

Cardiac murmurs and their hidden messages

Dr David P Moore

Mitral valve prolapse

Mitral valve prolapse (MVP) is the most common cardiac valvular abnormality in this country. With its associated auscultatory findings and a plethora of associated non-specific symptoms, it is a frequently encountered condition, albeit usually one with a benign outcome. This article looks at the structural abnormalities encountered in MVP, the associated clinical features and the potential for some rare but serious complications.

Historical

Mid-systolic clicks and associated late systolic murmurs were first described in the medical literature in the 19th century, but it was as recently as the early 1960s that the syndrome was described and associated with characteristic valve abnormalities, firstly by Reid and then by Barlow and Pocock. Since then, the subject has been intensively studied and theories on the role of MVP in heart failure, atrial fibrillation, syncope and stroke were enthusiastically propounded. Prevalences varying from 2% to 17% of the adult population have been reported, a level of variation which owes much to both inconsistencies in diagnostic criteria and selection bias in many of the early studies.

In more recent years, population-based studies have defined both the incidence and the prognosis much more reliably, and at last we have a basis on which to discuss the condition with concerned patients and their relatives. In this article, the natural history, diagnostic criteria, symptomatology and therapeutic options for MVP will be discussed.

Symptomatology

The majority of subjects with MVP are entirely asymptomatic. Diagnosis is made at routine examination or sometimes when the individual presents with non-specific symptoms or with cardiac or neurological symptoms, which are a direct result of MVP. Not infrequently, the first presentation will be with complications of the disorder. Although the non-specific symptoms described below are widely recognised, one large population-based study failed to demonstrate any difference in the incidence of chest pain and dyspnoea between normal individuals and those with MVP.

Non-specific symptoms

A range of non-specific symptoms is recognised, with a constellation of chest pain, palpitations and presyncope being the commonest presentations. MVP presenting with these features and without major haemodynamic abnormalities is referred to as mitral valve prolapse syndrome.

Chest pain occurs in about two thirds of patients with the syndrome and although rarely confused with angina pectoris, it is frequently a cause of concern, as it is usually left sided with sharp or piercing qualities. Much research effort has focused on establishing a mechanism for chest pain in MVP; myocardial ischaemia is not demonstrable in the great majority, although other causes of chest pain, such as coronary vasospasm and oesophageal spasm, appear to be commoner in MVP than in the general population.

Palpitations occur in close to 50% of patients with MVP syndrome: investigations sometimes confirm supraventricular tachycardias, but ambulatory monitoring with well annotated diaries have been reported to show a rather low concordance between actual and perceived arrhythmia incidence in MVP syndrome.

Postural hypotension is encountered quite often and may account for some of the presenting symptoms.

Autonomic dysfunction characterised by abnormal (usually exaggerated) heart rate and BP responses to a variety of stimuli and sometimes hypersensitivity to catecholamines. Some authors have described a spectrum of abnormal haemodynamic responses to physiologic stimuli, which could explain the symptoms encountered in the syndrome and which have been characterised as a neuroendocrinopathy. Florid symptoms such as these are uncommon, however.

Therapy for non-specific symptoms

Asymptomatic patients do not require any therapy (except for antibiotic prophylaxis, see below); most of the symptoms of MVP syndrome respond well to a combination of beta blockers and reassurance.

Mitral regurgitation

In the post rheumatic era, MVP is the leading cause of isolated mitral regurgitation (MR) in all western countries, and many authors have emphasised the importance of progressive MR and other complications. Epidemiological

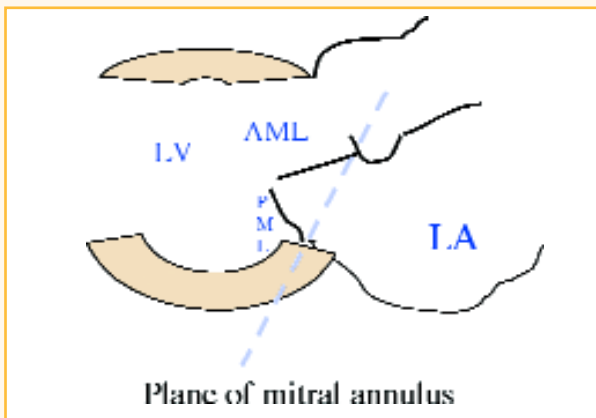


Figure 1. Mitral valve prolapse. (a) is a diagrammatic representation of the mitral valve and its annulus in the parasternal long axis projection.



Figure 1(b). 2-D echo image showing plane of annulus and normal mitral valve in systole.



Figure 1(c). 2-D image showing MVP.

