Early detection of left ventricular dysfunction in patients with mitral regurgitation due to flail leaflet is still a challenge

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This editorial refers to ‘Prognostic and therapeutic implications of pulmonary hypertension complicating degenerative mitral regurgitation due to flail leaflet: A Multicentre Long-term International Study’, by A. Barbieri et al., on page 751

Lack of normal mitral leaflet apposition and abnormal pointing of the flail component into the left atrium (LA) during systole are typical features of mitral leaflet flail which generate haemodynamically relevant mitral regurgitation (MR). The most common reason for mitral leaflet flail is chord rupture.† Rarely, severe prolapse with the leaflet tip bulging into the LA causing severe MR can also occur without chord rupture.‡ The flow direction impacting the mitral leaflets and anatomical features of the leaflets in patients with mitral valve prolapse (MVP) may facilitate chord rupture. Rupture of the chord or papillary muscle is the major cause of acute severe MR due to mitral leaflet flail. Flail mitral leaflet is associated with significant risk of developing left ventricular (LV) dysfunction, atrial fibrillation, pulmonary hypertension, tricuspid regurgitation (TR), heart failure, and sudden death.† – 3

Although MVP has a higher prevalence in younger women, mitral leaflet flail often affects males >50 years of age.†,‡ The aetiology of mitral leaflet flail is complex. Prolapsed myxomatous mitral valves show collagen and elastic tissue alterations, and in spontaneously ruptured mitral chords the myxomatous process often involves mitral chords and papillary muscles. In spontaneously ruptured chords, collagen types III and AB are often absent. Impaired mechanical properties due to collagen alterations and acid mucopolysaccharide accumulation in the mitral leaflets and chords may lead to spontaneous chord rupture. Myxoid chords are more extensible and weaker than normal chords and the failure resistance is more likely to be compromised in the chord than in the leaflet.‡,§ Relevant fibrosis of the myxoid chords, particularly near their insertion into the leaflets, is also frequent and can contribute to the alteration of mechanical properties. Other aetiologies that can be implicated are bacterial endocarditis and mitral annular calcification. The chords of the posterior leaflet are shorter and thinner than those of the anterior mitral leaflet. Therefore, the posterior mitral leaflet is more vulnerable to stress. Being also more liable to myxomatous processes the posterior leaflet is more frequently the origin of mitral leaflet flail. Mitral leaflet flail appears to be predominantly characterized by independent P2 (55%) flail, followed by entire posterior leaflet flail (8%), P2,3 flail (7%), and A2 flail (7%).†

Progressive heart failure is the most common cause of death in patients with mitral leaflet flail. Mitral valve surgery (valve repair or replacement) is the only treatment which provides sustained relief of symptoms and prevents the development or further progression of heart failure.§ Mitral valve repair aiming to restore leaflet coaptation is superior to valve replacement in terms of both morbidity and mortality. Early valve repair in patients with severe MR before deterioration of LV size, geometry, or function increases the likelihood of post-operative normalization of LV function.¶ Clinical outcomes after mitral valve surgery depend on patient- and disease-specific factors as well as on surgery-related factors. Improvement of surgical techniques in experienced centres has resulted in mortality rates of ~1, 2, and 4–5% for patients <65, 65–75, and >75 years of age, respectively.¶

The optimal timing for surgery in MR is still an issue of discussion. Development of mitral valve repair techniques associated with low perioperative mortality has lowered the threshold for surgery, when repair is feasible. According to American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, chronic severe MR in asymptomatic patients with left ventricular ejection fraction (LVEF) >60% is a class IIa indication for valve repair (level of evidence: B).¶ Recent studies support this recommendation, showing that the outcome of asymptomatic patients with severe degenerative MR is better with an early surgical approach.¶,†⁰ Nevertheless, many patients are still referred to
surgery late in the course of the disease, which has a negative impact on the post-operative outcome. Although it is well established that pre-operative LVEF reduction has a negative impact on patient outcome after mitral valve surgery, the vast majority of cardiologists still have serious doubts regarding the indication for surgery in patients with LVEF ≥60%. A Canadian survey suggested that only 16% of cardiologists would correctly refer patients with New York Heart Association (NYHA) class II and moderately severe MR for surgery if the LV function appears normal (LVEF >60%). More than 55% would wait until the LVEF dropped below 60%, while 21% would refer only when the LVEF decreased below 50%, and 63% would wait until the patients become more symptomatic (NYHA class III and IV). This attitude might be explained by misinterpretations of the LVEF in patients with considerable MR.

