Mitral stenosis

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Mitral stenosis is a common disease that causes substantial morbidity worldwide. The disease is most prevalent in developing countries, but is increasingly being identified in an atypical form in developed countries. All treatments that increase valve area improve morbidity. Mortality improves with surgery; the benefit of percutaneous balloon valvuloplasty to mortality might be similar to that of surgery but needs further study. Percutaneous balloon valvuloplasty is the treatment of choice for patients in whom treatment is indicated, except for those with suboptimum valve morphology, and even these patients are sometimes treated with this procedure if surgery is not feasible or if surgical risk is prohibitive. We review the pathology, diagnosis, and treatment options for patients with mitral stenosis.

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Introduction

Although mitral stenosis is now rare in developed countries, it has been recognised for more than 300 years—Vieussens described the disease in 1705—and has provided major milestones in cardiology. It was the first disease to be diagnosed with echocardiography,[1] and the first valve lesion to be successfully treated by surgery[2] or percutaneous balloon valvuloplasty (PBV).[3] Mitral stenosis remains an important cause of morbidity despite the ease with which it can be diagnosed and treated.

Mitrial stenosis is highly prevalent in developing countries[4] because of its association with the prevalence of rheumatic fever, but is also seen in developed countries.[5] Patients often have distinct social and demographic indicators dependent on their country of residence: in developing countries, patients tend to be young with a pliable valve,[6] whereas in developed countries patients are of increased age with several comorbidities.[7,8]

Epidemiology

Two-thirds of the world's population live in developing countries with a high prevalence of rheumatic fever or rheumatic heart disease (eg, 6 per 1000 schoolchildren in India *vs* 0·5 per 1000 in developed countries[4]), resulting in a large population with mitral stenosis. In a survey of rheumatic fever in India,[4] the mean age of presentation was 15·1 years (SD 4·4), and two-thirds of the participants had signs of mitral stenosis, of whom half had limiting symptoms. Up to 30 million schoolchildren and young adults have chronic rheumatic heart disease worldwide, and nearly a third of these also have mitral stenosis.[9,10]

Progression of mitral stenosis in developing countries is malignant and intervention is often necessary during teenage years.[11] In developed countries,[7] prevalence detected by echocardiography is about 0·02–0·2%.[12] The natural history is distorted by a predominance of data from PBV centres in developed countries because patients from these centres are older than are patients in developing countries, have comorbidities,[13] and have suboptimum outcome with interventions (table).[21,22]

Search strategy and selection criteria

We searched Medline for original articles published in English between January, 1970, and March, 2008, using the root search term "mitral stenosis". We checked reference lists of selected articles for further relevant articles. Only directly relevant articles are included in the reference list of this report.

Aetiology

Although mitral stenosis most frequently follows rheumatic fever, fewer than half of affected patients remember having rheumatic fever. Persistent inflammatory valve damage[23] and haemodynamic injury contribute to gradual progression; the rate of progression and time to clinical detection is strongly associated with repeated episodes of rheumatic fever.[24] This correlation could partly explain the different natural history of mitral stenosis across the world.[10,24,25]

Degenerative causes are common in developed countries (eg, 12·5% in Euro Heart Survey[7]). In 6–8% of patients with severe mitral annular calcification, who are often elderly or dialysis-dependent, calcium encroaching into the valve leaflets causes mitral stenosis.[26] For these patients, physical findings are atypical and surgical options are often unattractive.

Other rare causes are congenital deformities, which often present very early in infancy or childhood (eg, parachute mitral valve, double orifice mitral valve, supra mitral ring[27]); infiltrating diseases (eg, mucopolysaccharidosis); diseases affecting multiple systems (eg, Fabry's disease, systemic lupus erythematosus, and rheumatoid arthritis), but this cause is very rare; valve stenosis after mitral valve repair; and disorders associated with abnormal serotonin metabolism (eg, carcinoid and methysergide treatment).

Pathology

The main features are leaflet thickening, nodularity, and commissural fusion, all of which result in narrowing of the valve to the shape of a fish mouth (figure 1).[28] The leaflets might be calcified. Chordal fusion and shortening adds a further resistance to blood flow. Continued inflammation, injury, and repair affect the effectiveness of treatment, and treatments are tailored to target these features of disease.[29,30]

Whether left-ventricular systolic function is truly reduced in patients with mitral stenosis and the clinical significance of reduction is unknown. A third of patients

	Kothari et al (1998)[14]	Gamra et al (2003)[15]	Arora et al (2002)[16]	John et al (1983)[17]*	Chen et al (1995)[18]	Iung et al (2004)[8]	Palacios et al (2002)[19]	Shaw et al (2003)[20]
Country	India	Tunisia	India	India	China	France	USA	UK
Women	..	68%	..	46%	70%	80%	82%	95%
Age (years)	11 (1·2)	16 (2·8)	27·2 (11·2)	27·3 (9·3)	36·8 (12·3)	47 (15)	55 (15)	76 (4·4)
NYHA stage II	29%	..	..	..	55·5%	28%	24·1%	..
NYHA stage III	64%	..	..	57·5%	38·8%	67%	61·2%	..
NYHA stage IV	6%	69%†	87·5%†	41·5%	5·6%	3·5%	13·3%	..
Previous commissurotomy	0%	..	13·6%	..	4·2%	15·6%	24%	18%
Previous embolism	..	11%	..	14·4%	..	9·5%	..	..
Atrial fibrillation	0%	6%	14·5%	12·5%	27·2%	31%	50%	85%
Calcified valve	..	..	2·1%	15·3%	31%	27%	10%‡	..
Mitral valve area (cm²)	0·66 (0·04)	0·63 (0·1)	0·7 (0·2)	0·5 (··)	1·1 (0·3)	1·03 (0·23)	0·9 (0·3)	0·86 (0·27)
Mitral gradient (mm Hg)	24·3 (7·7)	23 (8)	29·5 (7)	..	18·3 (5·1)	10·3 (4·6)	14 (6)	11·4 (4·7)
Grade 2 mitral regurgitation	..	0·9%	18·9%	12·8%	13·2%§	2·6%	6·5%	..
Low ejection fraction	..	..	..	..	..	..	..	13%
Coronary artery disease	..	..	..	..	..	..	..	38%
Aortic valve involvement	13·3%¶	..	12·7%¶	15·5%¶	17·1%¶	..	..	23%‖
Left-atrial thrombus	..	..	..	..	..	..	..	18%
Suitability for mitral valve replacement	..	..	..	..	..	..	..	40%

Data are number of patients (%) or mean (SD). ··=data unavailable. NYHA=New York Heart Association stage of disease. *Surgical series from 1980s for comparison with more recent data. †Data for NYHA stages III and IV. ‡Grades 3–4. §Less than grade 3. ¶Aortic regurgitation. ‖Aortic stenosis.

