valvulopathies, abnormalities of the left ventricle are not the consequence but the cause of the valve disease. Ischaemic mitral regurgitation is more a pathology of the muscle than the valve and the characteristics of the underlying coronary disease are important determinants of clinical presentation and prognosis.

Important advances in the understanding of pathophysiology, evaluation, and prognosis have occurred during recent years and confirmed that ischaemic mitral regurgitation has many specific features which differentiates it from organic regurgitations. The evaluation of the results of the different therapeutic methods has also improved, even if their relevance in clinical practice is limited by the heterogeneity of the disease and the number of confounding factors.

**PATHOPHYSIOLOGY**

Except in cases of papillary muscle rupture, ischaemic mitral regurgitation is a functional mitral regurgitation characterised by structurally normal leaflets and subvalvar apparatus. Mitral regurgitation is the consequence of a restriction in the motion of the leaflets—that is, a type 3 according to the Carpentier's classification. Leaflet tethering displaces the coaptation zone from the mitral annulus towards the apex of the left ventricle, thereby determining an incomplete closure of the mitral valve in systole, also called systolic tenting because of the echocardiographic aspect (fig 1).

The modifications of the geometry and motion of the subvalvular apparatus as a consequence of ischaemic cardiopathy are the main determinants of ischaemic mitral regurgitation. Local remodelling of the left ventricle displaces papillary muscles and leads to a traction on the mitral leaflets. Incomplete leaflet closure may also be the consequence of abnormalities in the regional wall motion observed after a myocardial infarction or in severe chronic myocardial ischaemia. Reversible abnormalities of wall motion may explain a transient increase in the volume of ischaemic mitral regurgitation during episodes of myocardial ischaemia.

The relationship between the displacement of papillary muscles, leaflet tethering, and the development of mitral regurgitation has been demonstrated in experimental models with the use of three dimensional echocardiography. Experimental studies have also shown that severe ischaemic mitral regurgitation was observed only after left ventricular dilatation and remodelling, but not when segmental abnormalities of wall motion were not associated with left ventricular dilatation. Echocardiographic studies in patients with functional mitral regurgitation and left ventricular dysfunction confirmed that the degree of mitral regurgitation was related to the importance of systolic tenting and not to the severity of systolic dysfunction. The main determinants of systolic tenting were apical and posterior displacement of anterior and posterior papillary muscles and segmental wall motion abnormalities of the underlying myocardium. The mechanisms of functional mitral regurgitation did not differ between ischaemic and non-ischaemic left ventricular dysfunction.

Incomplete leaflet closure is also favoured by the imbalance between increased tethering forces and decreased ventricular forces acting to close the leaflets. These decreased ventricular forces are the consequence of left ventricular contractile dysfunction.

Incomplete leaflet coaptation is aggravated by the dilatation of the mitral annulus and the decrease in systolic annular contraction, but isolated annular dilatation does not create functional mitral regurgitation.

Other mechanisms may be encountered less frequently, in particular leaflet prolapse (Carpentier’s type 2) when an infarcted papillary muscle is elongated.

**EVALUATION OF ISCHAEMIC MITRAL REGURGITATION**

**Clinical evaluation**

Patients with papillary muscle rupture present with acute and massive regurgitation severely compromising haemodynamic status at the acute phase of myocardial infarction. This justifies
performing emergency echocardiography in the case of acute myocardial infarction associated with cardiogenic shock or pulmonary oedema, in order to avoid any delay in the management of such patients.

In patients with functional ischaemic mitral regurgitation, the main risk is to misdiagnose or to underestimate mitral regurgitation, in particular in patients whose clinical presentation is ischaemic cardiopathy with a low intensity systolic murmur. The intensity of cardiac murmur is generally well correlated with the regurgitant volume in patients with organic mitral regurgitation, but severe functional ischaemic mitral regurgitation may be associated with low intensity cardiac murmur, in particular because of low output. Low intensity murmurs should not be considered as trivial in patients with ischaemic heart disease and should always lead to a careful echocardiographic examination, which is the only means to assess correctly the mechanism and volume of the regurgitation.

