Assessment of subclinical left ventricular dysfunction in asymptomatic mitral regurgitation

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Abstract The management of asymptomatic severe mitral regurgitation is showing an increasing trend towards early surgery. However, in situations where either the valve or the patient is not optimal for surgery, watchful waiting remains a reasonable policy. In this situation, the longstanding challenge of assessing left ventricular function in the setting of severe mitral regurgitation has been simplified by a number of investigations, including stress echocardiography and myocardial imaging. This paper reviews the evidence base for each of these techniques.

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The retreat of rheumatic heart disease, together with aging of the population in Western countries have caused degenerative mitral valve disease (valve prolapse or flail leaflets) to become the most frequent cause of organic mitral regurgitation (MR). Significant improvements in surgical technique have resulted in valve repair being accepted as the optimal surgical treatment, due to a lower peri-operative mortality¹ and better long-term outcome resulting from preservation of left ventricular (LV) function and avoidance of prosthetic valve related complications.² The management of asymptomatic patients with severe MR however remains controversial. While some investigators still advocate routine early surgery for all patients,³ a recent study demonstrated that a "watchful waiting" strategy was associated with a good peri- and post-operative clinical outcome.⁴ To date, there has been no prospective randomised study comparing these two therapeutic approaches.

Rationale for early surgery in the asymptomatic patient

The optimal timing of surgery in patients with asymptomatic severe MR remains a challenge. Due to adaptive remodelling of the left ventricle and...
atrium and patient adaptation to the disease, patients can remain asymptomatic or minimally symptomatic for prolonged periods, even in the presence of severe MR. However, MR is a progressive disease, with an average increase of 7.5 ml per year for regurgitant volume and 5.9 mm² per year for the effective regurgitant orifice, as well as progressive LV remodelling, leading eventually to the development of LV dysfunction, which may be irreversible. Another major concern for patients with asymptomatic severe MR is the risk of sudden cardiac death, with an absolute risk of 1–2.5% over 6 years. The major determinants of sudden cardiac death in MR are LV dysfunction, redundant leaflets and severe MR.

Although LV ejection fraction (EF) is the most powerful predictor of post-operative LV dysfunction and subsequent cardiac morbidity and mortality (Fig. 1), it is influenced by alterations in heart rate and loading. While a reduced EF portends a poor prognosis, the converse is not true, as irreversible LV dysfunction may develop insidiously in the asymptomatic patient, and may be “unmasked” only after successful surgical correction of the MR, resulting in significant post-operative cardiac morbidity and mortality.

Early mitral valve repair surgery on the basis of severe MR alone is supported by evidence of the effectiveness of valve repair and the poor long term outcome incurred by deferring surgery until symptoms develop. However, some patients are not good surgical candidates, due to advanced age or co-morbidities, in which case operation may be inadvisable, irrespective of other considerations. Because the morbidity and mortality from mitral valve replacement is significantly greater than that from mitral valve repair, the next step is to identify whether the valve is repairable. Some valves are not repairable (e.g. rheumatic valves), and predictors of unsuccessful repair are central regurgitant jets, severe annular dilatation, and involvement of ≥3 leaflet segments—especially if the anterior leaflet is involved.

Only when the patient is suitable for major surgery and the valve is repairable do considerations regarding the timing of surgery for asymptomatic valve disease become important. Moreover, valve repair carries a small operative mortality (1%) even in the best centres, and the durability of valve repair for degenerative mitral valve disease is not guaranteed, with a reported recurrence rate of MR (greater than grade 1+) of 8.3% per year post-repair (Table 1). Finally, from a public health standpoint, broad adoption of surgery for asymptomatic mitral regurgitation (MR) would carry a high workload, as this problem is common, accounting for 32% of single native left sided valve disease in a recent European study, and is likely to become more common as the population ages.

Definition of the optimum time for surgery in the asymptomatic patient

The decision to operate on the patient with MR is a complex process that involves a comprehensive evaluation of the patient’s symptoms, MR severity (by quantitative Doppler echocardiography), adverse haemodynamic effects of MR (on the left ventricle, left atrium and right ventricle), feasibility of surgical repair and the operative risk to the patient (Fig. 2).

