CHIRURGIE CARDIAQUE / CARDIAC SURGEY

SURGICAL ASPECTS OF RHEUMATIC HEART DISEASE: PART 2

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Overview

The overall global growth or expansion of cardiac surgery favors the developing countries and emerging economies. At present, it is estimated that over 2 million open-heart operations are performed annually worldwide. It is also estimated that over 10,000 cardiothoracic surgeons, in over 3,000 centers, that include specialty clinics, hospitals or institutes, be that public, private or charitable, are involved in that effort. Well over one million of these operations are performed in North America and Europe. This represents ready access or availability for less than 700 million of the 7 billion global population. An estimated backlog of 15-20 million people with heart disease are in need of corrective cardiac surgery worldwide. Whereas coronary artery disease is the dominant indication for cardiac surgery in the developed countries, rheumatic and congenital cardiac diseases continue to be more prevalent in the developing countries or emerging economies. Yet coronary artery disease and degenerative valve disease are also increasing in these countries as the global population health and lifespan improves and rises. As the social, economic, environmental, political, and demographic conditions in these countries evolve, adapt, and advance, there will be a concomitant increase in cardiac services that include prevention, awareness, diagnostic evaluation, medical management, interventional treatment, surgical procedures, rehabilitation, and early, mid-term, and long-term follow-up.

Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) remain a serious and prevalent international concern. The global prevalence of RHD is 12-15 million, of which >2.4 million are children 5-14 years of age. The annual incidence is >300,000, and the annual mortality >350,000. Rheumatic mitral valve disease is the most common condition, especially in children. The incidence is greater in females, and <25% give a history of prior ARF. This represents 30-40% of all cardiac hospital admissions in developing countries. In sub-Saharan Africa (SSA), the echocardiogram (ECHO) in clinically silent patients detects from 7.5 to 56.6/1,000, as opposed to the <1.0 to 14/1,000 prevalence in clinically detected RHD.

Regarding surgery, although open mitral valve repair has become the preferred procedure for degenerative and ischemic mitral valve problems, this procedure has not gained wide application for rheumatic disease, mainly because of complex pathology, technical difficulties, and debatable long term results, especially in children. Historically, mitral valve commissurotomy (MVC), both closed and open have been successful for rheumatic mitral stenosis, with excellent long term results. Presently, interventional percutaneous balloon valvuloplasty (PBV), when available and feasible, is the favored approach, despite higher cost than closed MVC. Open repair for rheumatic

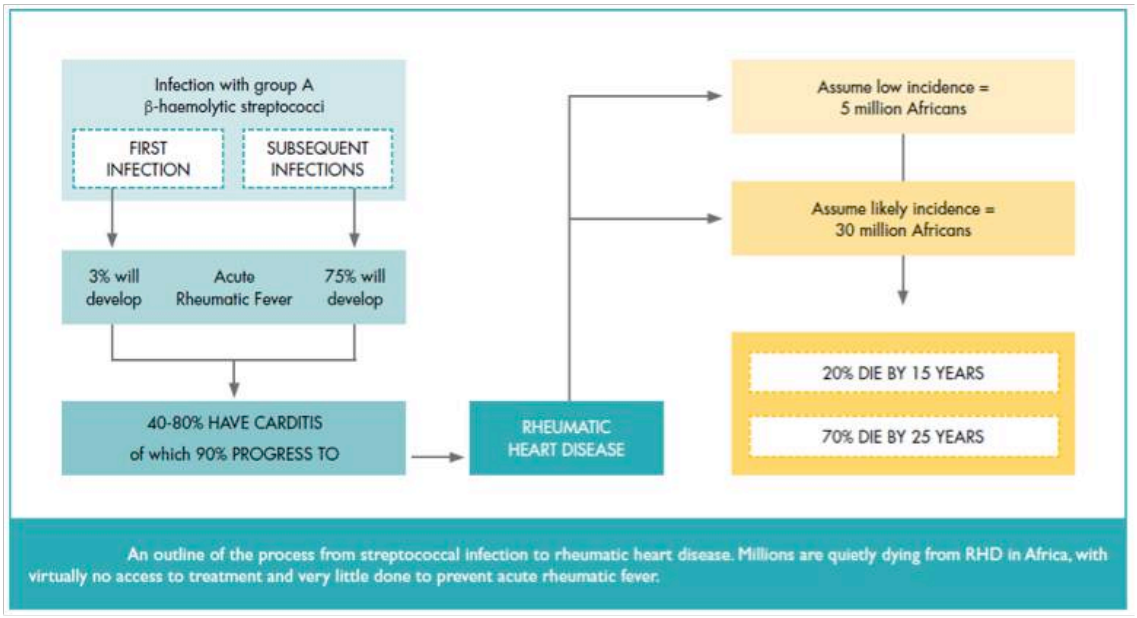
mitral regurgitation, though durable in experienced centers, has mixed long term results in children < 20 years of age. Other approaches, including valve replacement with mechanical or bioprosthetic valves, mitral Ross II procedure, mitral homografts, and leaflet extension using autologous or non-autologous pericardial substitutes, have all been described and advocated. Interventional percutaneous and trans-cardiac approaches to the mitral and aortic valves are now available in advanced centers, yet remain in the clinical investigative phases. Access for testing, monitoring, and regulation of anticoagulation in low and middle income populations remains a formidable challenge, as does appropriate surgical considerations and options in child-bearing females. The decreased growth potential and reduced durability of bioprosthetic valves in young patients, with attendant cost and need for reoperation, are also major considerations.
The present part 2 review in a 5 part series highlights current medical and interventional treatment of predominate rheumatic mitral valve stenosis.

Key Words
Acute Rheumatic Fever, Rheumatic Heart Disease, Mitral commissurotomy, Percutaneous balloon valvotomy, valve surgery, valve repair

Introduction

Incidence / Prevalence

It is difficult to ascertain the true global estimate of the incidence and prevalence of RHD, since ARF and RHD are usually reported together. As noted, the raw global estimate is that 10-15 million people have documented RHD[1]. In the USA, the national prevalence of valve disease from all causes is 2.5% or >750,000 individuals[2]. With virtually no RHD in that prevalence, the increase in cardiac valve related disease is secondary to increasing age and degenerative diseases, as predicted in the Gaziano report of epidemiological transition[3]. It is estimated that 70% of ARF will develop RHD, and that 70% of RHD involves the mitral valve. It is also estimated that >50% victims of RHD will require an interventional or surgical procedure during their lifetime. Table 1 summarizes the development of RHD from GAS[4]. In sub Saharan Africa (SSA), the incidence of clinically detected RHD is 14 per 100,000 per year, and the prevalence is 1-14 per 1,000. When 2D ECHO is used as a screening tool to detect clinically silent children, the prevalence in SSA, based on 31 surveys conducted in Mozambique, Uganda and in Senegal, increases to 7.5-56.6 per 1,000 children[5].



An outline of the process from streptococcal infection to rheumatic heart disease. Millions are quietly dying from RHD in Africa, with virtually no access to treatment and very little done to prevent acute rheumatic fever.

The European Heart Survey of valvular heart disease evaluated the etiology of native valve disease and noted >90% rheumatic etiology for mitral stenosis, and >50% rheumatic etiology for multiple valve disease (6). Further time-course analysis of mitral stenosis and combined MS/ MR revealed an increasing incidence after the second decade of life despite a decrease in rheumatic inflammatory activity (Figure 1) [7].

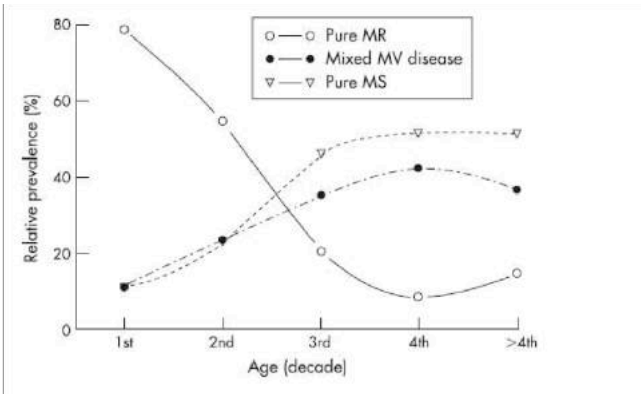
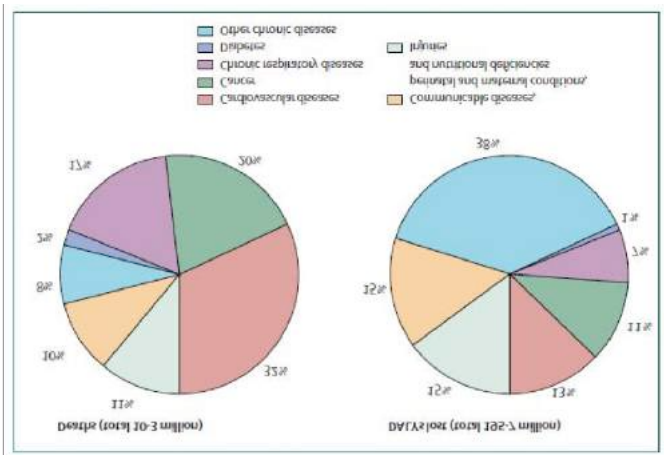


Figure 1[7]*: Time-course(by decade) of the relative prevalance of mitral valve(MV) disease, and pure mtral stenosis (MS). Reproduced from Marcus RH, Sareli P, Pocock WA, et al. The spectrum of severe rheumatic mitral valve disease in a developing contry. Correlations among clinical presentation, surgical pathologic finding, and hemodynamic sequeloe.*

The annual number of cardiac valve operations from all causes, continues to increase in both the developed countries and emerging economies. Fifty nine per cent of all open heart operations at the Cleveland Clinic in 2011 were isolated or combined valve procedures[8]. This reflects the increase in degenerative valve disease in an aging population. At Fu Wai Hospital in Beijing, China 7,606 open heart operations were performed in 2008[9]. Of these, 2,189 (28.8%) were valve procedures, with the majority being congenital cases. More than 40% of valve procedures, though declining, were secondary to RHD. This is a reflection of the double burden of disease i.e. the persistent prevalence of RHD, which is a sequel of streptococcal infections, and the increasing incidence of degenerative valve disease, a non-communicable disease (Figure 2)[10]. The severity of valve disease in China is high, given that 23.51% of the valve operations at Fu Wai Hospital were multiple valve procedures. In contrast, in the USA, 11% of all valve procedures performed from 1993 through 2007 were multiple valve procedures, and only 10.3% of the valve operations were for mitral stenosis[11].

Diagnosis



Fiugure 2[10]*: Estimated proportions of total deaths and DALYs lost for all ages in China,2005*

The diagnosis of RHD involves a detailed history and physical examination, with emphasis on a history of ARF or recurrent episodes of ARF. Yet, <25% can give an accurate or documented history of an ARF event. Many individuals either did not seek medical attention for initial GAS infection because of mild symptoms, or developed ARF without symptoms or associated clinical manifestations. Assessment of cardiac clinical symptoms utilize the New York Heart Association Functional Classification (Class I-IV), or the American College of Cardiology/ American Heart Association (ACC/AHA) Classification (Stage A-D) (Table 2, 3)[12,13]. Hurst[12] has emphasized the importance of the complete NYHA classification that includes the etiology, anatomy, physiology, functional classification, and objective assessment of cardiac disease.

The major symptoms associated with valve disease are reflective of the extent of valvular and myocardial involvement which lead to right, left, or biventricular heart failure. They include fatigue, decreased exercise tolerance, dyspnea on exertion or at rest, chest pain, dizziness, and syncope. Dyspnea results from MV obstruction with subsequent decrease in lung compliance, and decreased vital capacity (VC) secondary to pulmonary vascular congestion and interstitial pulmonary edema. Clinical signs include heart murmurs, and evidence of right, left, or combined heart failure. These include neck vein distension, lung rales, hepatomegaly, ascites, or peripheral edema[14].

***Table 2**: NYHA/ACC-AHA[12,13]*

Class 1: No symtoms with ordinary activity
Class II: Symptoms with ordinary activity
Slight limitation of activity
Class III: Symptoms with less than ordinary activity. Marked limitation of activity
Class IV: Symptoms with any physical activity or Even at rest

* O'Rouke Ra, Shaver JA, Silverman ME. The history, examination and cardiac auscultation. In : Fuster V. O'Rouke Ra, Walsh RA, Poole-Wilson P. editors. Hurst's.
The heart. 12 edition. McGraw Hill Medical, New York, NY. P. 215-293.

***Table 3**[13]*

Stages of progression of Valvular Heart Disease (VHD)
A- At risk Patients with risk factors for developement of VHD.
B- Progresive Patients with progressive VHD (mild-to-moderate severity and asymptomatic)
C1- Asymptomatic severe patients with severe VHD in whom the left or right ventricle remains compensated
C2- Asymptomatic patients with severe VHD, with sdecompensation of the left or right ventricle
D- Symptomatic servere patients who have developed symptoms as a result of VHD

◇◇

Cardiac auscultation has become a lost art with the development of sophisticated diagnostic modalities. However it remains an extremely useful and a valuable clinical tool, especially in initial diagnosis, and subsequent clinical monitoring and follow-up, especially in developing countries where ECHO is not available[15]. The characteristic ausculatory finding in rheumatic mitral stenosis is the opening snap (OS) and diastolic rumble[15]. The OS of the mitral valve is caused by a sudden tensing of the valve leaflets after the valve cusps have completed their opening excursion. It is most readily audible at the apex. If present, it indicates that the mitral valve has at least some mobility[16]. In addition the first heart sound (S1) is loud and the second heart sound (S2) is split into 2 components A2 and P2. P2 is increased with pulmonary hypertension. With MR there is a long holosystolic murmur that radiates laterally to the axilla.

For aortic stenosis, the finding is a harsh crescendo-decrescendo systolic ejection murmur over the aortic area and radiating to the neck. For aortic insufficiency the murmur is heard in early diastole with the patient upright and leaning forward. For mitral regurgitation it is a pansystolic harsh murmur at the apex, and radiates to the left axilla. With severe MR or AR and decreased left ventricular function the murmur may be absent. The systolic murmur of tricuspid regurgitation (TR) changes in intensity with respiration. The classical Kusmaul sign of TR is distension of the jugular veins on inspiration.

Diagnostic laboratory studies include complete blood count, erythrocyte sedimentation rate ESR, and C-reactive protein to assess persistent rheumatic activity.

The complete diagnostic evaluation of RHD includes a subjective clinical evaluation, and objective diagnostic studies (CXR, ECG, 2D ECHO, 3D ECHO, CT, MRI). Coronary angiography and cardiac catheterization can be used to further assess anatomy and hemodynamics, especially pulmonary hypertension, as well as the coronary anatomy in older patients, or those at risk for coronary artery disease. The chest x-ray is an essential diagnostic screening test (Figures 3, 4). The cardiothoracic ratio is important with a >0.60 ratio being significant. Other findings include left atrial enlargement, enlarged pulmonary artery, increased pulmonary vascular markings ("sergeant major whisker sign"), pulmonary edema, Kerly b lines, and pleural effusion.

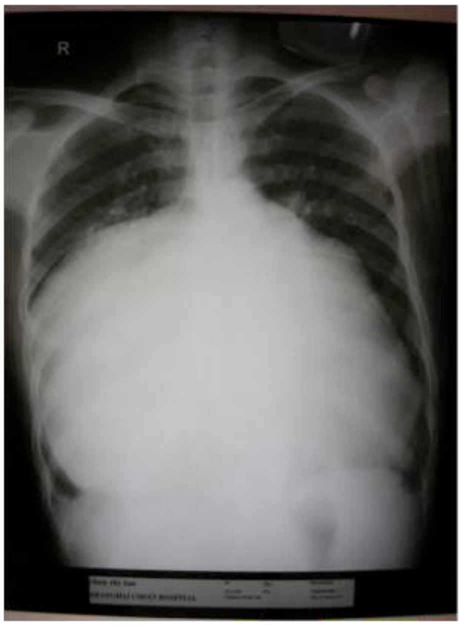


***Figure 3.** Enlarged cardiac silhouette with CT ratio of almost 1:1. (Courtesy of AT Pezzella)*

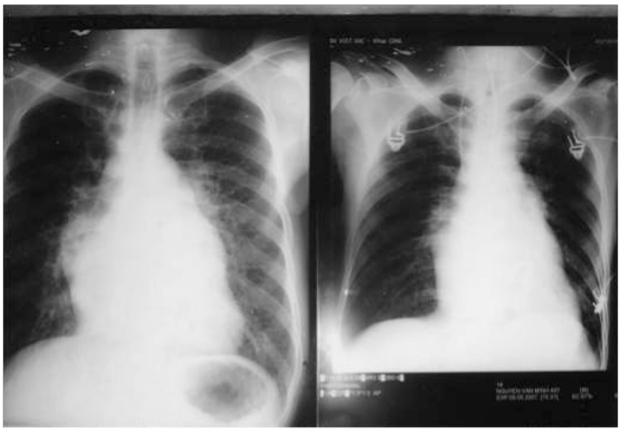


***Figure 4.** Pre and postoperative views demonstrating preoperative cardiomegaly, dilated main pulmonary arteries, and pulmonary edema. (Courtesy of AT Pezzella)*

The transthoracic 2D ECHO (TTE) has emerged as the most useful diagnostic tool, given the ready availability and interpretation. The TTE provides an accurate diagnostic modality in both the screening, initial evaluation of acute RHD, and subsequent chronic RHD monitoring (Figure5) [17,18,19]. Tranesophageal echocardiogram (TEE)

also extends the diagnostic capability and accuracy for complex disease, and for interventional or operative scenarios. Table 4[20] summarizes complete ECHO evaluation criteria for aortic and mitral valve abnormalities. Real-time three dimensional echocardiography (RT3DE), where available, has become extremely helpful in planning operative strategies, as well as intraoperative assessment of valve repair or valve replacement (Figure6)[21]. It gives more information regarding the functional and anatomic properties of the cardiac structures in real time (especially post RMV assessment of extent of mitral commissural splits, leaflet lacerations, and degree of MR). RT3DE is also superior to 2D ECHO in chamber quantification and MVA assessment of mitral stenosis [22,23]. Other diagnostic modalities for heart valve assessment include cardiovascular magnetic resonance (MR), and multi-detector row computed tomography (CT), though not readily available in LMIC's[24]. MR is able to give accurate assessment of LV volumes and systolic function, whereas CT provides evaluation of coronary artery disease and spacial resolution for planimetry of stenotic heart valves.

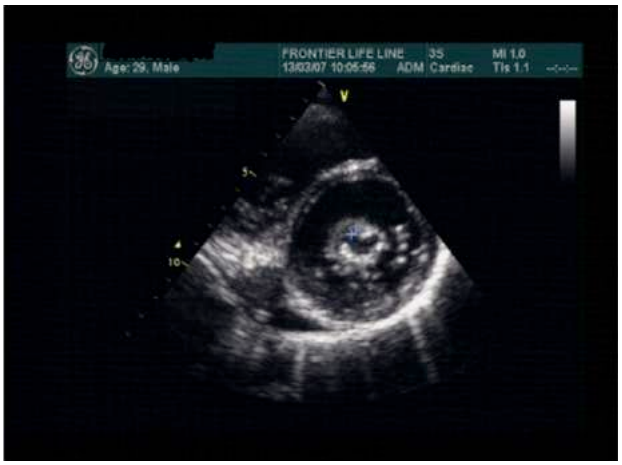


Figure 5. *Parasternal short axis view showing calcified doming of mitral valve orifice- "button-hole", "fish mouth". (Courtesy of Dr KM Cherian, Frontier Lifeline, Chennai, India)*

Table 4. [20, 21] ***Summary of ECHO findings***

Mitral Regurgitation severity
-Effective regurgitant orifice area (EROA): mild-<0.20 cm2; moderate-0.2-0.39; severe- >0.40.
-MR volume (mL/beat): mild->30; moderate- 30-90; severe >60.
-MR fraction: >55%.
-Jet area (central jets): mild < 3cm2 or 20% of LA; moderate- 4-10cm2; severe->10cm2 or 40% of LA.
-Jet density and contour: mild- soft and parabolic; moderate- dense, variable contour; severe- dense, triangular with early peaking.
-Vena contracta width (VC): mild <0.3; moderate- 0.30-0.69; severe- >0.40.
-Pulmonary vein systolic reversal of flow: mild systolic dominance; moderate systolic blunting; severe systolic reversal.
-Suggestive: LA size >55mm; color flow area >40% LA size
-MV leaflet tenting area: >6cm2
-Increased E velocity
-LVEDD >70mm
_LVESD >55mm
Mitral stenosis
MVA- Normal 4-6 cm2
-Mild 1.6-2cm2
-Moderate 1.1-1.5cm2
-Severe <1.ocm2
-Resting mean gradient >10mm Hg
-PHT >220 milliseconds
Aortic regurgitation
-LVDD >75mm/LVE
-Regurgitant jet width/LVOT diameter ratio >60%
-Vina contracta width >6cm
-AR PHT <250 milliseconds
Aortic stenosis
-Peak aortic velocity >4.5m/s (0.3m/s/year)
-Mean pressure gradient >50mm Hg
-AVA <0.75cm
-LVOT: AOV/TVI <0.25

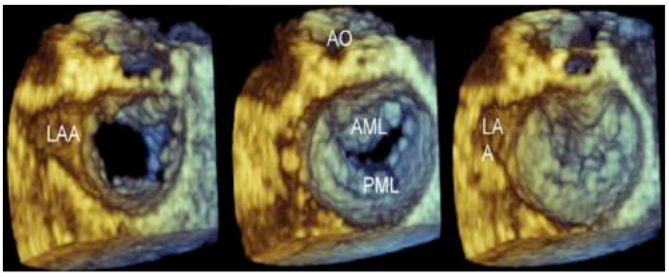


Figure 6. *3D *ECHO of normal mitral valve.* From: Shiota T. 3D echocardiography: The present and the future. J Cardiology 2008;52:169-185.*

Invasive cardiac catheterization is not indicated for younger patients, but is recommended in patients> 40 years old to assess coronary anatomy. The hemodynamic changes are particularly important in patients with myocardial dysfunction, and suspected pulmonary hypertension[16,25]. Carabello[16] also stresses that pulmonary hypertension at the time of corrective intervention or surgery is a prognostic indicator of decreased long term survival.
The guidelines for the management of valvular heart disease have been well outlined, based on evidence based medicine, by the ACC/AHA, and the Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology[13,26,27]. Table 5[13] summarizes the severity and classification of valve disease in the adult. These figures do not accurately assess mixed stenosis/regurgitation, or multiple valve involvement. The correlation of the clinical and objective diagnostic findings remains a challenge with regards to clinical management/treatment.
The progressive nature of RHD is important to understand. The latency period from ARF to asymptomatic and then symptomatic valve dysfunction ranges from 20-40 years in developed countries, yet is shorter in LMIC's (7). The symptoms of RHD are related to valve dysfunction and subsequent singular or combined effects on the LV, RV, or pulmonary vascular bed.

The associated clinical problems or sequelae related to mitral RHD include: enlarged LA enlargement , atrial fibrillation, cardiomyopathy induced tachyarrhymias, LA clot, systemic emboli, stroke, elevated pulmonary artery pressure (PAP), endocarditis, functional TR, and RV/LV failure[16, 25]. In LMIC's the major hospital admission problem is heart failure. The overall mortality of RHD is due to atrial fibrillation with embolic stroke, and heart failure related to progressive mitral, aortic, and tricuspid valve dysfunction. In developing countries and emerging economies a major challenge is delayed recognition, as well as access and availability of care, and the ability to provide comprehensive evaluation and management.

Figure 5[26]. *Classification of the Severity of the Valve Disease in Adults*

A. Left-sided valve disease

Aortic Stenosis

Indicator	Mild	Moderate	Severe
Jet velocity (m/s)	Less than 3.0	3.0-4.0	Greater than 4.0
Mean gradient (mm Hg)*	Less than 25	25-40	Greater than 40
Valve area (cm^2)	Greater than 1.5	1.0-1.5	Less than 1.0
Valve area index (cm^2/m^2)			Less than 0.6

Mitral Stenosis

	Mild	Moderate	Severe
Mean gradient (mm Hg)*	Less than 5	5-10	Greater than 10
Pulmonary artery systolic pressure (mm Hg)	Less than 30	30-50	Greater than 50
Valve area (cm^2)	Greater than 1.5	1.0-1.5	Less than 1.0

Aortic Regurgitation

	Mild	Moderate	Severe
Qualitative			
Angiographic grade	1+	2+	3-4+
Color Doppler jet width	Central jet, width less than 25% of LVOT	Greater than mild but no signs of severe AR	Central jet, width greater than 65% LVOT
Doppler vena contracta width (cm)	Less than 0.3	0.3-0.6	Greater than 0.6
Quantitative (cath or echo)			
Regurgitant volume (ml/beat)	Less than 30	30-59	Greater than or equal to 60
Regurgitant fraction (%)	Less than 30	30-49	Greater than or equal to 50
Regurgitant orifice area (cm^2)	Less than 0.10	0.10-0.29	Greater than or equal to 0.30
Additional Essential Criteria			
Left ventricular size			Increased

Mitral Regurgitation

	Mild	Moderate	Severe
Qualitative			
Angiographic grade	1+	2+	3-4+
Color Doppler jet area	Small, central jet (less than 4 cm^2 or less than 20% LA area)	Signs of MR greater than mild present, but no criteria for severe MR	Vena contracta width greater than 0.7 cm with large central MR jet (area greater than 40% of LA area) or with a wall-impinging jet of any size, swirling in LA
Doppler vena contracta width (cm)	Less than 0.3	0.3 – 0.69	Greater than or equal to 0.70
Quantitative (cath or echo)			
Regurgitant volume (ml/beat)	Less than 30	30-59	Greater than or equal to 60
Regurgitant fraction (%)	Less than 30	30-49	Greater than or equal to 50
Regurgitant orifice area (cm^2)	Less than 0.20	0.2-0.39	Greater than or equal to 0.40
Additional Essential Criteria			
Left atrial size			Enlarged
Left ventricular size			Enlarged

B. Right-sided valve disease

Characteristic	
Severe tricuspid stenosis:	Valve area less than 1.0 cm^2
Severe tricuspid regurgitation:	Vena contracta width greater than 0.7 cm and Systolic flow reversal in hepatic veins
Severe pulmonic stenosis:	Jet velocity greater than 4 m/s or maximum gradient greater than 60 mm Hg
Severe pulmonic regurgitation:	Color jet fills outflow tract Dense continuous wave Doppler signal with a steep deceleration slope

*Valve gradients are flow dependent and when used as estimates of severity of valve stenosis should be assessed with knowledge of cardiac output or forward flow across the valve. Modified from the Journal of the American Society of Echocardiography. 16. Zoghbi WA. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. 777–802. Copyright 2003. with permission from American Society of Echocardiography.

AR = aortic regurgitation; **cath** = catheterization; **echo** = echocardiography; **LA** = left atrial atrium; **LVOT** = left ventricular outflow tract; **MR** = mitral regurgitation

Rheumatic Mitral Valve Stenosis

Rheumatic mitral valve disease (RMVD) deserves particular attention since rheumatic mitral stenosis and/or insufficiency involve 65-75% of all RHD patients, and remains a significant problem in the developing world. It is also 2-3 times more common in women[16]. The natural history has been well studied[7]. Selzer and Cohn[28], in 1972, summarized previous studies which revealed that the latent period from acute carditis to symptomatic mitral stenosis averaged 19 years. They also highlighted a 40% incidence of atrial fibrillation that, presumably, was the result of left atrial enlargement and increased left atrial pressure. Atrial fibrosis and atrophy were postulated to be a deterrent to successful cardioversion, be it medical, interventional, or surgical. The incidence of systemic emboli was 9-14%, with 60-75% of individuals having a stroke. Myocardial factor and bacterial endocarditis were not considered significant problems. They stressed the 3 distinct pathological types of mitral stenosis: 1. Focused commissural fusion; 2. Cusp or leaflet fibrosis with subsequent calcification; and 3. Chordal involvement with fusion, thickening, and shortening. Combinations of all 3 types could occur. This is of therapeutic significance since appropriate treatment options require an accurate anatomical description of the valve pathology, and lesion(s) specific corrections.

Management/Treatment Options for RMVD [26]

It is important to consider a number of issues when discussing management options in LMIC's where the prevalence of RMVD is greater. Access to cardiac services is difficult in both rural and even large urban areas. Long waiting lists and substandard evaluation compounds the problem. Cost is also a major issue given the cost of medications, and frequent hospitalizations.

In general, treatment should begin when symptoms develop. However, late presentation or late referral patterns remain a challenge. Government support may not be available or is limited. Patients usually have to pay for the valves, drugs, and disposables using "out of pocket" resources, given limited health insurance coverage, and meager funds from the charitable trust hospitals, or private centers. Poor patients have limited access to the private hospitals, since these facilities provide limited charity care, and only in a few countries is there mandated total or partial financial support from the private sector. The majority of the patients are children and adolescents (5-18 years of age), and have an aggressive form of RMVD. Percutaneous valvotomy, though less invasive than surgery, is expensive. The cost of each percutaneous balloon is >$1,000. In many countries the balloons are reused at least 3 times to decrease cost. Disposables and medication for surgery average $2-$3,000 per patient. The remaining clinical issues remain debatable. These include valve repair, mechanical valve versus bioprosthetic valve, anticoagulation and monitoring, child bearing females, redo operations, and complications following surgery. The success of treatment is related to the NYHA functional status. For NYHA I medical treatment is adequate. However, for more advanced heart failure classification NYHA II-IV, interventional catheterization, or surgical treatment is recommended[16,19].

Medical Therapy

The overall medical management of RHD revolves around the anatomical valve sequelae (isolated MS, MR, AS, AR, or combinations), and the resultant pathophysiological dysfunction[26]. The overall approach must include the prevention of acute rheumatic fever (ARF), the prevention of infectious endocarditis, and the treatment of the sequelae of valve disease that includes heart failure, pulmonary hypertension, atrial fibrillation, thromboemboli, or endocarditis[26]. This is a major challenge in LMIC's where late presentation or late referral is common. Single valve, mixed valve, and multiple valve involvement are the anatomical problems, and all of them can elicit one or more pathophysiological conditions. Medical management includes diuretics, decreased salt intake, digoxin, anticoagulation, beta blockers (avoid atenolol in pregnant patients), calcium channel blockers, potassium supplement, afterload reduction with ACE inhibitors (e.g. captopril or enalopril), pulmonary vascular dilators, and secondary antibiotic prophylaxis. With longstanding RHD, advanced heart failure requires aggressive management (Figure 7)[29].

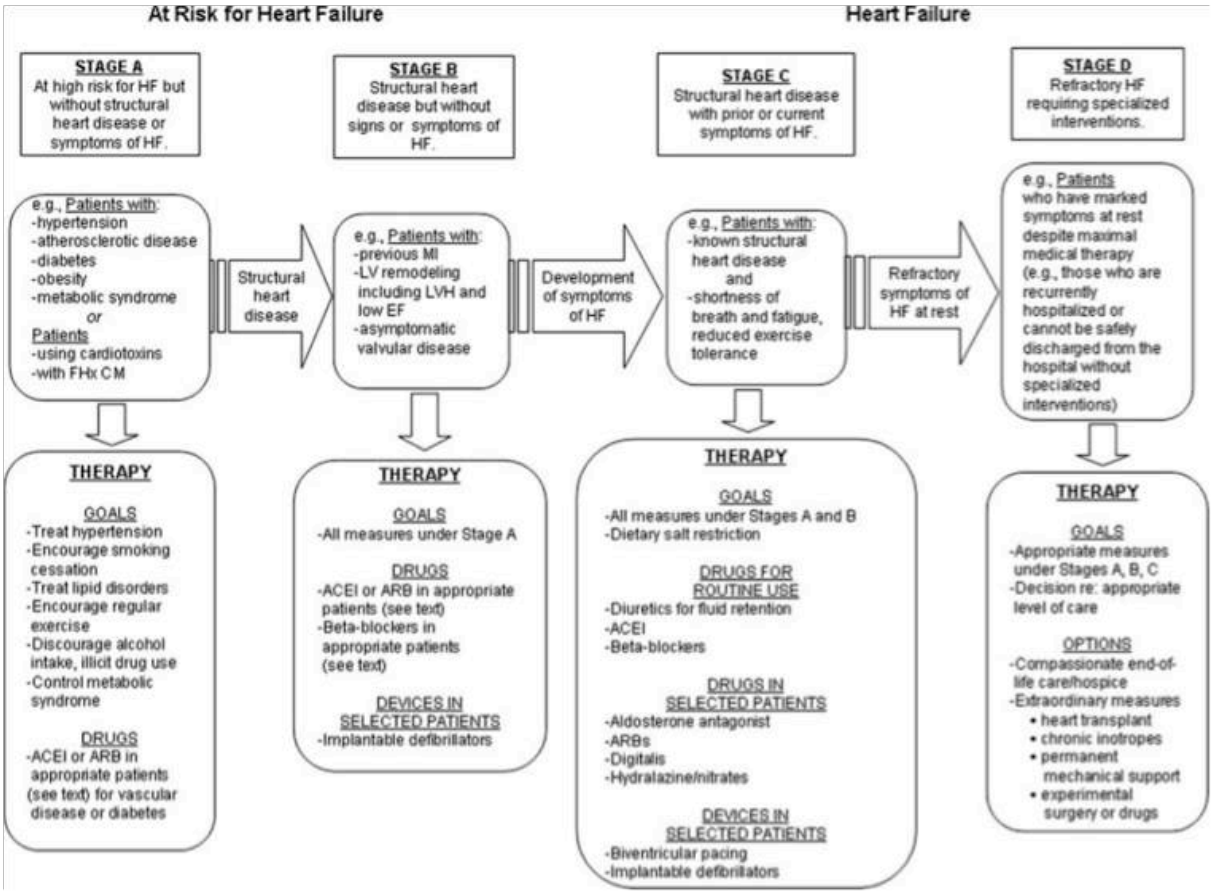
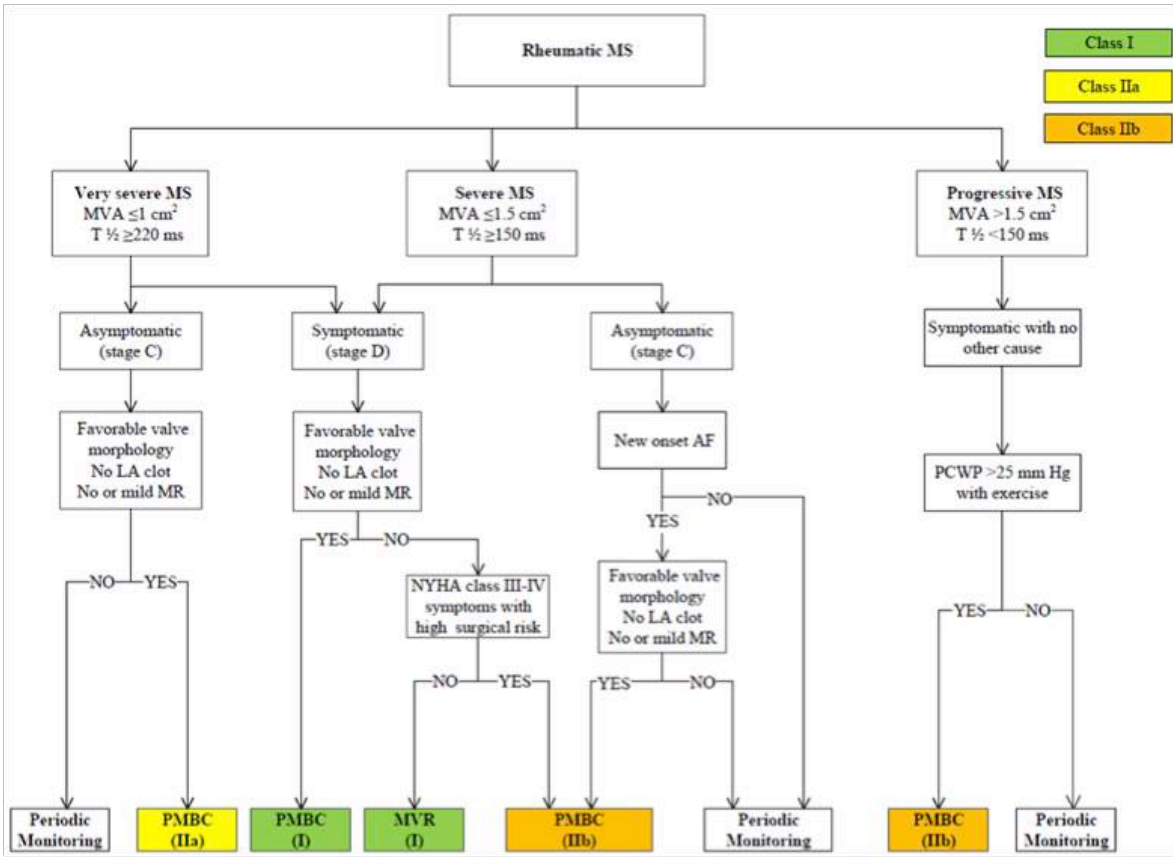


Figure 7. (http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.109.192064)



AF indicates atrial fibrillation; LA, left atrial; MR, mitral regurgitation; MS, mitral stenosis; MVA, mitral valve area;MVR, mitral valve surgery (repair or replacement); NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PMBC, percutaneous mitral balloon commissurotomy; and T ½, pressure half-time.

Figure 8. (26) Indications for Intervention for Rheumatic MS

Paroxysmal or chronic sustained atrial fibrillation is a significant problem that complicates >60% of RHD. The risk of systemic emboli and stroke with attendant morbidity and death, as well as risks associated with anticoagulation is significant[16]. This requires consideration for aggressive control that includes rate control with beta blockers and calcium channel blockers, as well as attempts with medical or electrical cardioversion. Long term anticoagulation is usually required[30]. This will be discussed further in parts 3 and 4. The recommendations also apply to postoperative treatment of AF. Endocarditis complicates RHD in 14% of patients. Berkowitz[31] noted a 9.7% incidence of endocarditis in children with RHD from 8 reviewed studies. Endocarditis will be discussed further in parts 3-5.

Interventional Therapy

Percutaneous Balloon Valvuloplasty (PBV)

With rheumatic mitral stenosis the most common mechanism is fusion of the commissures. This is the basis for catheter based procedures which have increased in recent years[32-35]. In the USA, >1,500 PBV's are performed per year. The global number is unknown, as is the global availability of PBV or surgery. Grading mitral valve disease and clinical management algorithms are summarized in Figure 8[13,27]. Both the Wilkins and Iung/Cormier morphology grading scores were developed to provide guidelines and patient selection for either catheter-based interventional or surgical treatment (Table 6, 7). An ECHO score of <8 provides an optimal outcome from PVB, whereas scores >11 are sub- optimal. Scores of 9 to 11 are not predictable. The Iung/Cormier score gives a more quantitative assessment of the subvalvular apparatus (SVA). This may be more predictive of PBV success, though not documented in the literature (--). The overall target goal of PVB is to achieve a mitral valve area (MVA) of at least 1.5-2.0 cm2 (Normal MVA is 4-6 cm 2), minimal residual MR, preserved LV function, and varying degrees of decreased PAP. Although these echocardiographic features can predict the likelihood of immediate success, they do not identify the future risks of subsequent mitral regurgitation. Based on pathologic data from patients who developed severe post-procedural MR, the Padial ECHO score was developed which included uneven distribution of thickness and calcification of both mitral leaflets, and the degree of commissural and subvalvular involvement (Table 8)[36]. Other 2D ECHO scores have also been devised (Chen, Reid, and Nobuyoshi scores). Soliman et al. (37) have reported the RT3D-TEE modality developed by Anwar et al. (Table 9)[37].

This technique allows better evaluation of the functional valve, and both valvular and subvalvular morphology. It also helps define the valvular orifice area. This is especially true for better localization of the valve commissures and areas of calcification.

The percutaneous balloon valvotomy (PBV) technique or balloon mitral valvotomy (PBV) was introduced in 1984 by Inoue (Figures 9,10)[38]. Subsequent early clinical series have documented the effectiveness of the procedure[39-43].

Table 6. *Wilkin's Mitral Valve Morphology Score**

Grade	Mobility	Valvular Thickening	Valvular Thickening	Subvalvular Thickening
	Highly mobile valve with only leaflet tips restricted	Leaflets near normal in thickness (4-5 mm)	Single area of increased echo brightness	Minimal thickening just below mitral leaflets
	Middle and base portions of leaflets have reduced mobility	Thickening of leaflet midportions, marked thickening of margins	Scattered areas of brightness confined to leaflet margins	Thickening of chordal structures extending up to one third of chordal length
	Valve continues to move forward in diastole, mainly from base	Thickening extending through entire leaflet (5-8 mm)	Brightness extending into midportions of leafletst	Thickening extending to distal third of chords
	No or minimal forward movement of leaflets in diastole	Thickening Marked thickening of all leaflet tissue (> 8-10 mm)	Extensive brightness throughout most of leaflet tissue	Extensive thickening and shortening of all chordal structures extending down to papillary muscles

**Total ECHO score is derived from an analysis of mitral leaflet mobility, valvar and subvalvar thickening, and calcification, and is graded from 0 to 4 according to the criteria given in the table. This yields a total score of 16.*
Wilkins GT, Weyman AF, Abscal VM, et a. Br Heart J 1988;60:299-308.

Table 7:

Anatomic scores predicting outcome after percutaneous mitral commissurotomy: Cormier's grading of mitral valve anatomy

Echocardiographic group	Mitral valve anatomy
Group 1	Pliable non-calcified anterior mitral leaflet and mild subvalvular disease (i.e. thin chordae ≥10 mm long)
Group 2	Pliable non-calcified anterior mitral leaflet and severe subvalvular disease (i.e. thickened chordae <10 mm long)
Group 3	Calcification of mitral valve of any extent, as assessed by fluoroscopy, whatever the state of subvalvular apparatus

**Iung B, Cormier B, Dicimetiere P, et al. Functional results 5 years after successful percutaneous mitral commissurotomy in a series of 528 patients and analysis of predictive factors. J Am Coll Cardiol 1996;27:407-414.*

Table 8 Padial Score[36].

Echocardiographic Score for Severe Mitral Regurgitation After Percutaneous Mitral Valvulotomy

I-II. Valvular thickening (score each leaflet separately)

1. Leaflet near normal (4-5 ram) or with only a thick segment
2. Leaflet fibrotic and/or calcified evenly; no thin areas
3. Leaflet fibrotic and/or calcified with uneven distribution; thinner segments are mildly thickened (5-8 mm)
4. Leaflet fibrotic and/or calcified with uneven distribution; thinner segments are near normal (4-5 mm)

III. Commissural calcification

1. Fibrosis and/or calcium in only one commissure
2. Both commissures mildly affected
3. Calcium in both commissures, one markedly affected
4. Calcium in both commissures, both markedly affected

IV. Subvatvular disease

1. Minimal thickening of chordal structures just below the valve
2. Thickening of chordae extending up to one-third of chordal length
3. Thickening to the distal third of the chordae
4. Extensive thickening and shortening of all chordae extending down tothe papillary muscle

The total score is the sum of these echocardiographic features (maximum 16)

Table 9[37]

New real time 3D ECHO (RT3DE) score for prediction of PVM outcome:
Each leaflet is divided into 3 scallops: Anterior leaflet- A1, A2, A3// Posterior leaflet- P1, P2, P3.The subvalvular apparatus is divided into 3 cut section of the anterior and posterior chordae at 3 levels: Proximal (valve level), middle and distal (papillary muscle level).
Each MV scallop is scored as follows:

Normal thickness & mobility = 0
Abnormal thickness or restricted mobility = 1
Nocalcification = 0
Calcification in middle scallop (A2 or P2) = 1
Calcification of commissural scallops of both leaflets=2
Scoring of subvalvular apparatus:
Chordal thickness normal =0
Abnormal thickness= 1
Chordal separation (distance in between>5mm=0, <5mm= 1

Absence of separation = 2

The RT3DE score of leaflets and the subvalvular apparatus range from 0-31 points. Total score of mild MV involvement is <8 points, moderate involvement 8-13 points, and severe involvement >14 points.

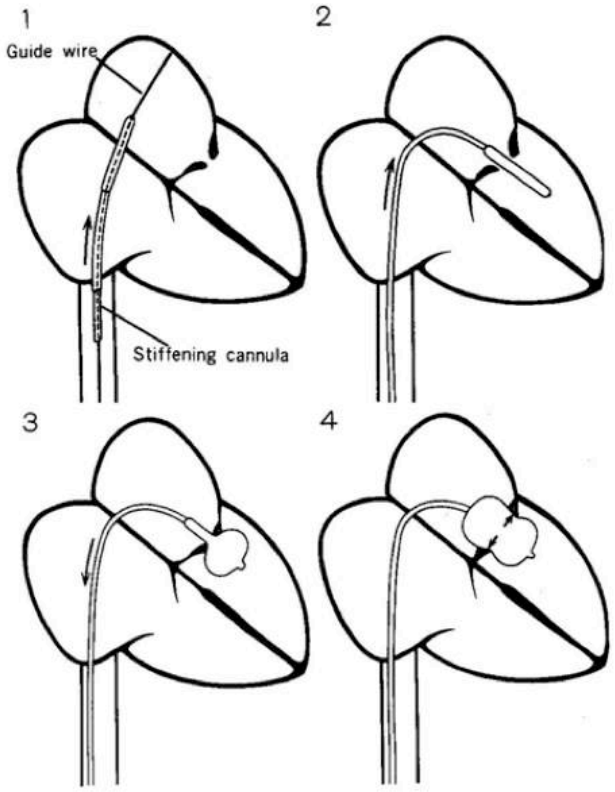


Figure 9[38] *Manipulation of the ballon catheter. 1, The ballon catheter, with a stiffening cannula inserted, is advanced over the guide wire and pushed into the left atrium. Then the stiffening cannula is removed. 2, The ballon catheter is inserted into the left ventricle with the aid of its own specific curvature. 3, In the left ventricle, only the distal half of the ballon is inflated. It is pulled until some resistance is felt, to bring it into contact with the left ventricular side of the mitral valve. 4, With further infusion, the ballon is inflated to full extent at the mitral orifice and there by separtes the fused commissures.*

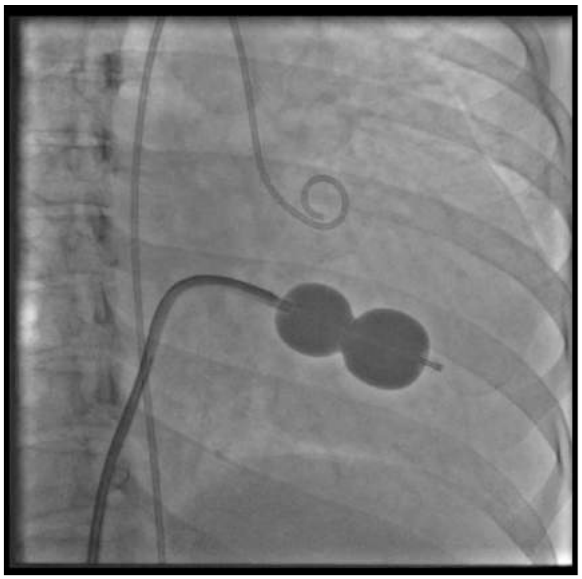


Figure 10. *Inoue inflated balloon across mitral valve via trans atrial septal approach. (Courtesy of Dr KM Cherian, Frontier Lifeline Cardiovascular Center, Chennai, India)*

The current indications and contraindications for PBV are summarized in Tables 10, 11 (13, 41). The majority of candidates are symptomatic. For asymptomatic patients, PBV may be indicated. This includes child bearing females, individuals requiring non-cardiac surgical procedures, or patients with severe MS and increased PAH at rest or with exercise (35). Patients with symptomatic MS, PAH, and heart failure may benefit from PBV as a bridge or destination therapy, especially when surgical correction is at high risk. Prophylactic PBV is not warranted for prevention of atrial fibrillation or systemic emboli (35). If a left atrial or left appendage thrombus is found, 3 months of anticoagulation with warfarin is usually recommended. If resolved, then PMB is performed. Otherwise surgery remains an option with or without resolution of the thrombus. Cost should be considered in situations where lower cost surgery is more readily available. Special situations include pregnancy and older patients. Pregnant females with MS usually develop symptoms in the 2nd trimester (mild- 26%; moderate- 38%; and severe- 67%) (35). PBV is usually recommended in the 22-36 week of gestation to minimize radiation. Older patients who develop severe or critical MS are at higher risk given associated comorbidity and other valve involvement, especially functional tricuspid secondary to pulmonary hypertension.

Table 10[26]

Indications

Indications for PBV (American College of Cardiology (ACC) and the American Heart Association (AHA).

Class I recommendations:

- Percutaneous mitral balloon valvotomy is effective for symptomatic patients (New York Heart Association [NYHA] functional class II, III, or IV) with moderate or severe MS and valve morphology favorable for percutaneous mitral balloon valvotomy in the absence of left atrial thrombus or moderate to severe mitral regurgitation (MR) (level of evidence: A)
- Percutaneous mitral balloon valvotomy is effective for asymptomatic patients with moderate or severe MS and

valve morphology that is favorable for percutaneous mitral balloon valvotomy who have pulmonary hypertension (pulmonary artery systolic pressure > 50 mm Hg at rest or > 60 mm Hg with exercise) in the absence of left atrial thrombus or moderate to severe MR (level of evidence: C)

Class IIa recommendations:

- Percutaneous mitral balloon valvotomy is reasonable for patients with moderate or severe MS who have a nonpliable calcified valve, are in NYHA functional class III–IV, and either are not candidates for surgery or are at high risk with surgery (level of evidence: C)

Class IIb recommendations:

- Percutaneous mitral balloon valvotomy may be considered for asymptomatic patients with moderate or severe MS and valve morphology favorable for percutaneous mitral balloon valvotomy who have new onset of atrial fibrillation in the absence of left atrial thrombus or moderate to severe MR (level of evidence: C)
- Percutaneous mitral balloon valvotomy may be considered for symptomatic patients (NYHA functional class II-IV) with mitral valve area greater than 1.5 cm2 if there is evidence of hemodynamically significant MS based on pulmonary artery systolic pressure greater than 60 mm Hg, pulmonary artery wedge pressure of 25 mm Hg or more, or mean mitral valve gradient greater than 15 mm Hg during exercise. (level of evidence:C)
- Percutaneous mitral balloon valvotomy may be considered as an alternative to surgery for patients with moderate or severe MS who have a nonpliable calcified valve and are in NYHA functional class III–IV (level of evidence: C)

Table 11[34, 45, 46]

Contraindications (relative or absolute):

Mild MS MVA 1.5cm2
Moderate to severe MR
Persistent left atrial or left atrial appendage thrombosis
Massive or bicommissural calcification of fused commissures
Need for other open-heart surgery
Contraindications for transseptal catheterization
Severe associated aortic valve disease
Severe organic tricuspid stenosis or severe functional regurgitation with enlarged annulus

There are at least 4 techniques available for PBV: the traditional Inoue balloon[38]; the double balloon[41,42]; the multitrack system, which is a refinement of the double-balloon technique that employs a monorail system requiring only 1 guide wire and allows easier dilation than the standard technique[43], and the Cribier metallic commissurotome or valvulotome[44]. The latter is practical insofar that the device is reusable, though it involves a more complex procedure.

The technical aspects of PBV have been well described[38,45,46]. TEE is usually performed before and during the procedure to determine the presence of left atrial and left atrial appendage thrombus, guiding the catheter placement, as well as determining the suitability of PBV in the presence of commissural calcification. The presence of severe calcification of 1 or both commissures is an independent determinant of success. TEE can guide the catheter across the atrial septum during transseptal puncture at the level of the fossa ovalis, directing the catheter across the mitral valve, and to confirm that the balloon is properly seated across the mitral valve. Both retrograde (transarterial) and antegrade (transvenous/transseptal) approaches have been described. The retrograde approach eliminates the risk of atrial septal defect but carries the risk of potential arterial damage. At present, the antegrade approach with transseptal catheterization is used via the femoral vein or jugular venous route. