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STRUCTURAL HEART DISEASE (RJ SIEGEL AND NC WUNDERLICH, SECTION EDITORS)

Rheumatic Mitral Valve Stenosis: Diagnosis and Treatment Options

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Abstract

Purpose of Review This review provides an update on rheumatic mitral stenosis. Acute rheumatic fever (RF), the sequela of group A β-hemolytic streptococcal infection, is the major etiology for mitral stenosis (MS).

Recent Findings While the incidence of acute RF in the Western world had substantially declined over the past five decades, this trend is reversing due to immigration from non-industrialized countries where rheumatic heart disease (RHD) is higher. Pre-procedural evaluation for treatment of MS using a multimodality approach with 2D and 3D transthoracic and transesophageal echo, stress echo, cardiac CT scanning, and cardiac MRI as well as hemodynamic assessment by cardiac catheterization is discussed. The current methods of percutaneous mitral balloon commissurotomy (PMBC) and surgery are also discussed. New data on long-term follow-up after PMBC is also presented.

Summary For severe rheumatic MS, medical therapy is ineffective and definitive therapy entails PMBC in patients with suitable morphological mitral valve (MV) characteristics, or surgery. As procedural outcomes depend heavily on appropriate case selection, definitive imaging and interpretation are crucial. It is also important to understand the indications as well as morphological MV characteristics to identify the appropriate treatment with PMBC or surgery.

Keywords Rheumatic heart disease · Rheumatic fever · Mitral stenosis · Percutaneous intervention · Percutaneous mitral balloon valvuloplasty · Commissurotomy · Echocardiography · Closed mitral valve commissurotomy · Open surgical mitral commissurotomy

Abbreviations

3D	Three-dimensional
2D	Two-dimensional
AF	Atrial fibrillation
ASD	Atrial septal defect
CT	Computed tomography
GAS	Group A β-hemolytic streptococcus
ICE	Intracardiac echocardiography
RF	Rheumatic fever
RHD	Rheumatic heart disease
LA	Left atrium
LAA	Left atrial appendage
LV	Left ventricle
MR	Mitral regurgitation
MS	Mitral stenosis
MV	Mitral valve
MVA	Mitral valve area
PAH	Pulmonary arterial hypertension
PMBC	Percutaneous mitral balloon commissurotomy
PHT	Pressure-half-time

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SR Sinus rhythm
TTE Transthoracic echocardiography
TEE Transesophageal echocardiography
TSP Transseptal puncture

Introduction: the Scope of the Problem

Acute rheumatic fever (RF) is an autoimmune inflammatory process that develops as a sequela of group A β-hemolytic streptococcal (GAS) tonsillopharyngitis. It may lead to rheumatic heart disease (RHD) and it constitutes the major etiology of mitral stenosis (MS) [1]. The incidence of acute RF in the past five decades has markedly declined in the Western world [2••]. However, even in industrialized countries, RHD still represents up to 22% of valvular heart diseases (data from Europe), affecting mainly young immigrants or older people [2••].

In developing countries, rheumatic MS remains the most common valvular heart disease. Studies systematically using echocardiographic screening have shown that the prevalence of RHD is significantly underestimated [3, 4]. Worldwide, it is estimated that there are 15.6 million cases of RHD with about 470,000 new cases of acute RF occurring annually. Approximately 60% of these patients will develop RHD, and about 1.5% of these patients die from complications of the disease each year.

RF leads to carditis and valvulitis. As part of the "healing" response to mitral valvulitis, both valve thickening and fusion of the mitral valve (MV) commissures develop. This results in restricted MV leaflets with narrowing of the MV orifice. The rheumatic process also affects the subvalvular apparatus resulting in the fusion of chordae tendineae and the papillary muscles. Other etiologies of MS (e.g., degenerative MS, congenital MS, infiltrative diseases, inflammatory diseases, carcinoid heart disease, or drug-induced alterations of the MV) are rare and commissural fusion—the requisite lesion for a successful percutaneous mitral balloon commissurotomy (PMBC)—is usually not present in these cases.

Natural History of Rheumatic MS

Acute RF causes a pancarditis and a valvulitis, and mitral regurgitation (MR) constitutes the most common valve abnormality at this early stage. Therefore, very young patients (< 10 years of age) present predominantly with pure MR. However, as patients get older, mixed mitral and aortic valve diseases emerge as a dominant MV lesion from the second decade of life and rheumatic MS increases in prevalence [5]. However, there is variability in the pattern of MV pathology among different endemic regions. While the clinical course of rheumatic MS is highly variable, a continuous progression of the disease over many years after acute RF is characteristic and it can be expected that the mitral valve area (MVA) will decrease about 0.1–0.3 cm^2 per year [6] depending on the individual risk. Early after acute RF, MS tends to progress slowly, followed by a more accelerated advancement that generally occurs later in life [1, 7]. In countries where RF is endemic, the progression of the disease can be particularly rapid, leading to severe MS in young adults and even in children. Three risk factors for progression towards chronic MV disease were identified in a prospective study: the severity of carditis, recurrences of RF, and a low socioeconomic level of the mother [8]. A relevant impairment of the MV anatomy (defined by a Wilkins score ≥ 8) and a peak mitral gradient ≥ 10 mmHg were also associated with a more rapid progression of MS.