The EF is the most widely used measure of LV systolic function. It is defined as the change in LV volume (i.e. stroke volume) divided by the initial volume (i.e. LV end-diastolic volume). It is important to be aware that EF is load sensitive and therefore only an index of contractile function, but not an index of contractility (i.e. inotropic state). Thus, with unchanged contractility any increase in afterload will lower the EF whereas an increase in preload and/or a decrease in afterload will result in a higher EF. MR increases LV preload usually without an increase in afterload, which may even decrease. This will result in higher LVEF values which misleadingly suggest a good contractile function, although in reality the normal LVEF can be maintained despite the presence of significant muscle dysfunction. The existence of impaired LV systolic function is usually detected only after mitral valve repair, because pre-operatively it was concealed by the effects of increased preload and decreased afterload. It is also important to realize that with aggravation of MR the regurgitant fraction increases to the detriment of forward stroke volume (SVf), and a normal LVEF will not exclude a low SVf because in patients with MR the difference between end-diastolic and end-systolic volume is the ‘total’ stroke volume [i.e. the sum of the regurgitant volume (MRV) plus the SVf] and not solely the SVf. The reproducible and simple SVf measurement by echocardiography is particularly useful for evaluations of LV systolic function in patients with relevant MR. Indirectly, SVf measurement also allows the indirect calculation of MRV which is often difficult to estimate directly because of the usually high turbulence and eccentricity of regurgitation jets in patients with mitral leaflet flail. Thus from the directly measurable LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and SVf, the more difficult directly measurable MRV can be calculated by the formula: MRV = LVEDV – (LVESV + SVf).

As shown in Figure 1, the LV volume overload produced by MR remains compensated as long as eccentric LV hypertrophy allows the maintenance of a normal SVf without a relevant increase in filling pressures. With aggravation of MR the LV dilates, the SVf decreases, and the left heart filling pressure rise generates a progressive increase in the pulmonary capillary wedge pressure and

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**Figure 1** Aetiopathogenesis and pathophysiological consequences of mitral leaflet flail. Once chronic mitral regurgitation has become severe and the left heart compensatory mechanisms to the volume overload which allowed the maintenance of normal forward stroke volume (SVf) without relevant increase of filling pressures are exhausted, the left ventricle (LV) dilates and LV geometry alteration plus contractile dysfunction further impair forward ejection. The LV end-systolic diameter (LVESD) increases beyond 40 mm, and pulmonary hypertension and elevated BNP (brain natriuretic peptide) plasma levels are detectable before LVEF alterations and often also before the onset of clinical symptoms.
pulmonary vascular resistance. The result will be pulmonary venous hypertension with right ventricular (RV) pressure overload causing RV hypertrophy, later right atrial dilation with increasing TR, and finally RV dysfunction. It is surprising that to date only a few papers on this issue have been published and that most studies focus mainly on the LVEF which is not useful for early detection of LV systolic dysfunction in patients with MR. The recognition of alterations in pulmonary haemodynamics which have an important impact on perioperative mortality is of major importance, especially in patients with normal LVEF. According to the ACC/AHA guidelines, surgery is reasonable for asymptomatic patients with chronic MR, normal LVEF, and pulmonary hypertension (PH) with pulmonary artery systolic pressure (PASP) >50 mmHg at rest (class IIa recommendation, level of evidence: C). The C level of evidence shows that to date the importance of PH is only a consensus opinion of experts which needs to be confirmed by clinical studies. The study recently published by Barbieri et al. is therefore of major clinical importance. The authors found that PH is a strong independent predictor for post-operative death, cardiovascular death, and heart failure. They also found that patients who underwent mitral valve surgery before the occurrence of PH have the most favourable post-surgical outcome. These data obtained during a long-term follow-up from a large number of patients who were treated in four centres in Europe and one in the USA may contribute to future improvements of the pre-operative assessment of patients with MR due to flail leaflets. The results are also in agreement with previous observations that patients with PH who underwent mitral valve replacement for severe MR are at higher risk for early post-operative mortality.

Although the excellent outcomes after valve repair and the worse impact of altered LV function on post-operative patient outcome support the recommendation for valve repair in asymptomatic patients with severe MR, many cardiologists still prefer to recommend surgery only when left heart compensatory mechanisms to the volume overload are exhausted, leading to onset of symptoms, an increase in brain natriuretic peptide (BNP), evidence of LV dysfunction, PH, TR, atrial fibrillation (AF), etc. However, after LVEF reduction and/or appearance of AF, the post-operative outcome is impaired and LVEF alteration as well as AF can persist after surgery, PH and elevated BNP plasma levels in patients with severe MR are usually detectable before LVEF alteration. Although PH is also a risk factor for early post-operative mortality, being to a large extent reversible after valve surgery, it has no relevant influence on late survival. The data presented by Barbieri et al. strongly suggest that simple measurements of PASP by echocardiography can indeed be very useful for optimal timing of surgery in patients with severe MR, before the first evidence of potentially irreversible LVEF alterations which impair the long-term post-operative outcome.

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References