Table: **Range of patients with mitral stenosis treated by percutaneous balloon valvuloplasty**

have some systolic dysfunction probably due to internal constraint from a combination of a rigid mitral valve,[31] reduced preload,[32] and a reflex increase in afterload.[33] Although early studies have not found load-independent left-ventricular contractile dysfunction,[34] strain-rate imaging might show impaired long-axis function despite normal global systolic function.[35] Some patients might have systolic dysfunction that is not dependent on low preload.[36] Successful PBV is not associated with clinically significant changes in left-ventricular function, end-systolic wall stress, or preload-corrected ejection-fraction afterload relation,[33] except in rare reports.[37] Low ejection fraction does not seem to affect operative outcome.[36]

Diastolic function in patients with mitral stenosis is less well studied than systolic function is, but chamber compliance is abnormal[31] and superimposed diastolic dysfunction can negate the filling benefit of early diastolic suction.[38] Increased left-ventricular end-diastolic pressure correlates with poor outcome after PBV.[39,40] Right-ventricular function is often reduced because of pulmonary arterial hypertension, and affects prognosis for mitral valve disease.[41] Despite prompt reduction in pulmonary hypertension after valvuloplasty, improvement of the right-ventricular ejection fraction can be slow.[42] The left atrium is stiffer (large V wave, which affects pulmonary arterial pressure[43] and exercise capacity[44]) with reduced systolic flow and pump dysfunction proportional to the severity of mitral stenosis.[45] Atrial fibrillation worsens stiffness and left-atrial function, which PBV can improve,[46] but not entirely.[47]

Unlike aortic stenosis, the stenotic mitral valve behaves like a fixed orifice despite changes in flow and pressure[48] with exercise or dobutamine.[49] Thus, patients with severe mitral stenosis have little functional reserve and easily decompensate with tachycardia or high flow. However, the valve does regain some valve reserve (increased size with increased flow) after PBV.

Procoagulation abnormalities that are common in mitral stenosis are changes in platelet activity; increased concentration of fibrinopeptide A, thrombin-antithrombin III complex, and D-dimer; and changes in fibrinolytic activity. These changes have most obvious effects in the left atrium, probably originate in the left atrium or hypertensive pulmonary circulation, and are correlated poorly with disease severity.[50] Atrial fibrillation might also create or worsen many of these abnormalities. Anti-coagulation and PBV reduce hypercoagulability, which might partly explain the possible reduction of strokes after valvuloplasty.[51]

Pathophysiology

The normal mitral valve area is 4–6 cm² and a gradient is rare unless the valve is less than 2 cm². Pathophysiology is closely related to the amount of diastolic flow across the valve and the diastolic filling period (figures 2 and 3). Generally, symptoms of dyspnoea correlate with increasing

mean left-atrial pressure, which is inversely related to RR interval (figure 3). Atrial contraction helps to maintain flow across the stenotic mitral valve; atrial fibrillation, which is associated with tachycardia, irregular RR interval, and lack of atrial contraction, is often an important precipitating factor for symptoms of dyspnoea.

Symptoms start when mitral valve area (normally more than 4 cm²) reduces to 1·5 cm², and most patients have obvious symptoms when the area is less than 1 cm² (figure 3). Pulmonary oedema is rare but possible with mitral valve area of more than 1 cm², and affected patients are treated as for severe mitral stenosis. Atrial fibrillation, anaemia, pregnancy, and infection can create discordance between symptoms and mitral valve area. Severity of dyspnoea is associated with lung water,[52] and symptomatic relief is achieved with decreased lung water[53] rather than haemodynamic changes alone.[54] Patients with persistent severe mitral stenosis develop compensatory changes (eg, pulmonary arterial hypertension, dilated lymphatic vessels, and alveolar thickening) that moderate symptoms for a short period. Left-atrial and left-ventricular compliance changes due to age and pulmonary arterial hypertension can also affect symptoms and exercise capacity.[43,55,56]

Clinical presentation

Patients usually present with dyspnoea, often during exercise or in combination with disorders that increase heart rate or flow across the mitral valve.[57,58] The valve area narrows gradually by 0·1–0·3 cm² per year,[59] which explains the variable onset of symptoms. The disease course is accelerated in populations with recurrent rheumatic fever, in which the natural history is compressed to 5–10 years. Clinical presentation is affected by age-related comorbidities such as systemic hypertension, coronary artery disease, and diastolic dysfunction.[60] Frequency of adverse events increases with the onset of limiting symptoms or substantial pulmonary arterial hypertension in the presence of severe mitral stenosis.

Other rare symptoms include haemoptysis, chest pain (often due to pulmonary hypertension), and pressure effects on adjacent structures, for example from a dilated left atrium. Atypical presentations include fatigue (spontaneous or with diuresis) with a low transmitral gradient[61] and a syndrome of right heart failure with severe pulmonary arterial hypertension. Patients with pulmonary oedema rarely have severe pulmonary arterial hypertension, whereas those with severe hypertension (pulmonary vascular resistance >6–8 Wood units) seem to present with right heart failure[58] rather than pulmonary oedema. Occasionally, patients first present with embolic episodes related mostly to atrial fibrillation, or very rarely while in sinus rhythm. Death is mainly due to heart failure or systemic embolism.[57,58] Left-atrial myxoma, ball-valve thrombus, and cor triatriatum can be clinically mistaken as mitral stenosis and should be carefully excluded.

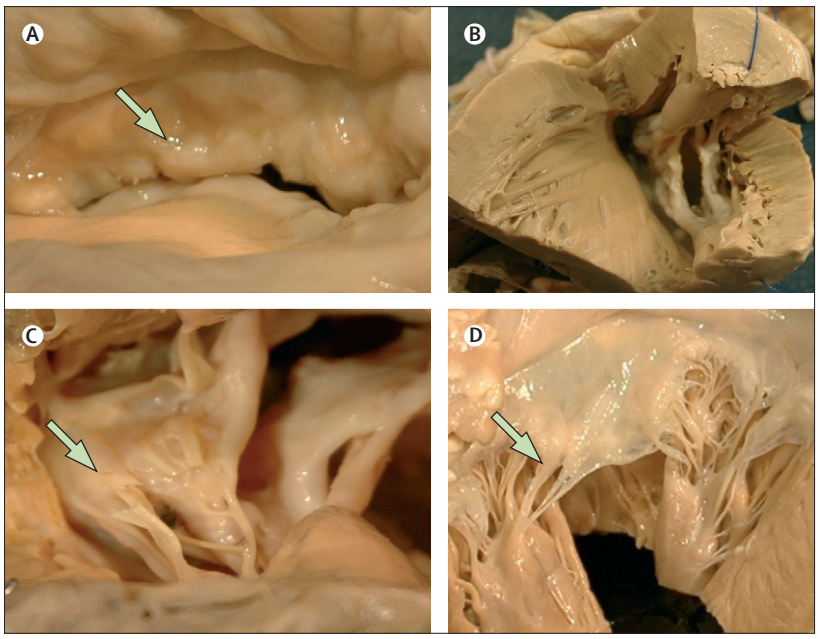

Figure 1: **Pathological specimens of the mitral valve in mitral stenosis**
Thickened, rigid, nodular appearance of the mitral valve leaflets viewed from the atria (A) and ventricle (B). Calcium is present in commissural ends of the valve, and the commissures are fused resulting in a valve shaped like a fish mouth. Subvalvular apparatus is thick, fused, and shortened (B, C). Healthy mitral valve leaflets (D).