As long as the MV orifice area remains larger than 1.5 cm^2, patients are generally not symptomatic and their 10-year survival is good [9].

Clinical manifestation of MS often occurs when there is an obligate increase in cardiac output and thus more transmitral flow which causes elevation of the resting transmitral gradient. This may occur with pregnancy, fever, arrhythmias, infection, thyrotoxicosis, or even exercise. The presence of atrial fibrillation (AF) in the setting of MS increases the rate of thromboembolic events 18-fold [10]. The leading cause of death in MS patients is heart failure (in ~ 60% of patients) and secondly, thromboembolic complications in ~ 20% of patients. The occurrence of symptoms usually indicates a poor prognosis if MS remains untreated [1, 7, 9, 11, 12].

Evaluation of Rheumatic MV Disease

Imaging Modalities to Evaluate MS

Echocardiography is currently the main imaging modality used to assess the anatomic severity and the hemodynamic consequences of MS. Echocardiography enables detailed assessment of MV pathology, extent of involvement of the subvalvular mitral apparatus, and concomitant involvement of other valves [13, 14•, 15].

In most cases, transthoracic echocardiography (TTE) is sufficient to grade MS and MR severity and to characterize the morphology of the MV. Transesophageal echocardiography (TEE) is needed in addition when the MV cannot be adequately imaged with TTE and prior to a percutaneous or surgical procedure in order to exclude intracardiac thrombi. Three-dimensional (3D) TTE and TEE imaging adds further and more detailed morphological and physiological information and should therefore be included in the routine evaluation of the MV. A stress echocardiography may be helpful in situations when there is a discrepancy between echocardiographic Doppler measurements at rest and symptoms [16••, 17••].

Experience is limited, but magnetic resonance imaging (CMR) and multislice computed tomography (CT) represent alternative imaging techniques to reliably perform a planimetry of the MV in the case of poor echocardiographic imaging quality. However, a recent study shows that CMR shows a strong agreement and excellent correlation with 3D TEE mitral valve areas. This paper indicates that CMR is a good alternative, non-invasive method for evaluation of rheumatic MS MVA [18]. CT may also be helpful to evaluate for associated coronary artery disease.

Assessment of MS Severity

According to current guidelines/recommendations for clinical practice, a multimodality approach that includes the calculation of MVA, the assessment of mean Doppler gradients, and hemodynamic consequences (particularly pulmonary artery pressures) should be used to characterize MS adequately [16••, 17••]. 3D methods to calculate MVA seem to be more accurate than 2D-derived calculations and should be included in the grading of MS severity [19, 20].

Evaluation of Associated Valve Lesions

Prior to performing PMBC, it is important to assess MR as pre-procedural MR ≥ 2+ is associated with worse outcomes [21] and poses a relative contraindication for performing PMBC [16••, 17••]. Therefore, the presence and severity of MR should be carefully evaluated prior to an intervention. Concomitant valve disorders are frequently associated with rheumatic MS and need to be evaluated. Though uncommon, the tricuspid valve can also be affected.

Assessment of Hemodynamic Consequences of MS

LA and LV

According to the severity and chronicity of MS, the increase in left atrium (LA) pressure is the main driver of LA enlargement and structural LA remodelling. An increase in LA size predisposes to the development of atrial fibrillation (AF), leading to reduced flow velocities and blood stasis within the LA and the left atrial appendage (LAA) as assessed by Doppler echocardiography. Additionally, the reduced flow within the LA leads to a decrease in systolic pulmonary vein flow [22] thereby increasing the risk of thrombus development.

In patients with MS, the left ventricle (LV) is usually normal in size, and diastolic filling is typically prolonged and reduced. The transmitral gradient is increased and prolonged. With the development of AF, the heart rate increases and diastolic filling time is reduced. This results in a further increase in the transmitral gradient. The loss of LA contraction may also contribute to the reduction in forward stroke volume in the setting of AF. Both mechanisms together result in a significant increase of the LA pressure.

Right Heart and PAH

With progression of the disease, pulmonary artery pressure (PAH) may develop. Chronic PAH can lead to right ventricular dilation, hypertrophy, and eventually right heart failure in advanced stages. The degree of PAH is an indicator for the overall hemodynamic consequences of MS. The presence of severe PAH is associated with a mean survival of < 3 years [23]. There are also regional variations in RHD with patients from South Asia often having more pulmonary vascular disease and PAH in the setting of MS. Pulmonary pressures should be serially evaluated in all patients with significant MS [16••, 17••]. A diameter ≥ 40 mm of the tricuspid annulus seems to be a predictor for developing severe tricuspid regurgitation following MV surgery [24] and should also be assessed particularly when a surgical procedure is planned.