The ACC/AHA guidelines provide a framework to assist the clinician select the appropriate management strategy (Table 2), but they are based on natural history data and on the consensus of experts, rather than on prospective randomised trials. Once the patient is symptomatic, early mitral valve surgery is mandatory. In asymptomatic patients, the occurrence of overt LV dysfunction (EF <60% or LV end-systolic diameter ≥4.5 cm) or

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Table 1: Benefits versus risks of surgery in patients with asymptomatic severe MR

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<tr>
<th>Benefits</th>
<th>Risks</th>
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<tr>
<td>(1) Increased morbidity and mortality if surgery deferred until symptoms develop or LV dysfunction occurs</td>
<td>(1) 1–2% operative mortality</td>
</tr>
<tr>
<td>(2) High success rate of MV repair in most centres</td>
<td>(2) Not all valves are repairable</td>
</tr>
<tr>
<td>(3) Comorbidities in elderly patients</td>
<td>(3) Per year of MR ≥2+ for degenerative MV disease</td>
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<tr>
<td>(4) Non-trivial recurrence of MR post-repair (8%) per year of MR ≥2+</td>
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Figure 1: Long term post-operative survival according to the preoperative echocardiographic EF. Note the excess mortality not only in patients with EF <50% but also in those with “low normal” EF of 50–59%. 

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1. Lee, R., & Marwick, T.H. (2019). The decision to operate on the patient with MR is a complex process that involves a comprehensive evaluation of the patient’s symptoms, MR severity (by quantitative Doppler echocardiography), adverse haemodynamic effects of MR (on the left ventricle, left atrium and right ventricle), feasibility of surgical repair and the operative risk to the patient (Fig. 2). The ACC/AHA guidelines provide a framework to assist the clinician select the appropriate management strategy (Table 2), but they are based on natural history data and on the consensus of experts, rather than on prospective randomised trials. Once the patient is symptomatic, early mitral valve surgery is mandatory. In asymptomatic patients, the occurrence of overt LV dysfunction (EF <60% or LV end-systolic diameter ≥4.5 cm) or...
the development of atrial fibrillation or resting pulmonary arterial hypertension (pulmonary artery systolic pressures $\geq 50$ mmHg) are accepted indications for surgery. An important consideration is the feasibility of low risk, successful repair (determined by aetiology of MR and local surgical results). Another essential component in the decision making process is the assessment of the surgical risk, which is mostly determined by the patient’s age, history of heart failure, underlying coronary artery disease, and co-morbidities.

The major challenge for the clinician therefore, is to detect LV contractile dysfunction at an early or subclinical stage so that surgical correction can be instituted to prevent the development of irreversible LV dysfunction.

**Detecting subclinical LV dysfunction in the asymptomatic patient**

Most standard echocardiographic parameters including EF and LV dimensions are pre- and after-load dependent, and their evaluation is influenced by the haemodynamic milieu of MR. A variety of echocardiographic and invasive haemodynamic parameters are useful in detecting subclinical LV dysfunction preoperatively in asymptomatic patients and may predict outcome following mitral valve surgery (e.g. LV end-systolic diameter\(^{15}\); LV dp/dt\(^{16}\); LV end-systolic wall stress/end-systolic volume ratio\(^{17}\); and peak elastance derived from the slope of LV end-systolic pressure volume curves\(^{18}\)). However, most of these techniques

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**Table 2** American College of Cardiology/American Heart Association guidelines for surgery for non-ischaemic severe mitral regurgitation

<table>
<thead>
<tr>
<th>Class I (evidence and/or general agreement that surgery is useful and effective)</th>
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<tbody>
<tr>
<td>(1) Symptoms caused by mitral regurgitation (acute or chronic)</td>
</tr>
<tr>
<td>(2) Asymptomatic patients with severe MR and mild-moderate LV dysfunction defined as an:</td>
</tr>
<tr>
<td>- ejection fraction 30–60% AND</td>
</tr>
<tr>
<td>- LV end-systolic dimension 45–55 mm</td>
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<th>Class IIA (conflicting evidence and/or divergence of opinion but the weight of evidence/opinion favours surgical intervention)</th>
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<tr>
<td>(1) Asymptomatic patients with normal LV function and</td>
</tr>
<tr>
<td>- atrial fibrillation OR</td>
</tr>
<tr>
<td>- pulmonary hypertension (&gt;50 mmHg at rest or &gt;60 mmHg with exercise)</td>
</tr>
<tr>
<td>(2) Asymptomatic patients with</td>
</tr>
<tr>
<td>- ejection fraction 50–60% OR</td>
</tr>
<tr>
<td>- LV end-systolic dimension 45–55 mm</td>
</tr>
<tr>
<td>(3) Severe left ventricular systolic dysfunction (ejection fraction &lt;30% and/or end-systolic dimension &gt;55 mm)</td>
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<td>if chordal preservation is highly likely</td>
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have limitations which may reduce their general applicability (Table 3).