Diagnosis

Physical signs of mitral stenosis have been well documented.[58] Moderate-to-severe disease is easily diagnosed by auscultation in the left-lateral position or after mild exercise, unless the patient has unfavourable body habitus (severe obesity or chronic obstructive pulmonary disease), pulmonary oedema, very low cardiac output, or rapid atrial fibrillation. Diagnostic sensitivity and specificity is about 85% and accuracy is similar to that of echocardiography (92% *vs* 97%).[62]

Clinical issues that need to be addressed include severity of disease, pliability of the valve, extent of mitral regurgitation and pulmonary arterial hypertension, and presence of atrial fibrillation. At present, severity of disease is assessed from symptoms (eg, shortness of breath, exercise intolerance), presence of long murmur (especially with presystolic accentuation in normal sinus rhythm or during long RR intervals in atrial fibrillation), short interval of A2 to opening snap (OS), and signs of pulmonary arterial hypertension or right ventricle overload. Pliability of the valve is assessed from loud S1 and prominent OS. Two useful assessment methods are electrocardiography, which most commonly shows left-atrial enlargement and right-ventricle pressure overload, often with atrial fibrillation, and chest radiography, which shows left-atrial enlargement, pulmonary arterial hypertension, and pulmonary congestion. However, imaging is the mainstay of diagnosis and treatment selection (figure 4).

Echocardiography is used to diagnose and judge stage of disease, assess mitral regurgitation, exclude conditions

that mimic mitral stenosis, and provide information about suitability for PBV (low echocardiography score,[69] absence of commissural calcium[70]). Both valve area and gradient can be accurately measured, but several measurements with more than one method are often needed to accurately estimate haemodynamics of the mitral valve.[48,71,72] The most reliable method to calculate valve area is planimetry with 2D echocardiography cross-section images, and even more reliability might be achieved with 3D echocardiography. However, 2D echocardiography underestimates the severity of mitral stenosis, especially moderate-to-severe disease, in up to half of patients also examined with 3D guided echocardiography,[73,74] and underestimates the extent of commissural splitting by PBV.

Another common assessment method for mitral valve area is pressure half-time—the time taken for the pressure to halve from the peak value—which is most effective for the native valve before surgical intervention. However, this method is affected by left-ventricular chamber compliance, left-ventricular chamber relaxation profile, and heart rate; rarely, the mitral valve area can be recorded as normal even with clear valve obstruction.