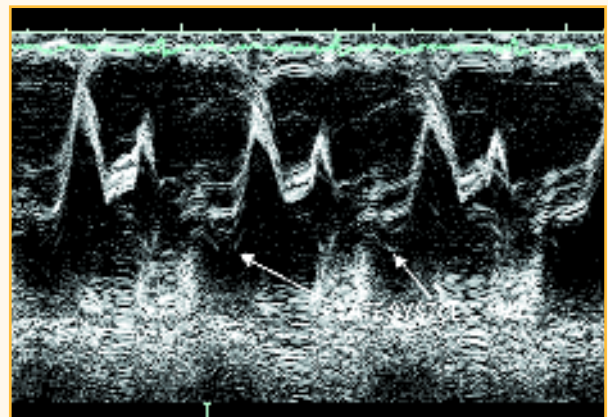


Figure 1(d). M-mode appearance of MVP. PMVL is arrowed as it prolapses in systole.

studies have shown the prevalence of severe MR to be low however, even in patients with classical MVP.

Epidemiology

The Framingham Heart Study has provided a wealth of data concerning the epidemiology of heart disease. A detailed echocardiographic study of the offspring of the original cohort was conducted in the 1990s using modern echo equipment and strict definitions of prolapse. The incidence of MVP in this population was 2.4%, with an equal distribution between men and women. Previously published studies, some based on hospital patient populations, had estimated the incidence at 5-15% or even higher, partly due to laxity in the definition of MVP, but, to a great extent, to referral bias. The incidence of arrhythmia, heart failure and cerebrovascular disease did not differ significantly from controls in this population.

Natural history

For the great majority of patients with MVP, the prognosis is excellent. The development of progressive MR is the most important determinant of an adverse outcome. Enlargement of the left atrium leads to atrial fibrillation and when MR is more than moderate, progressive left ventricular dilation is likely, eventually leading to congestive heart failure, with increased risk of a range of complications, including endocarditis and

serious arrhythmias. Sudden death is extremely uncommon in MVP, although there has been much interest in this complication. Atrial and ventricular ectopics and atrial fibrillation or non-sustained VT may occur in 15-30% of symptomatic MVP patients, but do not usually require specific treatment other than for sustained atrial fibrillation.

DIAGNOSIS

Clinical

MVP can still be readily diagnosed with the stethoscope, and has distinctive auscultatory features.

The mid systolic click of MVP is due to the abrupt tensing of the prolapsing scallop of the valve, as its posterior motion is arrested by the chordae tendinae. Experienced listeners can occasionally distinguish more than one click, especially where both leaflets or multiple scallops of one leaflet prolapse. If MR is present, there will usually be a mid to late systolic murmur following the click. Progression of MR due to the development of a flail valve may result in abolition of the click.

Echocardiographic

Mitral prolapse is defined as posterior movement of part or all of the leaflets beyond the plane of the fibromuscular mitral annulus (Figure 1). This requires a high quality echocardiogram to establish unequivocally. Formerly, the

diagnosis was made on the basis of M-mode echocardiograms, which require great expertise to perform and interpret correctly, as minor transducer angulation is capable of producing the erroneous impression of MVP in normal subjects. Many of the studies reporting a very high prevalence of MVP were based on M-mode echoes alone. Echocardiographic diagnosis is made on parasternal long axis views of the mitral valve with confirmation, if required, from apical windows. Apical images should not be used for the diagnosis of MVP without parasternal confirmation (see Figure 1a-d).

At least 2mm posterior displacement of at least one scallop of either leaflet is required for diagnosis. There may be in addition diffuse 'myxoid' thickening of the leaflet or evidence of redundant, billowing chordae tendinae.

Doppler ultrasound is extremely sensitive in the detection of MR, which is virtually ubiquitous in MVP.

Evaluation of larger degrees of MR requires a combination of measurements and echo techniques, including: 2-D: estimation of left atrial size and left ventricular volume.

Doppler techniques:

1. Colour flow mapping: estimation of area of MR jet. This technique is fraught with difficulties and is particularly prone to underestimate MR, due to MVP because of the tendency of the jet to adhere closely to the undersurface of the non-prolapsing leaflet and the interatrial septum or free wall.
2. Pulsed wave Doppler: detection of systolic pulmonary venous flow reversal is specific for severe MR but is often technically difficult or impossible.
3. PISA technique: a very promising Doppler technique for the quantification of MR volume, which relies on measurement of the velocity of the turbulent blood just before its regurgitation through the leaky valve (analogous to the vortex of water which forms above the plug as a bath is emptied). This is the first robust non-invasive measure of the haemodynamics of MR to become available. Theoretical difficulties occur where the regurgitant orifice is very distorted, but the measure is reliable enough for routine usage (Figure 3).

Transoesophageal echo is invaluable in establishing the precise anatomical abnormality in MVP. The prolapse is frequently confined to a single scallop of the leaflet and most commonly involves the posterior leaflet.

