Mitral valve surgery: wait and see vs. early operation

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Mitral valve repair represents the optimal surgical treatment for severe degenerative mitral regurgitation. According to the current guidelines, mitral repair is indicated in the presence of symptoms and/or signs of left ventricular (LV) dysfunction. In asymptomatic patients with preserved LV function, surgery should be considered in the presence of atrial fibrillation (AF) and/or pulmonary hypertension. In asymptomatic patients with preserved LV function, normal pulmonary artery pressure, and no episodes of AF, surgical timing is still an object of debate. The controversial issue is whether, in those circumstances, a ‘wait and see (watchful waiting)’ approach should be followed or an ‘early repair’ policy should be preferred. Indeed, a randomized trial comparing the two strategies has never been performed. In the absence of evidence-based arguments definitely supporting any particular course of action, advantages, drawbacks, and requirements for both strategies will be discussed in this review on the basis of the most significant observational studies which have focused on this issue.

Keywords
Mitral regurgitation • Mitral repair • Surgical timing • Wait and see • Early repair

Introduction

The most common aetiology of organic mitral regurgitation (MR) in industrialized countries is degenerative mitral disease, either as a result of myxomatous degeneration or of fibroelastic deficiency.1 Severe degenerative MR is a progressive condition leading to left ventricular (LV) failure, atrial fibrillation (AF), pulmonary hypertension (PHT), and death.1–3

Mitral valve (MV) repair represents the optimal surgical treatment for severe degenerative MR due to its well-documented advantages over valve replacement in terms of perioperative mortality, preservation of postoperative LV function, and long-term survival.4,5 Indeed, if performed before the onset of limiting symptoms or the development of LV dysfunction,6–7 MV repair is able to restore normal life expectancy and quality of life.8–10

Timing of surgery in severe degenerative mitral regurgitation

According to the current guidelines, mitral repair is indicated in patients with severe degenerative MR who are symptomatic and in those who, regardless of symptoms, show initial signs of LV dysfunction defined as an end-systolic diameter of ≥45 mm (ESC 2007 guidelines)11 or ≥40 mm (ACC/AHA 2006 guidelines)12 and/or an ejection fraction (EF) of <60% (Class I).

In asymptomatic patients with preserved LV function, surgery should be considered in the presence of AF and/or PHT (pulmonary artery systolic pressure >50 mmHg at rest) (Class IIa). In addition, according to the ACC/AHA guidelines, pulmonary artery systolic pressure >60 mmHg with exercise should be considered an indication to MV repair (Class IIa).12

Those Class I and IIa indications for surgery are the result of many observational studies which have demonstrated that preoperative symptoms,6–13 LV dysfunction,14 LV dilatation,15 PHT,16,17 and AF18 are all important predictors of poor outcome under medical management and are associated with considerable excess post-operative and late mortality after MV surgery. Therefore, patients with Class I or IIa indications for surgery should be referred for mitral repair without further delay.

However, severe degenerative MR is often discovered by chance in patients who are still free of any MR complication at the time of diagnosis. Those patients are asymptomatic and have preserved LV function and dimension, normal pulmonary artery pressure, and no episodes of AF. Surgical timing in those circumstances is particularly difficult and is still an object of debate.19,20

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The controversial issue is whether a ‘wait and see (watchful waiting)’ approach should be followed (delaying surgical referral until guidelines triggers for surgery are reached) or an ‘early repair’ policy (performing mitral repair before symptoms and other MR complications) should be preferred.

A randomized trial comparing the two approaches has never been performed and all the evidence currently available in the literature is derived from observational prospective or retrospective studies which inevitably carry the inherent risk of selection bias. Until such a trial will be conducted, if ever it will be, the benefit of one approach over another will not be definitely proven.

The current guidelines clearly reflect the controversial nature of this issue.

In asymptomatic patients with preserved LV function and no AF or PHT, the recommendation of ACC/AHA guidelines is that mitral repair should be considered only if the operative risk is low and the likelihood of a successful repair is >90% (Class IIa). More cautiously, the recommendation for early repair made by the European Society of cardiology is a Class IIb indication, which means that reconstructive MV surgery may be indicated in asymptomatic patients with preserved LV function, if the likelihood of durable repair is high and the surgical risk is low.

Despite the absence of evidence-based arguments definitely supporting any particular course of action, advantages and drawbacks of both strategies can be discussed considering the results of the most significant observational studies which have focused on this issue.