Enlargement of various resting LV dimensions (e.g. LV end-systolic diameter) is already accepted as a firm indication for surgery. However, this may not be as useful now, as an LV end-systolic diameter ≥4.5 cm is rarely seen in asymptomatic patients currently presenting for decisions regarding surgical intervention. LV dp/dt, derived from the continuous wave spectral Doppler pattern of the MR jet, is less load dependent than some standard echocardiographic markers. However, this may be difficult to obtain accurately from eccentric regurgitant jets (which are common in degenerative mitral valve prolapse). Markers of LV contractile function such as LV end-systolic wall stress/end-systolic volume ratio and peak elastance are load independent and considered by some to be the “gold standard”. Traditionally, these have been measured invasively, which is unattractive for a test for clinical follow up of these patients. While these parameters have been shown to provide prognostic information when measured non-invasively,19 the LV systolic pressure measurement may not correspond to peripheral pressure and therefore the parameters may not provide the same information as they have in the literature.

There is therefore a need for an easily measured, accurate, reproducible, and preferably load independent echocardiographic parameter to assist the clinician identify high risk patients who may benefit from surgery, and optimise the timing of surgery.

### Role of stress echocardiography in the asymptomatic patient?

Exercise stress echocardiography is often useful in the evaluation of patients with stenotic and regurgitant left sided valvular heart disease, especially when there is a discrepancy between the severity of the lesion and the symptoms (“echo-symptom mismatch”). In addition to providing an objective means of assessing the patient’s functional capacity, the clinician can also obtain useful haemodynamic information, especially in relation to exercise induced changes in pulmonary artery pressures and valve gradients.16 In patients who are limited by dyspnea, the finding of a pulmonary artery pressure >60 mmHg recorded after exercise is a readily measured feature that favours early surgery.

Exercise stress may also unmask latent or subclinical LV dysfunction in patients in whom the LV is compensated at rest. An inability to increase the ejection fraction (EF) or reduce the end-systolic volume with stress reflects the presence of an impaired contractile reserve, and have been shown to be reliable early markers for progressive deterioration in myocardial contractility.20 Previous work by Leung et al.21 has shown that evaluation of contractile reserve by exercise echocardiography could be used to identify subclinical LV dysfunction pre-operatively and accurately predict post-operative LV function early after mitral valve repair. In particular, the authors demonstrated the superiority of the exercise echocardiographic indices (exercise LV end-systolic volume index; peak exercise EF; EF increment post-exercise) over the resting indices in predicting early post-operative LV dysfunction (EF <50%).

Furthermore, we recently demonstrated that in asymptomatic patients with chronic severe MR and a normal resting EF an impaired contractile reserve (EF increment post-exercise <4%) not only predicts the development of late post-operative LV dysfunction (EF <50%) (Fig. 3), but also the occurrence of post-operative cardiac events (congestive heart failure and new onset atrial fibrillation) in surgically treated patients (Fig. 4), and progressive deterioration of LV function in medically treated patients. Conversely, an intact contractile reserve (EF increment post-exercise >4%) predicts preservation of LV function and a favourable clinical outcome irrespective of whether patients were treated medically or surgically. Additionally, evaluation of contractile reserve had an incremental value over rest LV end-systolic volumes in predicting late post-operative LV dysfunction.

Nonetheless, the predictive value of latent LV dysfunction is imperfect, reflecting the fact that LV impairment due to volume loading is potentially reversible after mitral surgery, as well as some potential technical issues with measuring this
Parameter. Measurement of post-exercise LV endsystolic and end-diastolic volumes from which EF is derived involves manual tracing of the endocardial borders. This could be technically difficult in some patients with a poor echocardiographic window, and is a potential limiting factor of this technique.