Stress Testing

Assessing the gradients across the MV and pulmonary pressures during a stress test (preferably physical exercise or alternatively using dobutamine) [25] provides additional information [16••]. This is especially important when evaluating asymptomatic patients or in those whose symptoms and MS severity do not correlate [26] and when evaluating women with MS who are contemplating pregnancy as pregnancy generally leads to an increase in cardiac output, heart rate, transmitral flow, and total blood volume, each of which can worsen transvalvular MV gradients. As a consequence, many women with MS develop their first symptoms during pregnancy. Exercise stress testing is helpful to assess how well women with MS will tolerate pregnancy and can further help identify those who may benefit from more frequent clinical assessment, medical therapy with beta blockers, and in selected cases, prophylactic PMBC or even surgery prior to conceiving [25, 27–29].

Assessment of MV Anatomy and Suitability for PMBC

The effectiveness of PMBC is based on the splitting of commissural fusion and is therefore related to the etiology of MS. Since the introduction of the Inoue balloon catheter in 1984 [30•], PMBC evolved as a safe and effective treatment option for MS patients [31–38] and is currently considered as the preferred technique to definitively treat selected symptomatic patients with rheumatic MS and suitable morphological and clinical characteristics [16••, 17••] when compared with surgical approaches.

However, while certain structural characteristics of the MV tend to predict better outcomes for PMBC, other MV anatomical findings might suggest PMBC to be less likely effective or even contraindicated.

A thorough assessment of anatomical MV characteristics and associated pathology is of paramount importance in the pre-procedural evaluation of MS patients. The detailed characterization of MV morphology as assessed by echocardiography in most cases will determine the best treatment options. The pathological process of RF results in a continuous progression of leaflet thickening, calcification, and commissural and/or fusion of the subvalvular apparatus, thus causing MV obstruction [39]. Typical echocardiographic features of restricted mitral leaflets are the "doming" or "hockey-stick" appearance of the anterior mitral leaflet and the immobility of the posterior mitral leaflet [40, 41].

Furthermore, certain anatomical features of the MV like leaflet mobility and flexibility, leaflet thickness, commissural fusion, leaflet/commissural calcification, and subvalvular extension of the fibrotic process are used to determine the extent of the RHD disease, the suitability for a PMBC procedure, and to predict outcome following PMBC by using different scoring systems. Some scoring systems have been validated in larger series and may be helpful in the decision making process in daily clinical practice [31, 42–44, 45•, 46–48, 49•] (Table 1).

Unfortunately, each system is limited by variable reproducibility as the scores are semi-quantitative; there is a trend to underestimate lesion complexity, particularly with regard to the extension of the subvalvular disease as it may be difficult to adequately assess the subvalvular mitral apparatus. 3D echocardiography can be very useful in this regard.

To date, no individual scoring system has been shown to be superior to another. Thus, the scoring systems should only be used in a complementary way, as a part of a comprehensive echocardiographic assessment of MV pathology and function. As there is a lack of uniformity in the application of these scoring systems prior to PMBC, some interventionalists consider, or even recommend, PMBC for patients with MS when commissural fusion is present and other clinical features are favorable even if echocardiographic scoring systems render unfavorable results (and we, the authors, are in accordance with that approach).

The following contraindications need to be ruled out prior to a PBMC [16••, 17••]:

- Mitral valve area (MVA) > 1.5 cm^2
- Presence of a thrombus in a left-sided cardiac chamber
- MR > mild
- Severe or bi-commissural calcification
- Absence of commissural fusion
- Severe concomitant valve disease
- Concomitant coronary artery disease requiring surgery

Cardiac Catheterization

The main indication for performing cardiac catheterization in the assessment of MS is to clarify if associated coronary artery disease is present. However, in cases where the echocardiographic findings are inconclusive, MVA can be evaluated by performing a right and left heart catheterization and applying the Gorlin equation using cardiac output obtained via thermodilution (when there is no significant tricuspid regurgitation) or the Fick method [16••, 17••]. The Gorlin equation cannot be reliably used when cardiac output is decreased or immediately after PMBC [55, 56].

Cardiac catheterization is also the only method available to directly measure absolute pressure within the cardiac chambers, and pulmonary vascular resistance can be calculated which may be important in clinical decision making in patients with severe pulmonary hypertension to estimate the risk of surgery.

Current Treatment Options

The optimal method and timing for treating a patient with MS is based upon various clinical parameters including the patients' functional status, the individual surgical risk, specific MV anatomical characteristics, concomitant diseases, and the institutional expertise [16••, 17••].

Medical Management

Medical therapy focuses mainly on three aspects of the disease: first, the prevention of recurrence of RF, secondly, the improvement of symptoms, and thirdly, the reduction of thromboembolic events. It should be noted that no medical treatment has shown to slow down the progression of MS once rheumatic MV disease is present.

In patients treated medically, a close follow-up is needed to enable timely intervention when indicated. Clinical and echocardiographic examinations are recommended every 3–5 years in asymptomatic patients with mild–moderate MS (MVA > 1.5 cm^2). If the MVA is between 1 and 1.5 cm^2, follow-up is recommended every 1–2 years in asymptomatic patients. An annual follow-up is recommended in those with an MVA of < 1.0 cm^2 and in symptomatic patients with severe MS (MVA < 1.5 cm^2). In our opinion, this subset of patients should undergo a definite surgical or transcatheter intervention. Even if the patients are asymptomatic, any precipitating event like infection, exercise, anemia, pregnancy, or the occurrence of AF may lead acutely to a dramatic worsening of the clinical status.

All patients should be re-evaluated with the development of symptoms or prior to as well as during pregnancy.

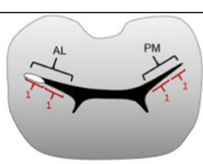
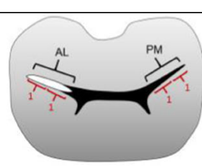
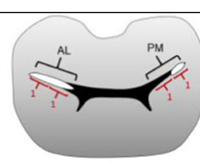
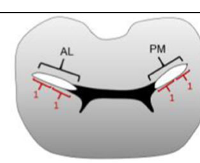
Prevention of RF

Acute RF can be primarily prevented in most cases when GAS infections of the pharynx are properly diagnosed and

Table 1 Echocardiographic scoring systems for rheumatic mitral valves

Wilkins or Abascal Score (45)				
Grade	**Scored MV characteristics**			
	Leaflet mobility	**Leaflet thickening**	**Leaflet calcification**	**Involvement of subvalvular apparatus**
1	highly mobile with only leaflet tips restricted	leaflet near normal in thickness (4-5 mm)	single area of increased echo brightness	minimal thickening just below the MV leaflets
2	leaflet mid and base portions have normal mobility	midleaflets normal, considerable thickening of leaflet margins (5-8mm)	scattered areas of brightness confined to leaflet margins	thickening of chordal structures extending to one third of the chordal length
3	valve continues to move forward in diastole, mainly from the base	thickening extending through the entire leaflets (5-8mm)	brightness extending into mid-portions of the leaflets	thickening extended to distal third of the chords
4	no or minimal forward movement of the leaflets in diastole	considerable thickening of all leaflet tissue (> 8-10mm)	extensive brightness throughout much of the tissue leaflet	extensive thickening and shortening of all chordal structures extending down to the papillary muscle
Interpretation of result	Score range: 4-16. A score > 8 suggests the MV may not be suitable to PMBC and is associated with poor short- and long-term results(27,32,45,69,83).			

Group assignment according to anatomical characteristics of the MV and the MV apparatus as assessed by 2D- echocardiography and fluoroscopy (Cormier Score)(31)			
	Group 1	**Group 2**	**Group 3**
Anatomical characteristics	Pliable, noncalcified anterior mitral leaflet and mild subvalvular disease, i.e. thin chordate ≥ 10mm long	Pliable noncalcified anterior mitral leaflet and severe subvalvular disease, i.e. thickened chordate < 10mm long	Calcification of mitral valve of any extent, as assessed by fluoroscopy, whatever the state of the subvalvular apparatus is
Interpretation of result	In a subset of 40 patients a Wilkins score in the range of 7 to 9 correlated with the echocardiographic group 1, a Wilkins score range 8 to 12 correlated with the echocardiographic group 2, and a Wilkins score range 10 to 15 with group(84). An echocardiographic grouping score ≥ 2 is associated with poor long-term results(85)		

Assessment of commissural calcium(45) This method quantifies the extent of calcification in both commissures by giving a half commissure of each commissure a score of 1 with the detection of intensive bright echoes as seen by 2D TTE			
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
			
Interpretation of result	Patients with a commissural calcium score grade 0-1 were found to have larger MVA and an improvement in symptoms than those with grade 2-3 after PMBC. Commissural calcification is one of the strongest predictors of outcome of PMBC(47) and may also		

	predict severe MR as a major complication of PMBC(86). A commissural calcium grade ≥2 is a predictor of poor immediate results(46,47)