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**Watchful waiting (wait and see) approach**

According to this method, asymptomatic patients with severe degenerative MR are regularly followed with clinical and echocardiographic examinations and sent to surgery as soon as they reach the indications recommended by current European Society of Cardiology and American Heart Association/American College of Cardiology guidelines (Classes I and IIa). Six-month follow-up intervals are recommended in order to avoid any delay in surgical referral. This time frame can be further shortened if deemed necessary and such a close monitoring of the patients should be performed in specific outpatient structures, possibly in dedicated heart valve clinics.

Good results with a ‘watchful waiting strategy’ have been reported by Rosenhek et al. One hundred and thirty-two patients were carefully followed in a dedicated valvular heart disease outpatient clinic for severe asymptomatic degenerative MR. All of them had normal LV function, sinus rhythm, and systolic pulmonary artery pressure (SPAP) ≤50 mmHg. A clinical and echocardiographic assessment was performed every 12 months in the presence of stable echocardiographic parameters or every 3–6 months if the echocardiographic measurements were approaching ESC cut-off values for surgery. Patients were referred to surgery as soon as they fulfilled one or more ESC surgical indications including symptoms, LV end-systolic diameter ≥45 mm (or ≥26 mm/m²), fractional shortening <0.32 or EF < 0.60, SPAP >...
50 mmHg, or recurrent AF. During a period of 8 years, 38 patients developed one or more criteria indicating a need for surgery (Figure 1). Of the 35 patients who underwent mitral surgery, 29 (82.9%) received a repair and 6 (17.1%) underwent mitral replacement with a mechanical prosthesis. Additional tricuspid valve repair was necessary in five patients (14.3%). Overall survival, including perioperative and late deaths after surgery, was 91 ± 3% at 8 years (Figure 2). This outcome was not significantly different from the expected survival, demonstrating that close follow-up in experienced hands and strict adherence to current recommendations can provide very good results.

**Is a watchful waiting approach certainly safe?**

Despite the good results reported by Rosenhek et al., the safety of a ‘watchful waiting’ approach is far from being definitely proven.

Indeed, the initial signs of incipient decompensation may be overlooked by insufficiently rigorous outpatient review and the onset of symptoms can be rather insidious and remain undetected, particularly in more sedentary patients.

Besides that, even when patients are submitted to regular and close follow-up, the excellent outcomes reported by Rosenhek et al. have not been confirmed by other groups.10,22–25 In particular, Montant et al. reported worse post-operative and late outcomes in asymptomatic patients with severe MR managed conservatively compared with those who were submitted to early repair. Interestingly, even patients who were closely monitored until surgical criteria were reached had a lower late survival compared with those who had been treated with early surgery.25

Those findings challenge the supposed safety of the ‘watchful waiting strategy’. Indeed, the worse results described by Montant et al. cannot be convincingly explained only by the older age and the possibly higher rate of fibroelastic deficiency of the patients included in his series compared with the population described by Rosenhek et al. It is certainly possible that in the series reported by Rosenhek et al., the patients were more closely monitored since 3- to 6-month intervals were used (if necessary) rather than 12-month follow-up. This might have favoured a more prompt referral for surgery. On the other hand, in Rosenhek’s study, there was no control group, the patients enrolled were very young, and only 35 patients were eventually submitted to surgery and had a good postoperative outcome. Unlike Rosenhek’s study, many other larger series reported poor postoperative results when surgery was performed after the development of symptoms.5,13 LV dilatation/dysfunction,14,15,26,27 chronic AF,18 or PHT.16,17

Compelling data have demonstrated that once important symptoms have developed, surgical treatment of MR is followed by considerable excess post-operative and late mortality.5,13 Similarly, waiting for an EF of <60%14,17 and/or for an LV end-systolic diameter of ≥40 mm15 is independently associated with increased mortality after surgery. Finally, referring patients to surgery once they have developed PHT (SPAP at rest ≥50 mmHg) leads to increased post-operative death and cardiovascular death.16 In one series, 8-year post-operative survival was 86.6% in patients with baseline SPAP <50 mmHg, when compared with 58.6% for pressure ≥50 mmHg.17

Those and other data suggest that early mitral repair, performed before the occurrence of MR complications, might be associated with better early and late post-operative outcomes. It can be argued that those observational studies have several limitations and that patients who are followed according to a watchful waiting strategy are different from those who present with advanced symptoms or severe LV dysfunction at their initial visit. Indeed, patients followed with a watchful waiting approach are referred to surgery at the very beginning of any MR complication. According to the supporters of a wait and see policy, this is the reason why they should not experience excess post-operative mortality. Nevertheless, by definition, those patients undergo mitral surgery with already some degree of structural and functional alteration of their cardiac chambers since symptoms, LV dilatation/dysfunction, AF, and/or PHT at rest have already developed. Therefore, the only question is whether those pathological modifications, in carefully monitored patients, are so early to have no prognostic implications. Despite the good results reported by Rosenhek et al., this seems rather unlikely. Compelling evidence shows that adverse changes in cardiac structure and function may occur in patients with severe MR even before the occurrence of Class I or IIa surgical triggers. The most meaningful prognostic implications of those silent pathological alterations will be briefly discussed.

**Markers of risk in asymptomatic severe mitral regurgitation before Class I or IIa indications for surgery**

Several studies have demonstrated that the severity of MR,10 left atrial (LA) dilatation (volume index ≥60 mL/m²),28,29 neurohormonal activation (elevated brain natriuretic peptide (BNP) levels),30–32 functional capacity,33,34 and exercise-induced changes in LV volumes, EF, and SPAP15,36 have all important correlations with the prognosis of the patients.

In asymptomatic patients with preserved LV dimension and function, the size of the LA is an important predictor of outcome under medical management even before the occurrence of AF and/or PHT. Patients with an LA volume index of ≥60 mL/m² experience more cardiac events and higher mortality compared with the normal population and compared with patients with MR and lower LA enlargement.28

Similarly, in patients with at least moderate MR and no surgical indications according to the ESC guidelines, the occurrence of exercise PHT (≥60 mmHg) was associated with an event-free survival rate of 35 ± 8% at 2 years when compared with 75 ± 7% for patients without exercise PHT.35 Furthermore, a series reported recently from the Mayo clinic noted that up to 25% of the patients with moderate MR may go on to have structural changes, without ever having been reported as having severe MR.37

The fact that the deleterious effects of chronic severe MR take place before the development of the typical MR complications is further proved by the observation that cardiopulmonary performance is already limited in many asymptomatic patients with severe degenerative MR.33 A reduced functional capacity (<84% than
expected) has been shown to be associated with a higher rate of cardiac events or need for surgery in patients with severe MR who are otherwise completely asymptomatic.\textsuperscript{24} This is not surprising considering that a number of patients with no symptoms and apparently normal EF have already a reduced LV contractile reserve whose prognostic implications are well known.\textsuperscript{38,39}

High BNP levels were shown to be associated with a significantly increased rate of congestive heart failure episodes, LV dysfunction, and death in asymptomatic patients with severe MR.\textsuperscript{10–12} Although a specific cut-off value indicating the need of elective surgery has not been identified so far, the negative consequences of high BNP values emphasize once more the silent deleterious effects of chronic severe MR under medical treatment before the occurrence of the classical MR complications.

Finally, the development of even mild symptoms may be associated with important LA enlargement and the development of tricuspid regurgitation showing that ‘asymptomatic’ does not necessarily mean the absence of structural and functional cardiac changes.\textsuperscript{13}

The above reported studies confirm that freedom from Class I and IIa triggers for surgery does not guarantee freedom from MR consequences and from their negative prognostic effects. Interestingly, although those markers are associated with significant risk under medical management, they may not expose the patients to excess post-operative risk. This means that as demonstrated for some of them,\textsuperscript{28} restoration of life expectancy can be obtained without increased post-operative mortality if surgery is promptly performed. Those indicators of initial MR decompensation should therefore be evaluated as part of the comprehensive risk assessment of the patients and should be considered earlier triggers for surgical valve repair if the operative risk is low and the probability of a durable mitral reconstruction is very high.