Doppler echocardiography
Transthoracic echocardiography is a key examination in patients with ischaemic mitral regurgitation. Transoesophageal echocardiography is mandatory when transthoracic examination gives suboptimal data, but this becomes less frequent with contemporary imaging techniques.

Bidimensional analysis shows restriction of leaflet motion and systolic tenting of a structurally normal valve (fig 2). This is necessary for diagnosing ischaemic mitral regurgitation and differentiating it from the coexistence of an organic mitral regurgitation and ischaemic heart disease.

Quantification of ischaemic mitral regurgitation is a particularly tough issue. Conventional Doppler flow mapping in the left atrium and measurement of the regurgitant jet width may be subject to errors, in particular because they may be affected by loading conditions, which are particularly impaired in ischaemic mitral regurgitation. Quantitative Doppler echocardiography using Doppler measurement of stroke volumes or, preferably, the analysis of flow convergence using the PISA method has been shown to be more reliable because the regurgitant volume and, in particular, the effective regurgitant orifice (ERO) are less load dependent. The quantification of ischaemic mitral regurgitation should be interpreted differently from organic mitral regurgitation. Regurgitant volumes are generally lower in ischaemic mitral regurgitations and recent data suggest that the thresholds for severe mitral regurgitation, based on their prognostic implications, should be 30 ml for regurgitant volume and 20 mm$^2$ for ERO in ischaemic mitral regurgitation, instead of the respective values of 60 ml and 40 mm$^2$ in organic mitral regurgitation.

Dobutamine stress echocardiography is widely used for the assessment of myocardial viability and/or ischaemia, singly or in association with radionuclide perfusion imaging. However, dobutamine stress echocardiography does not provide further information regarding ischaemic mitral regurgitation. The regurgitant volume generally decreases during dobutamine infusion, even in patients in whom dobutamine determines an ischaemic response of the myocardium.

The assessment of left ventricular dilatation and segmental and global wall motion provides information as regards diagnosis and prognosis. As in organic mitral regurgitation, left
ventricular systolic function indices are affected by the decreased afterload in mitral regurgitation and this tends to underestimate the severity of left ventricular dysfunction.

**Invasive investigations**

Left ventricular angiography is frequently associated with coronary angiography and some consider it as the reference method for the assessment of the volume of mitral regurgitation. This is mainly related to historical reasons, but grading using ventricular angiography is also subject to limitations, in particular due to the influence of loading conditions. Quantitative Doppler echocardiography provides more objective data regarding the prognostic role of the regurgitation than ventricular angiography.

**PROGNOSTIC IMPLICATIONS OF ISCHAEMIC MITRAL REGURGITATION**

**Papillary muscle rupture**

Spontaneous prognosis is catastrophic with a mortality of 75% at 24 hours and 95% at 48 hours. Incomplete ruptures are associated with a better haemodynamic tolerance.

**Functional ischaemic mitral regurgitation following acute myocardial infarction**

Data drawn from trials using thrombolysis for acute myocardial infarction have shown that ischaemic mitral regurgitation was associated with an increased one year mortality which correlated with the severity of regurgitation. In a series of 255 patients of whom 17% had mitral regurgitation, one year mortality was 11% in the absence of regurgitation versus 22% in those with regurgitation grade 1–2, and 52% for grades 3–4. It is difficult to assess the prognostic value of ischaemic mitral regurgitation per se, because it is associated with a number of factors which have a pejorative prognostic value: older age, higher incidence of diabetes, previous myocardial infarction, multi-vessel disease, and severe left ventricular systolic dysfunction.

However, multivariate analysis adjusted on other prognostic factors showed that regurgitation grade 3–4 was associated with an adjusted relative risk for one year mortality of 1.5 (p < 0.06).