Real-time transthoracic 3D echocardiographic score (adapted from Anwar et al.(47))						
Leaflets	**AML**			**PML**		
Leaflet segments	**A1**	**A2**	**A3**	**P1**	**P2**	**P3**
Leaflet thickness (0-6)(0= normal, 1= thickened)[a]	0-1	0-1	0-1	0-1	0-1	0-1
Leaflet mobility (0-6) (0=normal, 1= thickened)[a]	0-1	0-1	0-1	0-1	0-1	0-1
Leaflet calcification (0-10)(0=no,1-2=calcified)[b]	0-2	0-1	0-2	0-2	0-1	0-2
Subvalvular mitral apparatus[b]						
Affected part of the subvalvular apparatus	**Proximal third**		**Middle third**		**Distal third**	
Thickness (0-3)(0=normal,1=thickened)	0-1		0-1		0-1	
Separation (0-6)(0=normal,1=partial,2=no)	0,1,2		0,1,2		0,1,2	
Interpretation of result	[a]Normal=0, mild=1-2, moderate 3-4, severe 5-6 [b]Normal=0, mild= 1-2, moderate 3-5, severe = 6 The individual score points are added up, with the calculated total score ranging from 0- 31 points. Mild MV involvement is defined as < 8 points, moderate MV involvement 8-13 and severe MV involvement >14 points.					

Echo Score "Revisited" (to predict immediate outcome) (49)	
Echocardiographic variables	**Points for score (0-11)**
MVA ≤ 1cm²	2
Maximum leaflet displacement ≤ 12mm	3
Commissural area ratio ≥ 1.25	3
Subvalvular involvement	3
Interpretation of result	3 risk groups are defined: low (score 0 - 3); intermediate (score 4 - 5); high (score 6 - 11). This score is more predictive than the Wilkins score and is particularly useful for predicting outcomes for patients categorized in the intermediate-risk group

MV mitral valve, *AML* anterior mitral leaflet, *PML* posterior mitral leaflet, *MR* mitral regurgitation, *AL* anterolateral, *PM* posteromedial, *MVA* mitral valve area

adequately treated with antibiotics [57••]. GAS pharyngitis affects predominantly children between 5 and 15 years of age. As recurrent RF is associated with worsening or development of RHD, the prevention of recurrent GAS pharyngitis is the most effective method of preventing severe RHD. Prophylaxis should be initiated as soon as acute RF or RHD is diagnosed [57••]. RF recurrence can occur even when a symptomatic pharyngitis is treated optimally. Furthermore, recurrent episodes of RF may be asymptomatic and remain therefore undetected and untreated. Thus, secondary prophylaxis for RF should be given continuously for up to 10 years after the last attack of RF or until the patient is at least 21 years old to patients who had mild or healed carditis. However, in the setting of severe valvular damage that results in heart failure or valve surgery, RF secondary prophylaxis should be lifelong.