**Early repair**

Chronic severe MR can be responsible for the above-mentioned deleterious effects before the development of symptoms, LV dysfunction, AF, or PHT and even in patients with less than severe mitral insufficiency.\textsuperscript{37} Therefore, the best solution for the patient would be the correction of MR before the occurrence of any structural and functional cardiac alteration. This is exactly the aim of those who advocate an ‘early repair approach’: ‘neutralize’ severe MR when no pathological changes have occurred and leave the patient with normal ventricular and atrial chambers, no persistent or permanent rhythm disturbances, and very good long-term valve function. The final aim is to ensure survival and quality of life identical to the matched population. From a logic point of view, one would assume that asymptomatic patients with a competent repaired MV and normal cardiac dimensions and function would have a better long-term outcome than patients who have already developed significant cardiac changes due to severe long-standing MR. Several comparative studies between a wait and see and an ‘early surgery’ approach have shown that early repair is associated with improved long-term outcome and is the preferred method to manage severe organic MR.\textsuperscript{10,22–25} The limitations of those observational series have been repeatedly outlined\textsuperscript{40} including selection bias and occasional outpatient review rather than regular and close follow-up. The study by Montant \textit{et al.}, previously mentioned, was able to overcome some of those limitations by performing a propensity score-based comparison between the two strategies and by assessing the prognostic implications of regular (watchful waiting) compared with occasional follow-up in patients managed with a conservative approach.\textsuperscript{25} In this series, 192 asymptomatic patients (mean age $63 \pm 13$ years) with severe degenerative MR and without LV dilatation/dysfunction were prospectively followed for a median of 8.5 years. Patients were divided in two groups: an early surgery group including those who were submitted to mitral repair within 3 months from diagnosis and a ‘conservative approach group’ including patients who were followed under medical therapy and were referred for surgery at a later stage, usually when Class I ESC surgical triggers were reached. Outcomes were analysed between the two groups and subanalysis was performed among patients with AF and/or PHT as well as in patients free of any Class I or IIa indications for surgery. The asymptomatic patients submitted to early surgical correction had higher 10-year survival ($86 \pm 4$ vs. $50 \pm 7\%, P < 0.0001$) and lower morbidity than patients who were followed more conservatively. Similar results were obtained in patients with AF and/or PHT who had an extremely poor prognosis when treated conservatively.

Interestingly, patients undergoing early repair without any surgical indication according to the European guidelines (i.e. without symptoms, LV dilatation/dysfunction, AF, and/or PHT) had at 10 years a significantly better overall ($89 \pm 4$ vs. $62 \pm 7\%, P < 0.0001$), cardiovascular ($96 \pm 2$ vs. $79 \pm 7\%, P = 0.023$), and event-free survival ($82 \pm 5$ vs. $25 \pm 8\%, P < 0.0001$) compared with similar patients followed conservatively ($P < 0.0001$; Figure 3).

Among the asymptomatic patients treated conservatively, those who were followed by a registered cardiologist at least once a year had better long-term outcome compared with those who were not. However, despite this, overall 10-year survival was still lower in regularly followed patients from the conservative approach group than in patients having early surgery ($66 \pm 8$ vs. $86 \pm 4\%, P < 0.0001$; Figure 4). Finally, the 10-year propensity-matched score-adjusted hazards ratio for overall mortality, cardiac mortality, and cardiovascular events for the conservative treatment was $5.21, 4.83$, and $4.4$, respectively. In summary, in this study, the outcome of asymptomatic patients with severe degenerative MR was better with an ‘early surgery’ approach than with a conservative strategy even when regular and close (at least once a year) outpatient follow-ups were performed in order to guarantee a timely referral to surgery. Certainly, it has to be considered that this was not a randomized trial and that even the use of propensity matching might have not completely eliminate the residual influence of confounding factors. However, despite those limitations, the results reported by Montant \textit{et al.} remain extremely important and challenge the supposed safety of the ‘watchful waiting strategy’.

**Requirements for an ‘early surgery’ strategy**

An early repair policy in asymptomatic patients with severe MR can be considered only if the surgical risk is very low and the likelihood of a successful valve repair is $>90\%$.\textsuperscript{11,12}
In the absence of those conditions, an early repair approach cannot be justified and advocated. When assessing the feasibility of early surgery, the operative risk needs to be routinely evaluated and valve repairability has to be carefully established.

During the last decades, several different risk score algorithms have been developed to predict the surgical risk in individual patients. They usually estimate the risk of perioperative death, based on the occurrence of different risk factors. Since the accuracy of those risk scoring systems may be influenced by numerous factors, a perfect risk prediction algorithm in cardiac surgery is not available. However, some of them have shown superior performance and accuracy in open-heart surgery and should probably be preferred when assessing the operative risk in candidates to early MV repair.

As far as valve repairability is concerned, two-dimensional echo imaging using transthoracic and transoesophageal approaches provides most of the relevant information. However, particularly in complex MV lesions, real-time three-dimensional transoesophageal echocardiography has significantly enhanced the possibility to predict the feasibility of repair by giving a comprehensive and real-time dynamic view of the MV anatomy (Figure 5).