Use of ultrasound tissue characterisation to detect subclinical LV dysfunction

Integrated backscatter

The first available techniques for characterising the myocardium were based on the analysis of myocardial backscatter, caused by the scattering of ultrasound from small structures. The two parameters which are measured from the time-intensity curve include cyclic variation (CVIB), which appears to reflect the cross-linking of the myocardial contractile apparatus, and absolute levels of backscatter (IB), usually calibrated to adjacent areas of either very high or very low density (respectively, the pericardium and the ventricular chamber) that correspond to the reflectivity of the tissue. Hence, CVIB reflects myocardial contractile function, whereas IB is directly related to the myocardial collagen content, and therefore is a surrogate marker for myocardial fibrosis.

These techniques have successfully been used to identify myocardial viability and characterise myocardial diseases such as hypertrophic cardiomyopathy, and amyloid heart disease. Pacileo et al. demonstrated a significantly higher CIB in asymptomatic children with moderate congenital aortic stenosis, compared to age- and sex-matched normal controls, suggesting an increased amount of myocardial collagen in these patients. Recently, we also demonstrated an inverse correlation between CVIB and biopsy proven myocardial fibrosis in minimally symptomatic patients who underwent mitral valve surgery for severe MR (Fig. 5).

However, this technique remains technically very challenging, both because of a poor signal-to-noise ratio and anisotropy leading to differences in the waveforms depending on which part of the heart is being interrogated and from which angle.

Tissue Doppler imaging

Tissue Doppler imaging (TDI) is a routinely available echocardiographic technique which directly...
measures myocardial tissue velocity and permits the assessment of longitudinal global and regional LV function. Mitral annulus systolic velocity as measured by TDI can be used as an index of global LV systolic function and investigators have shown significant correlations between LV ejection fraction and peak mitral annulus systolic velocity. TDI has also been used to detect subclinical LV dysfunction in a variety of diseases. Myocardial velocity gradients have been shown to be abnormal in patients with subclinical LV dysfunction, and the degree of abnormality in hereditary diseases such as Friedrich’s ataxia appears to correlate with the degree of genetic abnormality. Moreover, abnormal tissue velocities can be used to differentiate between pathologic LV hypertrophy and athletic LV hypertrophy, and a particularly exciting application has been in the detection of patients with undeclared hypertrophic cardiomyopathy who have a family history of the disease and an abnormal genotype. For similar reasons TDI has been effective in the identification of transplant rejection and the detection of subclinical LV dysfunction in asymptomatic patients with severe aortic regurgitation.

Recently, Haluska et al. demonstrated a correlation between lower myocardial systolic velocities measured by TDI, both at rest and immediately after exercise, and reduced contractile reserve of the LV in patients with asymptomatic severe MR. Agricola et al. subsequently demonstrated that TDI derived mitral annulus systolic velocity can also predict early post-operative LV function in patients with asymptomatic severe MR undergoing mitral valve surgery. In all of these situations, the efficacy of TDI is very likely based upon its correlation with the degree of myocardial fibrosis, and the technique represents a more clinically feasible approach than previous attempts to identify subclinical heart disease with, for example, myocardial backscatter. However, TDI has a major limitation in that it cannot differentiate tissue movement due to active contraction from passive motion that results either from translational motion of the whole heart or from a “tethering” of normal surrounding tissue by a segment of diseased myocardium.

Strain rate imaging

This technique estimates spatial gradients in myocardial velocities between points oriented in the same plane and a known distance apart, allowing derivation of a longitudinal myocardial velocity gradient that is not influenced by global motion. Strain is the integral of SR over time and these measures represent the instantaneous deformation of the myocardium within the sampled region. Compared to the invasive “gold” standard of peak elastance derived from the slope of the LV end-systolic pressure volume curves, Greenberg et al. demonstrated that peak and mean systolic SR were more strongly correlated to LV contractility than peak mitral annulus systolic velocity. Weidemann et al. reported that systolic SR was strongly correlated to indices of both regional and global LV contractility (ratio of end-systolic strain to end-systolic wall stress and invasively derived dp/dt), whereas systolic strain was more reflective of changes in stroke volume.