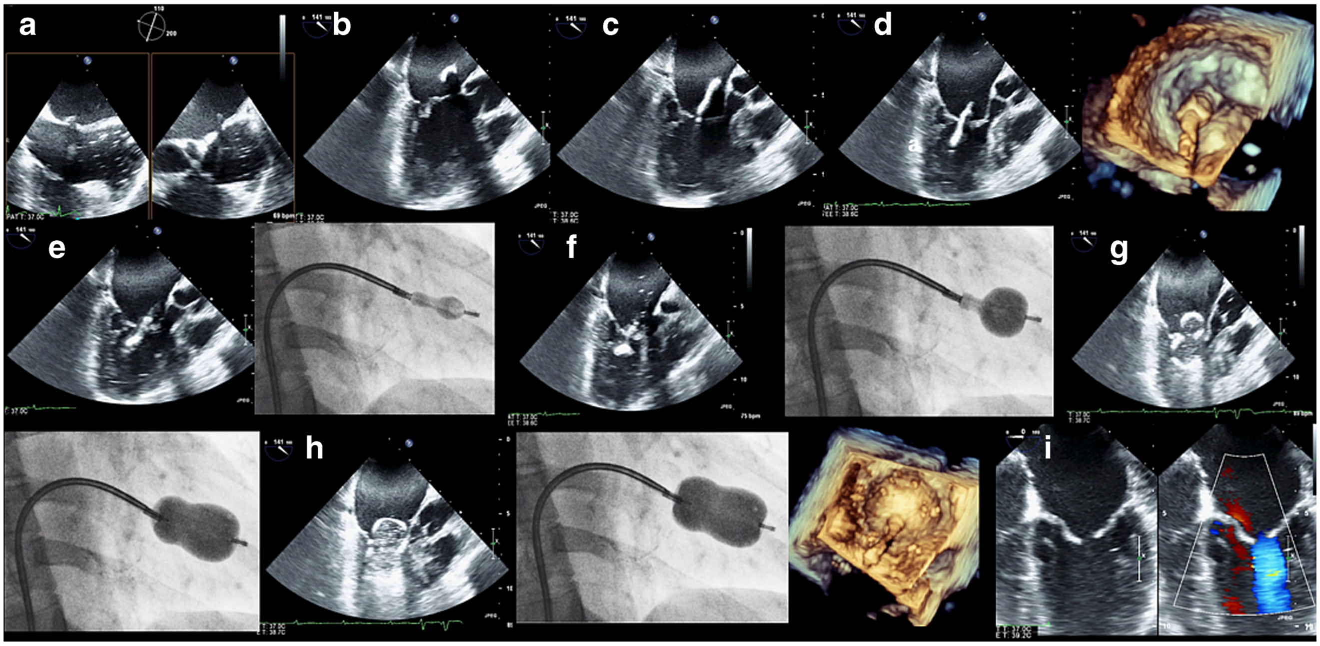


Fig. 1 PMBC step-by-step: **a** transseptal puncture (*x*-plane), **b** wire in the LA, **c** balloon in the LA with the wire removed, **d** balloon across the MV (2D and 3D TEE (LA aspect)), **e** minimal inflation of the distal part of the Inoue balloon (2D TEE and fluoroscopy), **f** further inflation of the distal part of the Inoue balloon (2D TEE/fluoroscopy), **g** the proximal part of the balloon is also inflated (2D TEE and fluoroscopy), **h** maximum inflation of the proximal and the distal part of the Inoue balloon (2D TEE/ fluoroscopy/ 3D TEE (LA aspect)), and **i** laminar flow across the MV in diastole after PMBC (2D TEE with color Doppler)

Symptomatic Treatment

Medical treatment options for symptomatic MS patients include primarily diuretics to relieve both left and right heart failure symptoms and beta blockers (or heart rate–regulating calcium channel blockers) to prolong the diastolic filling period, especially in patients in sinus rhythm (SR) which are symptomatic during exercise, as well as in patients with AF and a rapid ventricular response. In pregnant women, beta blockers (atenolol or propranolol) are particularly helpful as they significantly improve symptoms and decrease mean gradients and pulmonary pressure in most patients [58].

As for patients with MS, conversion to SR is superior to rate control in patients with AF [59], and restoration of SR should be considered taking multiple factors into account including the duration of AF, hemodynamic response to AF, LA size, prior episodes of AF, and a history of embolic events.

Prevention of Thromboembolism

Patients with untreated MS are at high risk for thromboembolic events. This risk is further aggravated in those with AF and prior embolic events. Anticoagulation (vitamin K antagonists or heparin) is therefore a class I indication in the guidelines in patients with MS and paroxysmal, persistent or permanent AF, prior embolic events, or a present thrombus [16••, 17••]. The efficacy of the non-vitamin K oral anticoagulant agents in preventing embolic events has not been studied in patients with MS and is explicitly not recommended [60••, 61].

In patients with MS in SR, it is controversial as to whether long-term anticoagulation should be given on the basis of LA enlargement or spontaneous contrast on TEE. The risk-benefit analysis does not clearly support systemic anticoagulant therapy, and only the ESC/EACTS guidelines give a class IIa recommendation for this patient group.

The combination of an antiplatelet drug plus moderate-intensity oral anticoagulation showed beneficial results in one randomized trial, but these need to be further confirmed and are not routinely recommended due to an increased bleeding risk [62].

PMBC (Fig. 1)

Different types of percutaneously inserted balloons can be used to perform PMBC: single-balloons, double-balloons, or an Inoue balloon. With the most frequently used Inoue balloon (Toray Medical Co, Ltd.), high procedural success rate (> 95%) can be achieved with a very low in hospital mortality. Satisfactory immediate results can be achieved in ~ 90% of patients [36] with an increase of MVA to an average of 1.9 ± 0.3 cm^2 and a significant symptomatic relief.

PMBC is generally performed in the cardiac catheterization laboratory with either conscious sedation or general anesthesia. Intracardiac thrombi should be excluded prior to performing a transseptal puncture (TSP) by the use of TEE

[63]. The presence of a thrombus in a left-sided cardiac chamber constitutes a relative contraindication to performing PMBC. In case thrombus formation is verified, the procedure should be postponed until the thrombus is resolved. Surgery is considered as the preferred treatment option when the thrombus persists. However, there is no uniform consensus regarding PMBC in the presence of thrombi. Some interventionalists report that it is feasible to perform PBMC using a modified Inoue technique in selected patients with laminar thrombus confined to the LAA. Others will undertake PMBC after 4–6 weeks of effective anticoagulation therapy [64]. Nonetheless, in order to avoid the potential risk of a peri-procedural catastrophic stroke, we strongly recommend not to perform a PMBC when a LA/LAA thrombus is present.

For most PMBC cases, an antegrade transvenous approach is used, where access to the LA is gained via a TSP. The optimal puncture site is usually located close to the mid-fossa, preferably slightly posterior and inferior. A Brockenbrough needle and catheter is typically used for TSP. Once TSP is successfully performed, echocardiography is helpful to confirm the absence of a hemopericardium prior to the administration of heparin (~ 3000–5000 IU).

The choice of an appropriate balloon size (available Inoue balloon sizes 24, 26, 28, and 30 mm) is important to avoid injury to the MV leaflets and to structures of the MV apparatus during balloon inflation. Different methods for sizing have been suggested based on the patient's height [65] or the body surface area or using the formula: height (cm)/10 + 10. However, the correlation between height as well as body surface area and MVA is not evident. In addition, annular calcification should also be taken into consideration as it may affect the MV orifice. In our practice, we choose the balloon size by measuring the maximal intercommissural diameter from the anterolateral to the posteromedial commissure in mid-diastole in a short axis TTE view [66], or, when TEE is performed, this measurement can be obtained from a transgastric short axis view or from a multiplanar 3D reconstruction of a TEE 3D data set of the MV.

Once access to the LA is gained, the selected balloon is inserted and directed from the LA across the MV into the LV. Fluoroscopy is used primarily, but TEE (or intracardiac echocardiography) is helpful in order to avoid catheters and wires entering the LAA cavity, to adequately position the balloon at the level of the MV, and to determine the best position of the balloon between the two mitral leaflets. The balloon should not be inflated in the subvalvular region as this can cause chordal rupture, tearing of the valve leaflets at a non-commissural region of the MV, and even damage to a papillary muscle. During balloon inflation with diluted contrast medium (contrast, saline = 1:5), the MV orifice is completely occluded and transient hemodynamic deterioration with static blood flow in the LA may occur. Therefore, a close monitoring of hemodynamic parameters is mandatory during each balloon inflation. The opening of the commissures after balloon inflation can be best identified fluoroscopically, when the constriction in the waist of the balloon at the level of the MV leaflets suddenly disappears [14•].

Criteria for ceasing a PMBC procedure include [16••, 17••] the following:

- MVA > 1 cm^2/m^2 body surface area
- Complete commissural opening in at least one commissure
- Occurrence or increase of MR > grade 1

Meticulous care during PMBC is required in high-risk patients such as elderly people, pregnant women, patients with very severe MS, extensive subvalvular involvement, severe calcification in the commissural areas, severe PAH, and in patients where the MV opens asymmetrically.

A PMBC is considered to be successful according to current guidelines when the MVA increases ≥ 1.5 cm^2, and no complications occur (particularly no MR grade > 2) [17••].

If the result is not satisfactory, balloon inflation can be repeated by increasing the balloon size step-wise in 1–2-mm increments until a MV opening ≥ 1.5 cm^2 is achieved or a relevant worsening of MR is seen.

The prediction of results after PMBC is multifactorial and includes a variety of clinical, anatomical, and hemodynamic parameters. Predictors of less favorable short- and long-term outcomes include an older age, previous commissurotomy, presence of AF, baseline MR, higher pulmonary artery pressure and pulmonary vascular resistance [67], higher echocardiographic grouping (≥ 2) or Wilkins (≥ 8) score, a commissural grade ≥ 2, severe subvalvular involvement, lower MVA post PMBC, and an MR grade ≥ 2+ post PMBC [14•].

In patients with restenosis after mitral commissurotomy, PMBC has also shown to be effective and to provide satisfactory immediate results irrespective of the type of past commissurotomy procedures done [68, 69]. After a good immediate result, one out of three patients remains free from surgery, and one out of five will have a good functional results at 20 years [69].

Peri-procedural Complications

The immediate detection of complications is mandatory during a PMBC procedure:

- Cardiac tamponade (incidence 0–2% [50, 70–73]): may be a consequence of a misplaced TSP when anatomical structures in the vicinity of the IAS (ascending aorta/ post-atrial pericardial space) are punctured unintentionally. Manipulation of catheters or wires within the LA/LAA cavities may also lead to injuries/perforation of the free LA wall and consequently to a hemopericardium. If it occurs, a pericardiocentesis should be performed or surgery if needed.

- Embolic events caused by air or thromboembolism (incidence 0–4% [50, 71–75]):

– Air embolism may occur when using large sheaths which allow air to enter the systemic circulation. This can be prevented by careful de-airing of the balloon and aspiration and flushing of catheters as well as keeping the hub of the catheter below the level of the heart during catheter insertion or removal.
– Thromboembolism may be caused by dislodging thrombotic material from the LAA or the LA wall. In addition, thrombi may form acutely on the catheters, wires, or the balloon itself. An adequate thrombus assessment before the procedure and the maintenance of the activated clotting time between 250 and 300 s during the procedure may help to minimize the risk of thromboembolic events

- Occurrence of relevant MR after PMBC (incidence 1.4–9.1% [21, 50, 71–75]): an increase or a new development of MR may be caused by commissural tearing, a rupture in a non-commissural region of the leaflets, inappropriate adaption of the leaflets due to severe calcification of the edges, or rupture of components of the subvalvular mitral apparatus. The choice of an adequate balloon size, proper balloon positioning during inflation, and a careful step-by-step balloon inflation under close echocardiographic monitoring may help to reduce this complication.
- The iatrogenic atrial septal defects (ASD) after the TSP may persist in some patients [76], but they are typically small and clinically irrelevant and do not appear to worsen long-term outcomes.