The mechanism of severe degenerative MR is of critical importance since MVs with anterior or bileaflet prolapse are significantly more difficult to repair than those with isolated posterior leaflet prolapse.
In many referral centres for mitral repair, early surgery is routinely performed in asymptomatic patients with a repair rate which is around 95% in most cases,\textsuperscript{40–49} an hospital mortality below 1%,\textsuperscript{13,50–55} and very good long-term outcomes.\textsuperscript{10,51–54,56} Freedom from reoperation is >90% at 10 years\textsuperscript{49,51–53,56,57} and >80% at 20 years,\textsuperscript{52,56} and long-term survival and quality of life are absolutely identical to that of the matched general population, provided that surgery is performed before the occurrence of symptoms and/or LV dysfunction.\textsuperscript{14,25,58}

The hospital mortality <1%, which is the standard in advanced repair centres (Table 1), is particularly low if we consider that asymptomatic patients with severe MR due to flail leaflets and normal LV function have a rate of sudden death of 0.8%/year.\textsuperscript{59}

Durability of mitral repair is extremely important if a policy of ‘early repair’ is adopted. Severe degenerative MR due to segmental prolapse of the posterior leaflet can be treated with a very low risk of reoperation. Conversely, the risk of repair failure significantly increases in patients with MR due to lesions involving the anterior leaflet or both leaflets and in those with extensive annular calcification.

More recently, comparable long-term results have been reported in patients with posterior, anterior, and bileaflet prolapse,\textsuperscript{51,60} and it is likely that in the most experienced centres, the progressive refinement of mitral repair strategies will neutralize anterior and bileaflet prolapse as incremental risk factors for recurrent MR after repair.

Although selected centres might offer excellent rates of valve repair, those results cannot be extrapolated to the vast majority of cardiac surgery units where mitral repair is a relatively uncommon procedure and many patients with potentially reparable valves receive a replacement instead.

In most of the ‘non-referral centres’ for MV repair, complex lesions involving the anterior leaflet or both leaflets are usually treated with mitral replacement as demonstrated by the fact that the overall rate of repair in the USA is only 41%.\textsuperscript{61} In Europe, the EuroHeart survey found that about one-third of the MV replacements for mitral insufficiency are performed because of a lack of local expertise in reconstructive surgery.\textsuperscript{62} For instance, in the UK, the rate of MV repair is extremely variable, ranging from 20 and 90%, depending on the hospitals.\textsuperscript{63}

In a recent US study,\textsuperscript{64} 28 507 patients underwent isolated MV operations (with or without concomitant tricuspid valve and/or AF surgery), by 1088 surgeons at 639 centres. Patients having mitral surgery with concomitant coronary artery bypass graft (possible ‘ischaemic’ MR) were excluded. There was marked variability in the annual frequency of MV repair compared with replacement. The median number of isolated MV operations per year was 5 (range 1–166). Following risk adjustment, age, sex, race, endocarditis, mitral pathology, urgency, and concomitant tricuspid or AF surgery were independently associated with altered probability of mitral repair. However, increased individual surgeon mitral volume was the most highly associated predictive factor, with an increased propensity to perform mitral repair both before and after all clinical covariate factor risk adjustments. Furthermore, predictive mitral repair rates increased with increasing surgeon annual MV volume, with a prominent observed threshold effect of \( \sim40 \) mitral cases per year per surgeon.

Until high-quality valve repair surgery will become widespread, an early repair strategy cannot be generally adopted. In asymptomatic patients without surgical triggers according to the current guidelines, an unsuccessful repair requiring unexpected prosthetic valve replacement should be a rather exceptional event since mortality and morbidity after MV replacement is not negligible.\textsuperscript{64,65} Therefore, there is no doubt that, at present, early surgery should be limited to the relatively small number of referral centres with proven expertise in mitral repair surgery providing an hospital mortality <1% and a repair rate for severe degenerative MR at least higher than 90%.

### Table 1

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<th>Author</th>
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### Conclusions

Surgical MV repair is the treatment of choice for severe degenerative MR. The choice between early repair and watchful waiting should be individualized according to the specific characteristics of the patient, the surgical risk, the likelihood of an effective and durable repair, and the local surgical expertise.

Early repair may represent the preferred approach if the operative risk is low and the likelihood of a high-quality repair is very
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high. At the moment, such an early repair strategy cannot be widely adopted and should be reserved to advanced repair centres.

A watchful waiting approach, on the other hand, should probably be preferred in the presence of high surgical risk and/or low probability of a durable repair which is typically the case in elderly patients with relevant co-morbidities and/or complex valve lesions.

Conflict of interest: none declared.

References