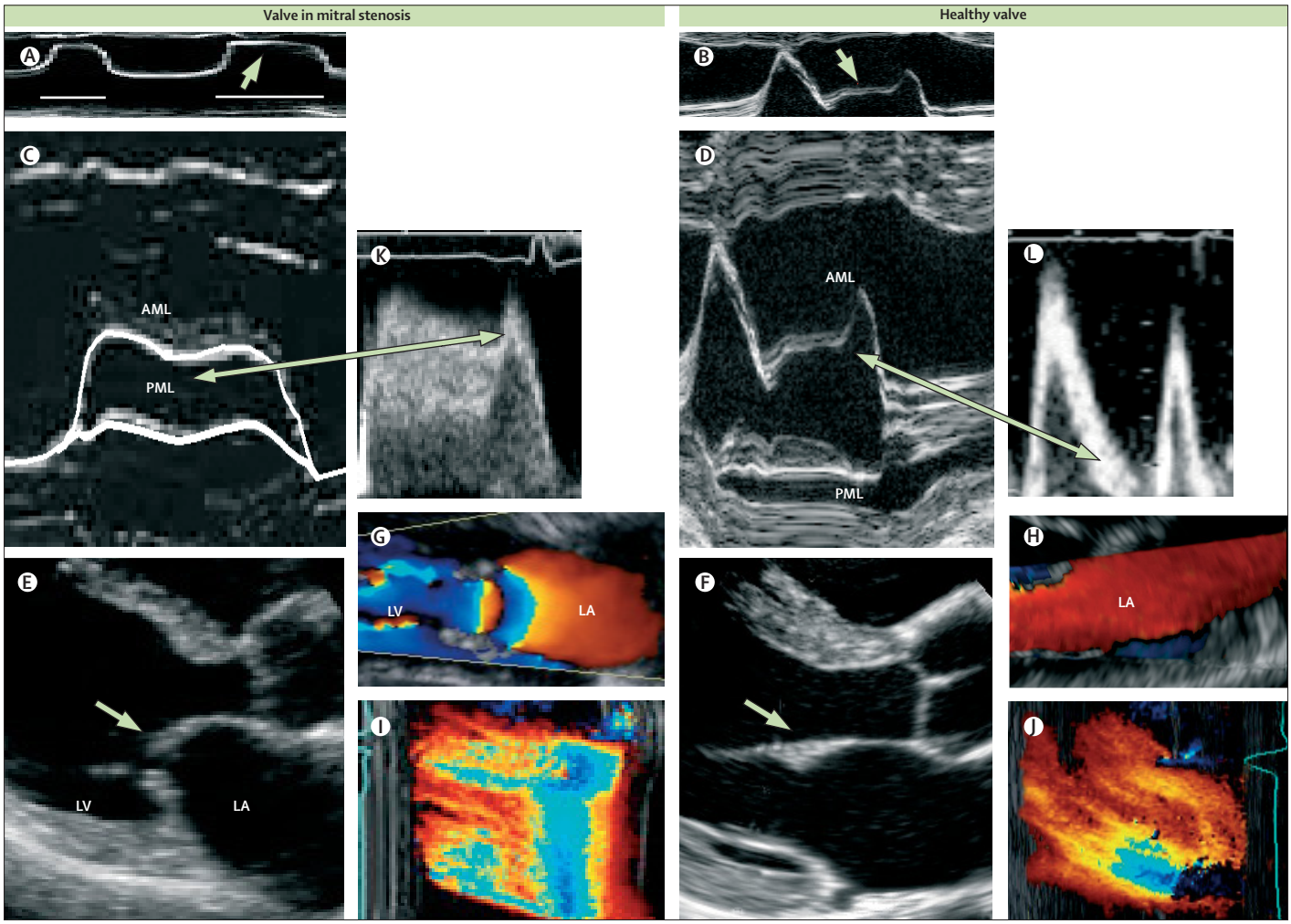

Figure 2: **Echocardiogram of mitral stenosis**
Main resistance to flow is at the valve opening with contribution from the subvalvular apparatus. In the valve with mitral stenosis, anterior mitral leaflet (AML) and posterior mitral leaflet (PML) are thick and move as a unit (A, C), whereas in the normal valve, AML and PML move separately (B, D) and have a mid-diastolic inward motion (arrow, B) that is decreased in mitral stenosis (arrow, A). Valve with mitral stenosis is affected by variation in filling time corresponding to cycle lengths in atrial fibrillation (A) with a shorter filling time indicating higher gradients. The AML is thick and domes (arrow, E) because of fusion at the commissural tips, that is absent in the normal valve (arrow, F). The flow channel is constricted and blood flow rushing into this narrow path results in a series of higher velocity shells (G) unlike smooth, non-restrictive flow normally (H). The shell velocity and diameter are useful for calculation of valve area. Plotting velocities along a linear line through the mitral valve shows the long length of turbulent flow with slow progression of the velocity fronts in mitral stenosis (G) unlike a smoother propagation in a normal valve (H); the difference in propagation is clear from doppler waveforms (I, J, K, L). In a healthy valve (L), a sharp, narrow forward wave (E wave) with rapid up and down stroke precedes a period of diastases with low gradient between the left atrium and ventricle because of mid-diastolic inward motion (B, D) and increased forward velocities due to atrial contraction (A wave). Increasing severity of mitral stenosis obliterates the normal mitral valve leaflet motion (C *vs* D), and reduces E wave deceleration (K), and diastases (indicating persisting left-atrial to left-ventricle gradient). E wave deceleration is proportional to the severity of mitral stenosis, and therefore the time for pressure to halve from the peak (pressure half-time) can be used to calculate valve area. The A wave contributes less to ventricular filling but still remains important since it allows filling with less increase in mean gradient (pre-systolic accentuation of murmur). A wave is lost in atrial fibrillation, resulting in further increase in left-atrial pressure and mean gradient to allow left-ventricle filling. LV=left ventricle. LA=left atrium.

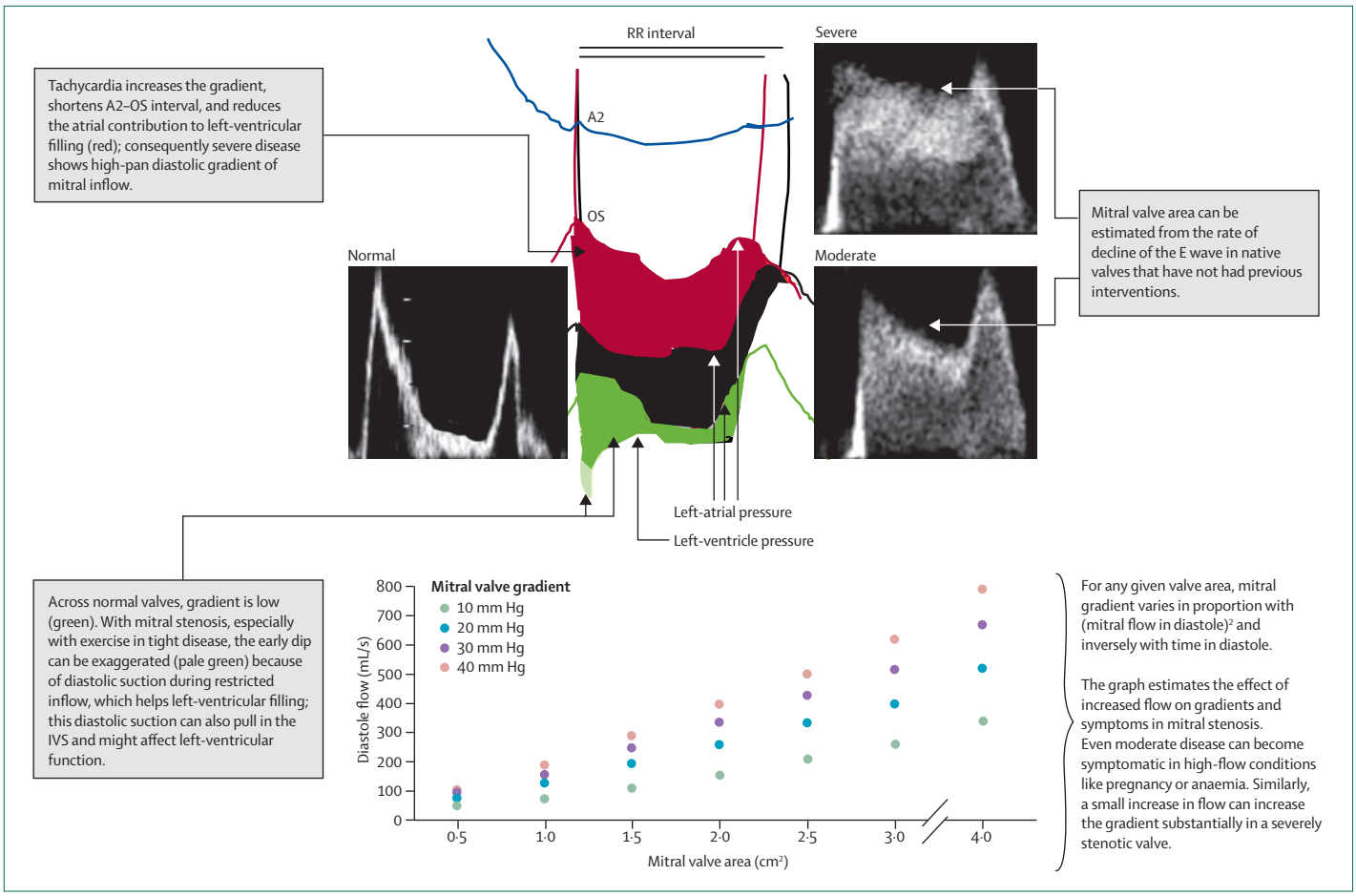

Figure 3: **Physiology of severity of mitral stenosis**
Gradient between left atrium and left ventricle is shown as normal to very low (green), moderate (black), and severe (red). Arrows indicate the extent of gradient towards the end of diastole. A2–OS=A2 to opening snap interval. IVS=interventricular septum.

Transoesophageal echocardiography provides an improved image of the anatomy, especially the commissural anatomy and calcification, and additional prognostic information. Cardiologists judge transoesophageal echocardiography to be nearly mandatory, if feasible, before PBV, and is the only practically efficient method to exclude the possibility of a clot in the left atrium or in the left-atrial appendage.

Exercise echocardiography is occasionally needed for patients with inconclusive symptoms or haemodynamics. Exercise can quantify haemodynamics or mitral regurgitation better than resting echocardiography can, assess disease severity in borderline symptomatic patients, and predict benefits from PBV.[75] Dobutamine stress echocardiography can predict event rates in symptomatic patients with moderate disease.[76] Use of cardiac catheterisation is rarely needed with imaging methods there are now available; occasionally this technique is used to assess discrepancies between symptoms and echocardiography findings, or to image coronary arteries in elderly patients. The role of techniques such as cardiac CT and MRI is being assessed.[65,66]

Conditions affecting mitral stenosis

Atrial fibrillation

Onset of atrial fibrillation, which is often caused by atrial inflammation and remodelling, is a pivotal moment in mitral stenosis. Atrial fibrillation occurs in 40–75% of patients who are symptomatic for mitral stenosis, precipitates such symptoms, greatly increases the risk of systemic embolisation, and reduces cardiac output and exercise capacity.[77,78] Exercise capacity is substantially improved by restoration of sinus rhythm,[77,78] especially in patients with small atria and short duration of symptoms.[79] Maintenance of sinus rhythm is variable across patients, with most[80] but not all studies[79] showing substantial difficulty.