Assessment After PMBC

After each balloon dilation, LA pressures should be measured invasively and the result should be evaluated echocardiographically in order to decide if an additional balloon inflation is needed or the procedure can to be concluded or complications occurred. The focus of the evaluation after each balloon inflation should be on the assessment of:

- MVA by using mean Doppler gradients, 2D, and 3D planimetry (3D planimetry is superior to 2D [77]). The PHT method is often inaccurate due to the iatrogenic ASDs, the alteration of hemodynamic parameters and the changes in the compliance of the LV/LA [78, 79])
- adequate commissural splitting (3D is superior to 2D echocardiography in detecting commissural splitting)
- mobility of the MV leaflets
- severity and origin of MR
- complications

Surgical Techniques

For patients with significant MS who are not candidates for PMBC, surgery should be considered.

Before the widespread use of cardiopulmonary bypass for cardiac surgery, a "closed" commissurotomy—introduced in 1948 [80]—constituted the only surgical option to treat rheumatic MS. Most commonly, a left thoracotomy is used as an access way to the MV. The stenotic MV is usually dilated via the LA by using the finger of the surgeon after the fusion of the commissures has been confirmed by palpation. Using this approach, the MV itself cannot be visualized directly. In case the "surgical finger technique" alone is not sufficient, a transventricular dilator is inserted through the LAA and directed across the MV. This dilator can be opened multiple times to split the fused commissures [80]. This technique does not require cardiopulmonary bypass, has shown to be effective [81], and is easily accessible, which explains its frequent use in developing countries until recently. Closed mitral commissurotomy may not be a permanent solution, but it may offer many years of palliation and remains an option particularly for pregnant women in less developed countries [82].

Open surgical techniques include open surgical commissurotomy and MV replacement.

A median sternotomy with cardiopulmonary bypass is most commonly used to perform open surgical commissurotomy. This approach has the advantage that the entire MV apparatus can be directly visualized from the LA and results can be further improved by releasing fused chordae, elongating shortened chordae, or implanting an additional annuloplasty ring when there is coexisting significant MR.

MV repair has shown to be associated with significant valve failure and re-operation (freedom from all late events including late death, re-operation, and progression of MR at 5 and 10 years was 68% and 56.4%, respectively) [83]. More recently, it has been shown that the evolution of surgical techniques, including avoidance of anterior leaflet resection, use of artificial chordae vs. chordal shortening procedures, and use of pre-shaped rigid rings, together with surgeons' greater experience, has greatly contributed to continuous improvement in the rate of repair and better results of surgery [84, 85]. MV repair is an option particularly for young patients with preserved SR in regions of the world with very limited access to medical treatment and low compliance concerning long-lasting anticoagulation therapy. As bioprosthetic MV replacement is associated with more re-operations compared to mechanical MV replacement [86], a mechanical MV is usually the preferred option in indicated cases because of its better durability and the fact that most patients will be in need of long-term anticoagulation due to AF.

Conclusion

Although the incidence of RF and the prevalence of RHD are decreasing in industrialized countries, a substantial occurrence of rheumatic MV disease exists globally, predominantly in developing countries where this condition is the most common cause of acquired heart disease for individuals under 40 years of age. It is important to make a diagnosis early in the course of RHD and to serially assess for disease progression, worsening valve disease, for the development of pulmonary hypertension and to assess female patients with MS prior to pregnancy to ensure that they can safely carry a pregnancy to term. Medical treatment focuses mainly on the prevention of RF, on the reduction of symptoms, and on the prevention of thromboembolism. However, medical therapy is not curative and does not influence the progression of the disease. Symptomatic patients with severe MS will most likely need an intervention. Definite treatment options include PMBC and surgical techniques. As procedural results depend heavily on adequate patient selection, a proper understanding of indications, patient selection criteria, and knowledge of the available techniques for definite treatment is of paramount importance for the optimal timing for an intervention and to optimize procedural results. Recent data on 1582 patients was reported by Meneguz-Moreno et al. They found that at long-term follow-up, up to 23 years, > 75% of patients had sustained the benefits of PVMV. Predictors of late favorable results were multifactorial and determined not only by postprocedural MVA but also by pre-procedural symptom class and patient age [87].

Compliance with Ethical Standards

Conflict of Interest Nina C. Wunderlich, Bharat Dalvi, Siew Yen Ho, Harald Küx, and Robert J. Siegel declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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