The SAVE (survival and ventricular enlargement) study suggested that even mild to moderate ischaemic mitral regurgitation could have a negative prognostic value. Of the 727 patients who had recent myocardial infarction (< 16 days) with an ejection fraction ≤ 40%, 106 and 33 had angiographic grade 1 and grade 2 regurgitation, respectively. Grade 1 or 2 regurgitation was a strong predictor of mid term mortality in multivariate analysis (adjusted relative risk 2.0, p < 0.002).

A recent series from the Mayo Clinic led to consistent findings in 303 patients presenting with ischaemic mitral regurgitation later after myocardial infarction (> 16 days), who were compared with 191 matched controls with myocardial infarction but no regurgitation. One strength of this work was the systematic use of quantitative Doppler echocardiography. Five year mortality was higher in patients who had ischaemic mitral regurgitation whatever the degree (fig 3). In multivariate analysis, mortality was increased in case of regurgitation with an ERO ≥ 20 mm² (adjusted relative risk 2.23, p < 0.003) and also for an ERO < 20 mm² (adjusted relative risk 1.65, p < 0.049). In addition to the demonstration of a continuous relation between the degree of mitral regurgitation and the prognosis, this study underlines the need to use lower thresholds for defining severe regurgitations in ischaemic than in organic mitral valve diseases.

The decrease of ischaemic mitral regurgitation has been reported in certain patients who underwent coronary reperfusion at the acute phase of myocardial infarction or later on. Nevertheless, these cases are issued from small series including selected patients, and when considering all patients having coronary reperfusion, ischaemic mitral regurgitation persisted in more than 50% of them at six months. Therefore, coronary reperfusion does not avoid the development of ischaemic mitral regurgitation after myocardial infarction.

**Functional ischaemic mitral regurgitation in chronic ischaemic cardiomyopathies**

As in post-infarction ischaemic mitral regurgitation, the mechanisms are related to left ventricular remodelling and/or segmental wall motion abnormalities. Ischaemic mitral regurgitation may occur in patients with severe chronic ischaemic heart disease without infarction in the myocardium underlying the papillary muscles.

It has been advocated that revascularisation of viable myocardium might be sufficient to decrease ischaemic mitral regurgitation because of the improvement of segmental wall motion. However, a recent series has shown that isolated coronary artery bypass grafting (CABG) induced only a modest decrease in the volume of the regurgitation, the mean grade being 3.0 preoperatively and 2.3 postoperatively.

In a series of 4221 patients who underwent percutaneous coronary angioplasty outside the setting of myocardial infarction, the 203 patients who had moderate or severe mitral regurgitation experienced a decreased three year survival as compared with those with absent or mild regurgitation. As in the series concerning the post-infarction period, patients with moderate or severe mitral regurgitation had a more severe coronary risk profile, and the respective part of mitral regurgitation and the other factors in this worse prognosis remains somewhat speculative.

When there is no viable myocardium, the association of a mitral regurgitation with a non-reversible left ventricular systolic dysfunction raises the same therapeutic problems as an idiopathic dilated cardiomypathy with functional mitral regurgitation. Most patients are medically treated or candidates for heart transplantation for end stage ischaemic cardiomyopathy. Mitral surgery can be considered in severe regurgitations, but the correction of mitral regurgitation determines an increase in afterload which may lead to a further deterioration of left ventricular systolic function. On the other hand, modifications in the shape of the left ventricle and decreased wall stress might have a positive impact on
myocardial performance. The major difficulty is to evaluate the respective parts played by mitral regurgitation and systolic dysfunction in the impairment of haemodynamics, and there is no method to do this in current practice.

**THERAPEUTIC METHODS IN ISCHAEMIC MITRAL REGURGITATION**

**Medical treatment**

Most studies on the acute effects of vasodilator treatment in mitral regurgitation have demonstrated a decrease in the regurgitant fraction and/or left ventricular volumes. The same findings have been reported after 3–12 months using angiotensin converting enzyme (ACE) inhibitors or AT1 receptor blockers. The effects of vasodilators vary according to the aetiology of mitral regurgitation and there are pathophysiological grounds to suggest that vasodilators may be of particular interest in patients with functional mitral regurgitation. The decrease in preload is probably beneficial in patients with ischaemic functional regurgitation who have left ventricular dysfunction and an increased preload at baseline. It could be hypothesised that the effects of vasodilators on ventricular dimensions and remodelling could reduce the area of the regurgitant orifice, while this is not the case in organic mitral regurgitation. The decrease in preload is probably beneficial in patients with functional mitral regurgitation who have left ventricular dysfunction and an increased preload at baseline. It could be hypothesised that the effects of vasodilators on ventricular dimensions and remodelling could reduce the area of the regurgitant orifice, while this is not the case in organic mitral regurgitation. However, unlike in aortic regurgitation, no trial has so far shown any clinical benefit of vasodilator treatment in patients with chronic mitral regurgitation.

β-blockers in patients with left ventricular systolic dysfunction have a positive effect on left ventricular remodelling and ejection fraction. Studies have demonstrated a reduction in the volume of mitral regurgitation in patients with heart failure and functional mitral regurgitation, including ischaemic cardiomyopathies. An experimental study suggests that ACE inhibitors and β-blockers have complementary favourable haemodynamic effects in left ventricular systolic dysfunction with functional mitral regurgitation.

Biventricular pacing improves symptoms of congestive heart failure in selected patients and the effect on the non-uniformity of ventricular activation may decrease functional mitral regurgitation.

**Surgical treatment of papillary muscle rupture**

Operative mortality for papillary muscle rupture is high, ranging from 20–50%, but it compares favourably with spontaneous recovery rates. The choice between valve replacement and repair with reimplantation of papillary muscle is debated. Conservative surgery is theoretically attractive in those patients who present with poor haemodynamic status, but it raises concerns regarding the duration of the procedure and the durability of repair, because of possible healing problems with the infarcted papillary muscle which may lead to residual or recurrent mitral regurgitation. This explains why valve replacement is frequently preferred. On the other hand, valve repair may frequently be used for treating patients with partial papillary muscle rupture.

**Surgical treatment of functional ischaemic mitral regurgitation**

Surgical treatment of functional ischaemic mitral regurgitation generally combines CABG and correction of mitral regurgitation by prosthetic valve replacement or valve repair. Whatever the technique used, it should be stressed that surgery for functional ischaemic mitral regurgitation carries a much higher risk than for non-ischaemic mitral regurgitation. In most recent series, operative mortality is approximately 10% (table 1). Further analysis of the literature should be done with caution, in particular when comparing the results of different series, most of them comprising limited numbers of patients. Ischaemic mitral regurgitation is a particularly heterogeneous disease, as regards the severity of coronary disease and valve disease. Patients’ characteristics differ between series, in particular concerning left ventricular function and the proportion of patients operated on an emergency basis. These differences mean that any analysis should be done with caution, in particular with regard to the lower mortality which is generally reported after valve repair as compared with valve replacement.

Mid term survival is highly variable but worse than in the case of non-ischaemic mitral regurgitation. Certain series, but not all, reported better late survival after valve repair than valve replacement (table 2). Comparisons are very difficult because of the presence of many confounding factors and potential selection bias. A series including a multivariate risk stratification of the patients led to the prediction that 70% of the patients were likely to benefit from valve repair compared to replacement, but even complex analyses cannot control for all potential confounding factors.

When valve replacement is performed, it should be associated with preservation of the subvalvar apparatus to limit postoperative deterioration of left ventricular function.

As with organic mitral regurgitation, the potential advantages of valve repair are a better preservation of left ventricular function and the avoidance of prosthetic related complications. Valve repair for functional ischaemic mitral regurgitation generally consists of reducing annular size using a significantly undersized annuloplasty. However, unlike

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**Table 1** Operative mortality in series of mitral valve repair or replacement associated with coronary artery bypass grafting (CABG) for ischaemic mitral regurgitation

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>CABG (%)</th>
<th>Operative mortality (%)</th>
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<tbody>
<tr>
<td>Valve replacement ± CABG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rankin et al15</td>
<td>32</td>
<td>100</td>
<td>53</td>
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<tr>
<td>Cohn et al13</td>
<td>56</td>
<td>89</td>
<td>8.9</td>
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<tr>
<td>Grossi et al12</td>
<td>71</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Valve repair ± CABG</td>
<td></td>
<td></td>
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<tr>
<td>Rankin et al14</td>
<td>23</td>
<td>100</td>
<td>26</td>
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<tr>
<td>Czer et al16</td>
<td>60</td>
<td>95</td>
<td>15</td>
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<tr>
<td>Cohn et al13</td>
<td>94</td>
<td>95</td>
<td>9.5</td>
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<tr>
<td>Grossi et al12</td>
<td>152</td>
<td>89</td>
<td>10</td>
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</table>
Table 2  Late results in series of mitral valve repair or replacement associated with coronary artery bypass grafting for ischaemic mitral regurgitation

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean age (years)</th>
<th>NYHA class IV (%)</th>
<th>Emergency surgery (%)</th>
<th>Five year survival (%)</th>
<th>Five year complication-free survival (%)</th>
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<tr>
<td>Cohn et al.</td>
<td>Valve replacement</td>
<td>56</td>
<td>69</td>
<td>98*</td>
<td>–</td>
<td>91 (5)</td>
</tr>
<tr>
<td></td>
<td>Valve repair</td>
<td>94</td>
<td>65</td>
<td>89*</td>
<td>–</td>
<td>56 (10)</td>
</tr>
<tr>
<td>Grossi et al.</td>
<td>Valve replacement</td>
<td>71</td>
<td>68</td>
<td>55</td>
<td>25</td>
<td>57 (13)</td>
</tr>
<tr>
<td></td>
<td>Valve repair</td>
<td>152</td>
<td>68</td>
<td>59</td>
<td>28</td>
<td>68 (9)</td>
</tr>
<tr>
<td>Gillinov et al</td>
<td>Valve replacement</td>
<td>85</td>
<td>67</td>
<td>60</td>
<td>29</td>
<td>36†</td>
</tr>
<tr>
<td></td>
<td>Valve repair</td>
<td>397</td>
<td>67</td>
<td>32</td>
<td>3</td>
<td>58‡</td>
</tr>
</tbody>
</table>

*NYHA class III or IV
†For the patients of the better risk group.
Survival and complication-free survival rates are expressed as mean (SD).
NYHA, New York Heart Association.

Management of ischaemic mitral regurgitation: key points

- Functional ischaemic mitral regurgitation is not caused by papillary muscle dysfunction; it is the consequence of abnormalities of the myocardium which modify the position of the subvalvar apparatus and determine incomplete leaflet closure.
- The intensity of systolic murmur of ischaemic mitral regurgitation is frequently low, but this should not lead to the conclusion that the valve disease is trivial.
- The use of quantitative Doppler echocardiography for grading the regurgitation is particularly important in ischaemic mitral regurgitation because usual Doppler mapping may be misleading.
- The thresholds used in quantitative Doppler echocardiography, in particular for the effective regurgitant area, should be lower in ischaemic than organic mitral regurgitation.
- Severe ischaemic mitral regurgitation should be corrected by undertaking mitral surgery in patients who are candidates for coronary artery bypass grafting.
- Operative mortality of mitral surgery is higher and long term results are less satisfying for ischaemic than organic mitral regurgitation, even when using valve repair.
- There is no consensus regarding the indications for surgery in patients with severe ischaemic mitral regurgitation and no viable myocardium.

Papillary muscle rupture
Natural history justifies emergency surgery in the absence of major comorbidities. Inotropic drugs and intra-aortic balloon pumping are generally used to improve the haemodynamic status but surgery should not be delayed, even if there is a transient haemodynamic improvement.