PBV does not seem to affect persistence of atrial fibrillation, but could allow conversion to normal sinus rhythm in suitable patients (left-atrial diameter <45 mm, duration of atrial fibrillation <1 year). However, patients with atrial fibrillation have several suboptimum outcomes with this intervention.[81] Frequency of embolism can be reduced by PBV,[51] but a substantial risk remains in patients with persistent atrial fibrillation (up to 15–20%

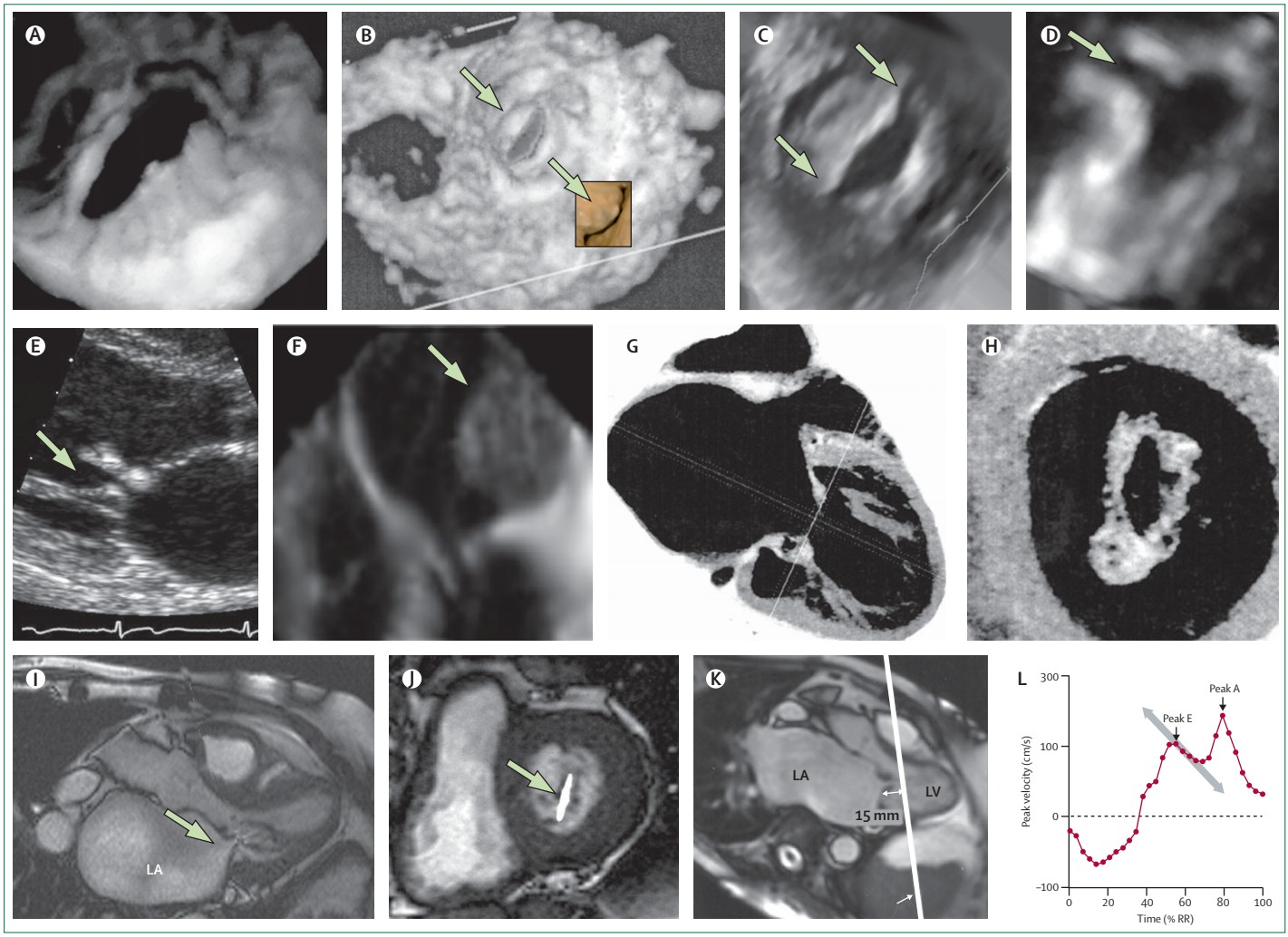

Figure 4: **Imaging of the mitral valve in mitral stenosis**
3D reconstruction from echocardiography images of a normal (A) and stenotic (B) mitral valve, with photomicrograph inset of a stenotic mitral valve from an unrelated patient to show similar valve appearance. Successful percutaneous balloon valvuloplasty (PBV) splits the commissures (arrows, C), but non-commissural splits result in severe mitral regurgitation (arrow, D). 2D echocardiography shows all pathological features of mitral stenosis: subvalvular apparatus is thickened and fused and calcium is present in the leaflets (E); left-atrial clot in a transoesophageal 2D echocardiography image (F). Features in E and especially F make patients unsuitable for PBV. CT angiography can show valve and subvalvular anatomy (G) and can be used to planimeter the valve (H). MRI can show valve structures in multiple axes (I–K) to help make valve area planimetry more accurate (I, J). Flow through the jet is clearly seen (K), and velocity encoding can be used to calculate the pressure half-time (L). Reproduced with permission from: BMJ Publishing Group (A[63]); Elsevier (B,[64] G and H,[65] I and J,[66] and K and L[67]); and Oxford University Press (C and D[68]). LA=left atrium. LV=left ventricle.

of patients with embolic events 5–10 years after surgery) after PBV or surgical valvotomy, which necessitates continuing anticoagulation. Addition of a maze procedure substantially reduces risk of embolism potential[82] by maintaining sinus rhythm more effectively.

Pulmonary hypertension

Pulmonary arterial hypertension is often found in symptomatic patients with mitral stenosis; it could have prognostic implications and trigger need for therapeutic interventions.[29] Mechanical factors, vascular remodelling, and endothelial changes mediate such hypertension,[83] and neurohormones might affect the course.[84,85] Moderate pulmonary arterial hypertension is often a passive response to left-sided obstruction, and is readily reversed with surgery or PBV. Most studies,[86] but not all,[87] show residual pulmonary arterial pressure of 30–40 mm Hg after PBV. Occasionally, patients with pulmonary arterial hypertension who are hyper-responders present with structural changes in the pulmonary bed,[88] and their hypertension is disproportionately severe[89] and might incompletely resolve after relief of mitral stenosis. Epoprostenol could have a role in combating pulmonary arterial hypertension in such patients.[90] Some cases of pulmonary arterial hypertension might also be due to endothelial dysfunction.[83,86]

Generally, pulmonary arterial hypertension is reversible, and continually resolves after intervention with increased pulmonary blood flow. The condition can recur in cases of mitral re-stenosis or substantial mitral

regurgitation. Moderate-to-severe tricuspid regurgitation is recorded in up to a third of patients with mitral stenosis immediately preceding PBV. It can be secondary to rheumatic disease or severe pulmonary arterial hypertension. Tricuspid regurgitation and right-ventricular remodelling is not often improved after PBV.[91] Surgical series of mitral valve replacement also suggest that rheumatic heart disease and a large left atrium with atrial fibrillation, both of which are present in mitral stenosis, are predictors of persistent tricuspid regurgitation.[92] Thus, PBV alone might not be sufficient treatment for patients with mitral stenosis and severe tricuspid regurgitation.

Pregnancy

Mitral stenosis is one of the most common lesions found during pregnancy[93,94] and the diagnosis is usually made when symptoms are precipitated by blood volume changes, often in the second trimester.[95] Mitral stenosis in pregnancy is associated with substantial morbidity (including pulmonary oedema), even in asymptomatic or minimally symptomatic patients with mild-to-moderate disease (mitral valve area 1–1·5 cm² in 36% of patients; >1·5 cm² in 53%), and despite adequate medical treatment. Cardiac complication rates in women with mild, moderate, and severe disease are 26%, 38%, and 67%, respectively.[96] Many patients with New York Heart Association (NYHA) class I or II symptoms also show worsening during pregnancy,[97] which suggests that early aggressive management could be preferable to continuing prolonged medical management. In India, researchers found improved outcomes with complications in less than a quarter of patients, and only 20% of patients needed caesarean section.[98]

Complications strongly correlate with NYHA class and age.[96,98] Maternal death is rare, even in developing countries. Echocardiographic valve area is a more constant value than, and should be used in preference to gradient for quantification of disease. Fetal complications include premature delivery and intrauterine growth retardation, and occur in 20% of pregnancies. Although haemodynamics improve post partum, complications such as pulmonary oedema are highly likely in the early period after delivery,[99] and are probably related to increased venous return after relief of inferior vena cava compression.

PBV and surgical valvotomy (closed mitral valvotomy in preference to methods needing cardiopulmonary bypass) seem to improve outcome,[100,101] but surgical series have been associated with greater maternal and fetal morbidity and mortality.[102] The usual indication that intervention is needed is the occurrence of severe symptoms (NYHA class III/IV or pulmonary oedema) that are refractory to medical treatment. Results of PBV are largely similar between pregnant and non-pregnant patients, although re-stenosis has been recorded in some subsequent pregnancies.[98] The effect of PBV on the fetus is controversial—evidence indicates both benefit[103] and absence of clear reduction in fetal morbidity or prematurity.[104]

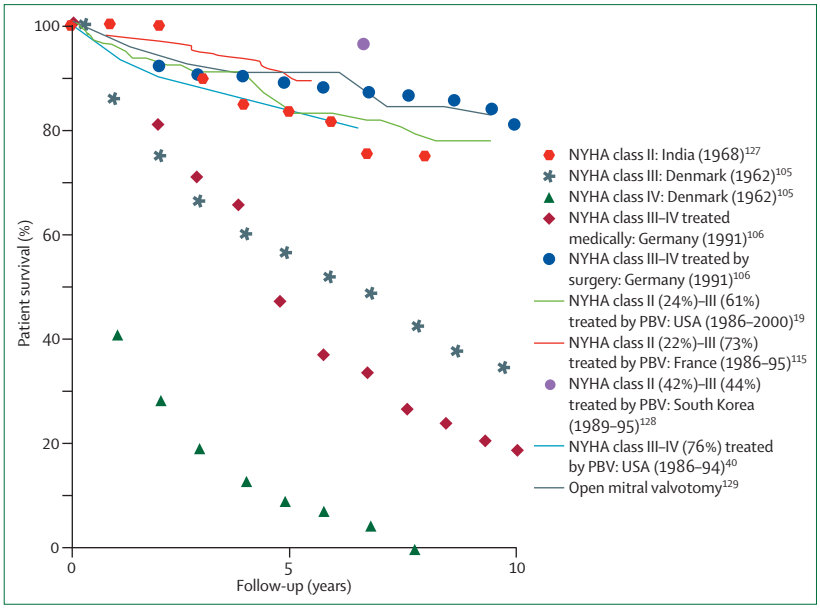

Figure 5: **Natural history of mitral stenosis and effect of intervention**
For some studies, percentage of patients with a specific stage of disease, or range of stages, is included. NYHA=New York Heart Association class of disease. PBV=percutaneous balloon valvuloplasty.

Natural history and prognosis after intervention

The natural history of untreated[57,58,105,106] and treated disease[19,107–127] has been well characterised. Such studies have identified some key features about disease progression and treatment (figures 5 and 6). First, progression in countries with recurrences of rheumatic fever tends to be rapid, whereas in those without rheumatic fever progression follows an indolent course. Second, all effective treatments that improve valve area reduce morbidity and very probably improve survival. PBV favourably changes the course of disease, and to an increased extent if the patient is in NYHA class III or IV before intervention. Although symptoms improve, the effect on natural history is less clear in NYHA class II patients; intervention very probably improves survival but this association has not been studied rigorously. Third, although PBV might improve symptoms and mortality, occurrence of adverse events is substantial and re-intervention is sometimes needed, especially in elderly patients with less favourable anatomy. Fourth, freedom from occurrence of adverse events after PBV differs greatly worldwide; age and echocardiography score are associated but are not fully responsible for the difference (figure 6). Fifth, when intervention is needed, PBV is preferred to surgery because of reduced morbidity and cost. However, unlike studies of PBV, which traditionally include patients who will most likely prove optimum for success, surgical series have often studied both good and suboptimum patients, according to NHYA class, with good overall results.