A number of studies also suggest that SR imaging may also be able to detect subclinical LV dysfunction in a variety of diseases before the development of abnormalities in conventional measures of LV performance, such as ejection fraction. In patients with cardiac AL (primary) amyloidosis, systolic strain and SR but not systolic velocity detect early LV systolic dysfunction. SR has also been used to demonstrate improvement in LV function in patients with Fabry’s disease after 12 months of enzyme replacement therapy. Systolic and early diastolic SR were lower and late diastolic SR was higher in asymptomatic patients with Friedrich ataxia compared with age-matched controls. Similarly, systolic myocardial SR was lower in hypertrophic cardiomyopathy patients compared with athletes, hypertensive patients or normal controls.

Recently, we demonstrated that SR imaging could detect subclinical LV dysfunction in patients with asymptomatic severe MR. Both systolic SR and strain were significantly higher in MR patients with a normal contractile reserve compared to those with a reduced contractile reserve (Fig. 6). Furthermore, peak systolic SR was the only resting echocardiographic parameter that could independently predict contractile reserve, with an accuracy superior to that of exercise LV end-systolic volume.

However, as with all the other techniques, SR imaging also has important limitations including signal noise. Issues with angle dependency are inherent to all TDI based techniques.

Place of plasma BNP in the evaluation of asymptomatic mitral regurgitation

Brain natriuretic peptide (BNP) is a cardiac neurohormone, and is released as prepro BNP and then enzymatically cleaved to the N-terminal-proBNP and BNP. Its release appears to be related to stretch of ventricular myocytes.
BNP activation has been shown to be a strong independent predictor of morbidity and mortality in patients with ischemic heart disease and congestive heart failure (CHF). The BNP assay is currently used for the diagnosis and screening of patients with suspected CHF, and also for evaluating the response to treatment in patients with established CHF.

The usefulness of BNP has also been evaluated in the setting of valvular heart disease. Plasma BNP levels increase with symptoms and severity of mitral regurgitation and reflect symptom onset and predict symptom-free survival in severe aortic stenosis. Recently, Detaint et al. demonstrated that BNP activation reflects the severe haemodynamic, atrial and ventricular consequences of MR, irrespective of its severity, suggesting that it may be a surrogate marker for adverse left atrial and ventricular remodelling. Furthermore, elevated BNP levels were independently predictive of morbidity and mortality on medical therapy.

However, BNP levels are affected by both age and gender, with significantly higher levels in older persons and in females. Interpretation of BNP should therefore include consideration of age and gender specific cut-off values. Another limitation is the lack of specificity of BNP, as it may be increased by a variety of non-cardiac disease processes such as renal failure, chronic obstructive pulmonary disease and pulmonary thromboembolic disease.

Conclusions

Stress echocardiography, tissue Doppler, strain rate and plasma BNP are promising tools that provide complementary information to that obtained by clinical and conventional echocardiographic parameters, and may assist the clinician in the evaluation, risk stratification and optimisation of the timing of surgery for asymptomatic patients with chronic severe MR.

Fig. 7 outlines a flowchart that could be used to assist in the management of patients with chronic severe MR. Patients who are symptomatic (NYHA class >II) should undergo early mitral valve replacement.
surgery, preferably repair, regardless of LV dimensions or EF. Asymptomatic patients with an EF < 60% or LV end-systolic diameter ≥ 4.5 cm should also undergo mitral valve repair, as should those with atrial fibrillation or resting pulmonary arterial hypertension (pulmonary artery systolic pressures ≥ 50 mmHg), if low risk surgical repair is feasible. Patients in whom symptom status is indeterminate should undergo exercise testing to objectively assess and quantify the functional capacity. However, there remains a subset of asymptomatic patients, in whom there is an uncertainty regarding the potential benefits of surgery. These patients are usually older, have significant co-morbidities, and there may be a doubt regarding the feasibility of surgical repair. In these patients, evaluation of the contractile reserve by stress echocardiography, tissue Doppler or strain rate and measurement of plasma BNP levels may have a role in assisting the clinician decide on the best management strategy.

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