Functional ischaemic mitral regurgitation
The pejorative implications of ischaemic mitral regurgitation are clearly established, but it has not been demonstrated that surgical correction of the regurgitation improves outcome. On the other hand, operative risk is not minor and late results are difficult to evaluate in this particularly heterogenous disease. In the absence of randomised controlled trails, the low level of evidence in the literature in this field does not enable recommendations to be given. Nevertheless, the approach of different clinical situations may be summarised as follows in the light of our current knowledge.
In patients who have severe ischaemic mitral regurgitation (grade ≥ 3/4 or, better, ERO ≥ 20 mm²) and who should undergo CABG, correction of mitral regurgitation should be undertaken. Valve repair is frequently preferred, provided the surgeons have expertise with this technique and a careful intraoperative evaluation can be performed with the knowledge of potential pitfalls regarding quantification. When the type of coronary revascularisation is debated, the association of severe ischaemic mitral regurgitation leads to combined surgery rather than percutaneous intervention.

In patients who have severe ischaemic mitral regurgitation but no indication of coronary revascularisation, generally because there is no myocardial viability, the indication for isolated mitral surgery is debatable. Promising results have been reported by certain teams in non-controlled studies, but experience and follow up remain limited. There is no consensus for surgery in such situations and it should be ascertained whether mitral regurgitation remains severe after optimisation of medical treatment. The first line approach of these patients remains medical in most teams. Heart transplantation is the main alternative in end stage diseases. More recently, a debate has arisen concerning the opportunity to correct moderate ischaemic mitral regurgitation (grade 2/4, ERO < 20 mm²) in patients who should undergo CABG. The pejorative prognostic value of moderate ischaemic regurgitation, the uncertainties regarding the evolution of these regurgitations with ventricular remodelling, and the high risk of reoperation are incentives to associate valve repair with CABG and this is now the policy of certain teams. These widened indications should be balanced with the potential hazards which relate to the increased complexity of surgery and the lengthening of cardiopulmonary bypass in patients who have a poor left ventricular function.

While there are now strong incentives to consider early surgery in chronic organic degenerative mitral regurgitation, this should not be extrapolated to ischaemic mitral regurgitation, in particular because of the higher operative risk and the less satisfying late results.21

CONCLUSIONS
Ischaemic mitral regurgitation has important prognostic implications in patients with coronary heart disease. It should not be underestimated and this underlines the need for a complete evaluation in which Doppler echocardiography plays a major role, but should be interpreted specifically, in particular as regards quantification of the regurgitation. Therapeutic decisions are difficult and should involve a medico-surgical confrontation of all patient characteristics, if possible with surgeons who have expertise in the field of valve repair. Further evaluation of the different therapeutic options, including new repair techniques, is obviously mandatory to improve the answers to a number of questions pending, in particular the indications for surgery in patients with moderate ischaemic regurgitation and those with severe left ventricular dysfunction and no myocardial viability.

REFERENCES
  ▶ A clear and complete review of the mechanisms of ischaemic mitral regurgitation based on experimental studies from the leading team in this field.
  ▶ A detailed and quantitative echocardiographic analysis of the mechanisms of functional ischaemic regurgitation which confirms findings from experimental studies.
  ▶ This study demonstrates that ischaemic mitral regurgitation has a negative prognostic impact on long term survival that is proportional to the degree of regurgitation. It suggests that grading for ischaemic mitral regurgitation should use lower thresholds than for organic regurgitations.
  ▶ The first study to demonstrate that even moderate ischaemic mitral regurgitation is a factor predicting a poor outcome after myocardial infarction.
  ▶ This paper shows that isolated coronary artery bypass grafting is not a reliable method for correcting ischaemic mitral regurgitation. It also demonstrates that most Doppler echocardiography underestimates mitral regurgitation.
  ▶ A complete review of the pathophysiological mechanisms of action of vasodilators in valvar regurgitations.
  ▶ A recent study which evaluates late results of valve repair and replacement in ischaemic mitral regurgitation, including an analysis of predictive factors of outcome.
  ▶ This large surgical series includes a multivariate approach which tends to take into account the multiple differences in the patient characteristics to compare the late results of valve repair and replacement.
  ▶ An interesting experimental approach to developing new techniques of valve repair which could be better adapted to the mechanism of ischaemic mitral regurgitation.