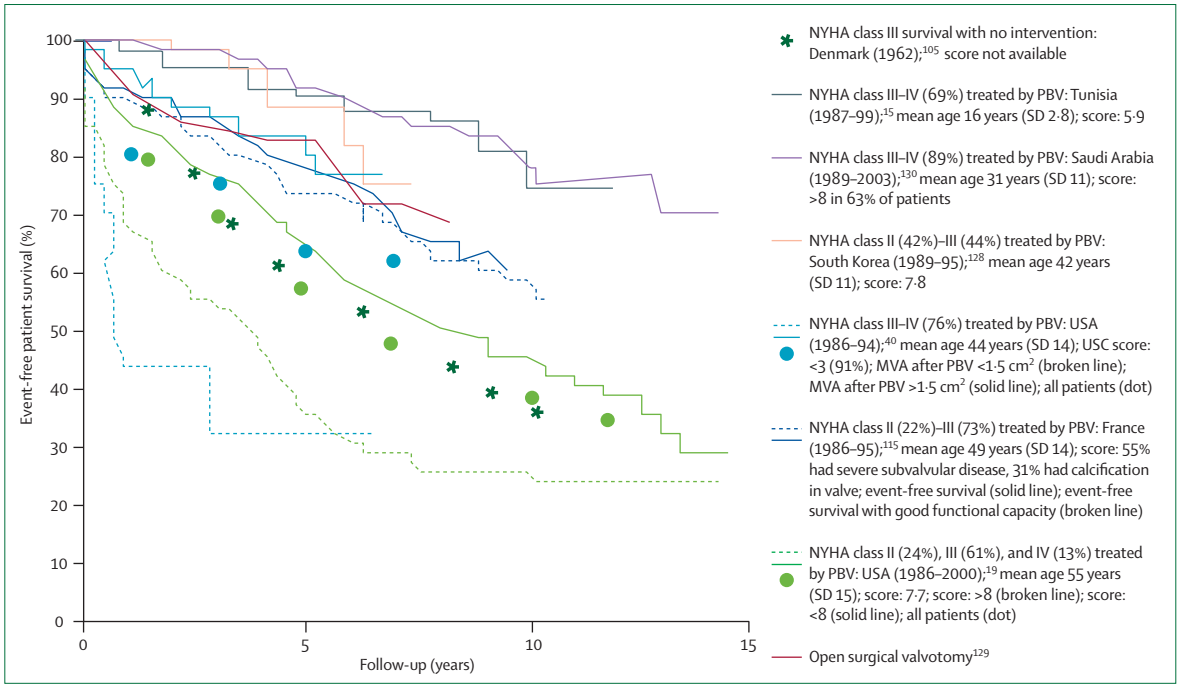

Figure 6: **Event-free patient survival after percutaneous balloon valvuloplasty**
For some studies, percentage of patients with a specific stage of disease, or range of stages, is included. Stage of disease was scored by Wilkin score; University of Southern California (USC) and Iung and colleagues[115] used separate scoring systems. Event-free patient survival was variably defined for different studies and mainly included combinations of death, mitral regurgitation, surgery for mitral regurgitation, and re-stenosis and its treatment. NYHA=New York Heart Association class of disease. PBV=percutaneous balloon valvuloplasty. MVA=mitral valve area.

Untreated mitral stenosis has a very poor prognosis once symptoms are evident, and probability of survival is inversely proportional to the severity of NYHA class. Both closed and open valvotomy improve prognosis. PBV probably improves overall survival: survival curves of predominantly NYHA class III patients after intervention are close to that of class II patients. Although symptoms improve in nearly all patients after successful PBV, the effect on survival is less evident in studies including a large proportion (up to 40–50%) of class II patients. Short-term and medium-term survival after PBV is similar to that recorded after open valvotomy, albeit with reduced initial morbidity, but comparison with surgery for very long-term follow-up is not yet available.

Morbid events such as the need for mitral valve replacement or re-intervention after re-stenosis are not uncommon after PBV. Echocardiography score, NYHA class, and especially age affect event-free survival. Age at intervention is closely associated with geographical region, which affects prevalence and progression of disease, and comorbidities. In developing countries—eg, Tunisia (young patients with low scores) and Saudi Arabia (young patients with high scores)—morbid events are less common after PBV than in developed countries—eg, Korea (middle-aged patients with high scores), and France and the USA (elderly patients with high scores). We believe that valves in countries with many rheumatic fever recurrences develop more commissural fusion than in countries with few or no recurrences, in which patients have valves with increased rigidity and participation of subvalvular components. Such geographical factors might affect results with PBV. Whether an association exists between geographical region and the components of the echocardiography score would be interesting to explore.

Treatment

Treatment by drugs or techniques other than surgery or PBV for mitral stenosis is not very effective and therefore interventional treatment is preferred except in cases of a strong contraindication. Drugs can be used to slow heart rate, deal with atrial fibrillation, do gentle diuresis, and correct secondary conditions such as anaemia, fever, infection, and volume overload. β blockers or calcium channel blockers (eg, diltiazem) are the mainstay for control of heart rate; but β blockers might worsen left-atrial appendage function (clinical significance unclear), and drugs that cross the placental barrier (eg, atenolol) during pregnancy have been associated with fetal growth retardation. ACE inhibitors have been tried in patients with mitral stenosis and heart failure with some,[131] but unproven, benefit. In view of the high occurrence of embolic episodes, suggesting use of prophylactic warfarin in patients with mitral stenosis and normal sinus rhythm is tempting but not a proven treatment. Hypercoagulable patients with mitral stenosis, patients with mitral stenosis and very large atria containing severe smoke or sludge in

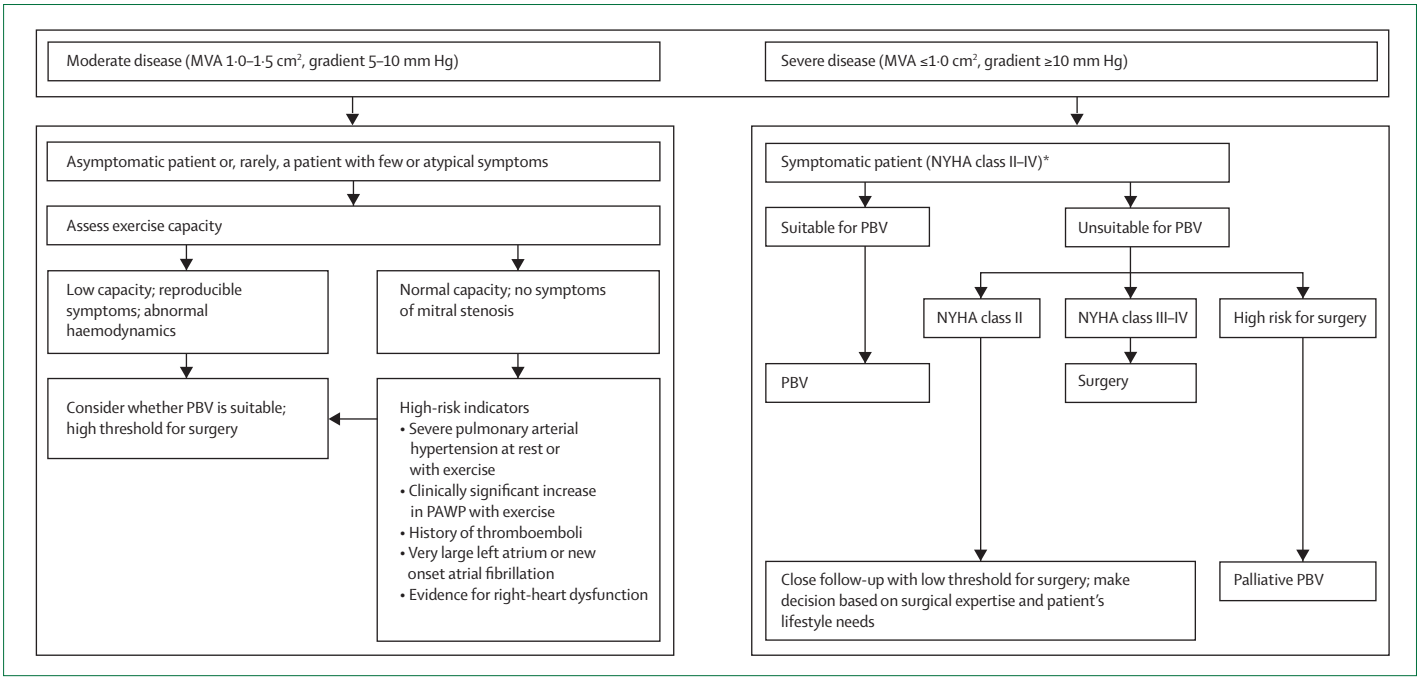

Figure 7: **Strategies for treating mitral stenosis**
MVA=mitral valve area. NYHA=New York Heart Association class of disease. PBV=percutaneous balloon valvuloplasty. PAWP=pulmonary arterial wedge pressure. *Severe mitral stenosis is rarely asymptomatic and, for such patients, we suggest use of the algorithm used for assessment of patients with moderate disease.

images of the left atrium, or patients with a history of previous embolism could benefit from anticoagulants, but no data is yet available to support universal recommendation of this approach. Prophylaxis for rheumatic and infective endocarditis prophylaxis should be used on the basis of present guidelines.