Determination of the detailed structure of the valve is crucial for evaluating patients who may require surgical repair or replacement of the mitral valve.

The middle scallop of the posterior leaflet is most frequently involved in MVP and conservative repair of the valve is increasingly an option for patients with anatomically favourable posterior leaflet prolapse (see Figure 2).

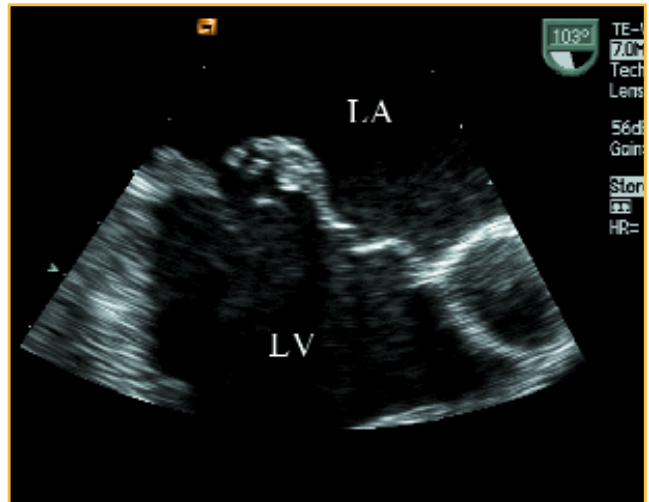


Figure 2. Severe prolapse with flail scallop and significant coaptation failure. Transoesophageal view.

Management

Many patients with MVP are completely asymptomatic and are made aware of their condition as the result of a routine medical examination, usually with a confirmatory echocardiogram. The diagnosis of a cardiac murmur is often very alarming, especially for young people who may have legitimate concerns about long-term prognosis, employment prospects, pregnancy risks and so forth. Asymptomatic MVP without MR requires no more than reassurance, possibly with infrequent echo follow-up (every five years or so).

MVP with associated MR requires advice on appropriate antibiotic prophylaxis for dental surgery or endoscopic procedures or other operations liable to be associated with bacteraemia.

Periodic echocardiographic follow-up is appropriate for patients with mild to moderate MR, obviously more frequently in the context of changing symptoms.

Symptomatic patients with MVP may be more challenging. As indicated above, some of the non-specific symptoms associated with the mitral valve prolapse syndrome may respond well to beta blockade. Where symptoms are related to increasing severity of MR, the possibility of surgical intervention may need to be considered.

A consensus is developing that surgery for MR should be performed before there is extensive irreversible ventricular remodelling. Atrial fibrillation is much more likely to occur and more likely to persist after intervention if there is substantial left atrial enlargement. Congestive heart failure resulting from severe MR is now the commonest indication for mitral valve surgery. Replacement is usually the operation of choice in older patients with myxomatous valve degeneration often affecting both leaflets and extensive valve and annular calcification making conservative surgery unattractive. However, repair

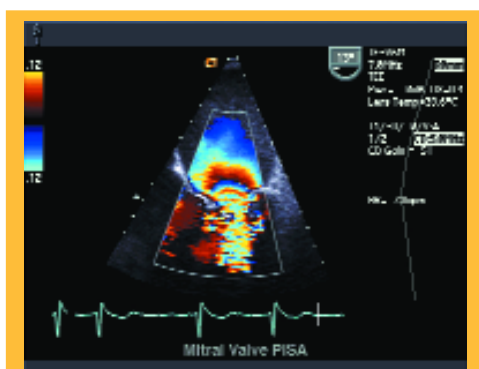


Figure 3. Severe mitral regurgitation in MVP seen from transoesophageal view. The colour Doppler in the proximal LA is seen to consist of hemispherical isovelocity shells. The radius and velocity of these shells can be used to calculate regurgitant volume (see text).

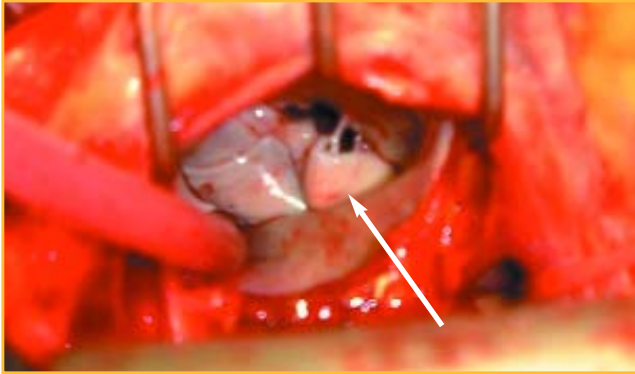


Figure 4. Surgical appearance of posterior mitral valve leaflet prolapse. The arrow points towards the flail P2 scallop. (Photo courtesy of Mr V. Young, St James's Hospital cardiothoracic unit, Dublin).

with annuloplasty is increasingly being undertaken by cardiac surgeons for younger patients, especially those with uncomplicated posterior leaflet prolapse and moderate to severe MR. Potential candidates for surgical repair will require extensive echocardiographic evaluation, including detailed transoesophageal evaluation to determine the number and site of the prolapsing scallops, the extent of MR and the valve and annular morphology. Transoesophageal echocardiography is also routinely used preoperatively to judge the functional outcome of mitral valve repairs.

Complications

Referral bias makes it extremely difficult to determine the real incidence of complications such as embolic stroke and infective endocarditis, but it seems clear that both occur with increased frequency in patients with MVP. MR and increased leaflet thickness are risk factors for endocarditis, whereas age appears to be the major risk factor for stroke in MVP. In general, men and those over 50 years of age appear to be at greater risk of complications. Specific antithrombotic strategies for MVP patients have not been devised. Most experts agree that warfarin is appropriate for those who have had embolic episodes, and is probably appropriate for those with atrial fibrillation. The efficacy of aspirin in stroke prevention in MVP has not been established. *Dr David P Moore, MB, MRCP, is director of non-invasive cardiology at the AMNCH, Tallaght.*

GUSTO IV AMI

Ashley Smyth

Sponsor: Centocor, Inc.

This study is a phase III, randomised, open-label trial evaluating the efficacy and safety of ReoPro (abciximab) in combination with reduced dose Retease/Repllysin (recombinant plasminogen activator, reteplase, r-PA) for the treatment of acute myocardial infarction (GUSTO IV AMI).

This will be a multinational, multicentre, randomised, open-label trial. Approximately 16,600 patients with acute myocardial infarction will be studied. The number of randomised patients will be equally distributed into one of the following two treatment groups, ReoPro combined with 5+5 U reteplase and low-dose weight-adjusted heparin (experimental treatment group) and full dose, 10+10 U reteplase with standard heparin (control group).

The primary objective of the study is to compare the effects of ReoPro in combination with reteplase administered as a 5+5 U double bolus and low dose weight-adjusted heparin (treatment), and conventional 10+10 U double bolus reteplase (control) with standard heparin on a primary endpoint of all cause mortality through 30 days of randomisation in patients with acute myocardial infarction. All patients will also receive concomitant 75 to 325mg per day of aspirin therapy for at least 30 days.

The secondary objectives are to compare the treatment and control groups with respect to the endpoints of:

- Combined endpoint of all cause 30-day mortality and non fatal disabling stroke through discharge from acute hospitalisation or 7 post randomisation, whichever is earlier.
- All cause mortality through one year.
- Incidence of haemorrhagic stroke through discharge from acute hospitalisation or 7 post randomisation, whichever is earlier.

The Doctors participating in this study in Ireland are Dr Crean in St James's Hospital, Dublin, Dr Barton, Portiuncula Hospital, Galway, Dr Daly, University Hospital, Galway and Dr Sullivan in Mallow General Hospital, Co Cork.

HERO-2

Ashley Smyth

Sponsors: The Medicines Company, Cambridge, MA, USA.

The HERO study is an open prospectively randomised comparison of hirulog versus heparin in patients receiving aspirin and thrombolysis (streptokinase) for the treatment of acute myocardial infarction.

Hirulog is a 20 amino acid synthetic peptide that directly inhibits free and clot-bound thrombin, and when used in appropriate regimens as an adjuvant during thrombolytic therapy, may prevent clot formation and extension and facilitate clot lysis. Following the results of the HERO trial, the sponsors are testing the hypothesis the hirulog will improve mortality outcomes in acute myocardial infarction as adjunctive therapy to streptokinase, particularly when administered before thrombolytic treatment.

The primary endpoint is to show that when compared with heparin, anticoagulant therapy with hirulog significantly reduces mortality at

30 days in patients presenting with acute myocardial infarction who are eligible for thrombolytic therapy with streptokinase, and who present within six hours of symptom onset. The secondary endpoint of the study is to show that hirulog reduces rates of in-hospital reinfarction and death at 30 days and does not increase the incidence of non-fatal disabling stroke or intracranial haemorrhage.

To be included in the study patients must have:

- >30 min of continuous symptoms
- ECG with: ST elevation > or = to 1mm in at least two limb leads or two leads, V4-V6
OR, ST elevation > or = to 2mm in at least contiguous precordial leads, V1-V3
OR, LBBB not known to be old.

There are five sites participating in this study in Ireland; Dr Barton in Portiuncula Hospital, Dr Sullivan in Mallow General Hospital, Dr Daly in UCH Galway, Dr Meany in Limerick Regional Hospital and Dr Sugrue in the Mater Hospital Dublin.