Recommendations about the appropriate time for interventional treatment[29,127,132,133] have classically been surgery or PBV for symptomatic patients with NYHA class III–IV disease, and, if feasible, PBV could be considered if symptoms are less severe. Other considerations include operator skill, valve anatomy, onset of complications even in absence of symptoms (eg, atrial fibrillation, pulmonary arterial hypertension, and embolic events), and sometimes exercise haemodynamics (figure 7). Several excellent treatment algorithms are based on expert opinion and outline the strategies for treatment,[29,126,131,133] one of which is shown in figure 7. In view of the suboptimum outcome with drug treatment,[127] we believe that even class II patients who are not suitable for PBV should be considered for surgery in an experienced surgical centre.

Surgery

Surgical options include closed or open valvotomy, and mitral valve replacement. Closed valvotomy is mostly done in developing countries when PBV is not an option; It is effective but less so than other methods. Open valvotomy allows controlled reconstruction of the valves, and simultaneous tricuspid valve repair or mitral valve replacement to be done if necessary. In fact data suggest that patients with mitral stenosis and severe tricuspid regurgitation do better with surgical repair than with PBV; less than 50% of such patients improve with PBV, especially if they also have atrial fibrillation or a large right ventricle.[134]

Mitral valve surgery has similar results to PBV, albeit with increased cost and morbidity.[108] Mitral valve replacement is a last resort in children, young adults, and women contemplating pregnancy, but is the treatment of choice in elderly patients with anatomy that is unfavourable for other options. Some risks are specific to mitral valve replacement, which carries higher mortality than does aortic valve replacement or mitral valve repair.[135] Patient prosthesis mismatch prevents regression of left-atrial enlargement and pulmonary arterial hypertension. In one study, 69% of patients were found to have moderate mismatch and a probability of 6-year survival of 84% (SD 1), and 9% had severe mismatch and a 74% (SD 5) 6-year probability of survival; by contrast, patients with no mismatch had a 90% (SD 2) 6-year probability of survival.[136] Mitral prosthetic stenosis can worsen with time because of the in-growth of pannus, especially with persistent inflammation around the prosthetic valve ring, and this growth can cause prosthetic leaflet entrapment.

Percutaneous balloon valvuloplasty

Since the advent of PBV in 1984,[3] the technique has become the mainstay of treatment for mitral stenosis. The technique is as effective as open valvotomy and more effective than closed valvotomy, with reduced morbidity

and cost in most patients, except for those with unfavourable anatomy.[107–110] In all permutations of the technique, a dilating device is passed—either antegrade (through the atrial septum) or retrograde (via the aorta)—across the mitral valve. Dilation splits the commissures and provides clinically significant improvement. Thickening, rigidity, calcification (especially commissural), and subvalvular pathology have strong prognostic importance for valvuloplasty (figure 1).

The Inoue balloon technique has been the method of choice, but the balloon used is largely dependent on site and operator expertise. Generally, the technique immediately doubles the mitral valve area and halves the gradient. Almost 90% of patients show clinically significant improvement in function with a final valve area of more than 1·5 cm² without severe mitral regurgitation.[8] Although shortness of breath improves rapidly, exercise tolerance improves gradually.[114] Most patients remain in NYHA class I or II. About 75% of patients are alive 7–10 years after intervention, and 60% are free of symptoms without secondary intervention for long periods of follow-up.[111]

Centre volume and patient selection consistently affect results.[112] Success rates range from more than 95% in ideal patients from highly selected centres, to about 80–85% in usual centres, and less than 50–60% in patients with suboptimum anatomy.[110] Patients with favourable morphology (echocardiography scores of less than 8 and no commissural calcium) have more than 90% procedural success, very low occurrence of complications (<2%), and acceptably low frequency of re-stenosis on follow-up. By contrast, those with high scores are often of increased age, have a smaller valve to start with, end up with a small valve area after intervention, and have substatially worse frequency of event-free survival (death, mitral regurgitation, valve replacement, and re-stenosis). However, even in patients with good echocardiography scores, frequency of events (death, mainly mitral valve surgery, and repeat percutaneous mitral valvotomy) begins to progressively increase 5 years after intervention (50% of patients die and 62% need re-intervention at 8–12 years of follow-up).[19] Procedural mortality is 0–3%, and is mainly due to tamponade or severe mitral regurgitation. Morbidity includes haemopericardium (0·5–12%), embolism (0·5–5%), severe mitral regurgitation (2–10%, although 25% of patients increase severity by one grade) most often due to non-commissural tear,[113] and urgent surgery (<1%). Transient atrial septal defects are common after transseptal access, but substantial shunting occurs in less than 5% of patients.

Long-term improvement is related to immediate success after the procedure, which is measured by increased valve area, reduced valve gradient, and absence of mitral regurg itation.[19,39,40,115–117] Late deterioration in such patients is due to either re-stenosis that is often a function of suboptimum patient anatomy before intervention (about 10–40% of patients have re-stenosis dependent on Wilkins score before intervention[118]), or sometimes unrelated cardiac conditions in elderly patients. Re-stenosis can often be treated with repeat PBV; even though results are poorer than are those after the first intervention, the need for mitral valve replacement can be delayed in many patients.

PBV is not suitable for patients with very high echocardiography scores, moderate or severe mitral regurgitation, left-atrial thrombus, clinically significant tricuspid regurgitation that needs treatment, impossible or dangerous access to the mitral valve, or rarely, valve stenosis due to disorders other than commissural fusion (mostly non-rheumatic, or very occasionally re-stenosis after valvotomy). Patients who need cardiac surgery for another indication are comprehensively treated by surgery alone. Non-surgical candidates should be offered PBV if needed, since the intervention is tolerated well and immediate results are fair, though patients continue to be limited by non-cardiac issues.[119]

Intervention in mild disease[123] or even selected asymptomatic patients[124] with ideal anatomy—such as those with dense spontaneous contrast in the left atrium, or recurrent atrial fibrillation[132]—is the prophylactic PBV option. Such intervention should be balanced against the indolent natural history, predictive value of symptoms for intervention, the absence of a clinically significant risk of sudden cardiac death or left-ventricular dysfunction even if we get the timing wrong, and the small possibility of iatrogenic complications including death and the need for mitral valve replacement. Both European and American guidelines have discouraged intervention in mild mitral stenosis but some allowance is made for intervention in carefully selected asymptomatic patients with ideal anatomy,[29,133] and future studies might yet tilt the balance in favour of early intervention.

Contributors

YC and JN contributed to planning of the report, the review of published work, analysis of the data, and writing of the report. SW helped revise the report. All authors approved the final version of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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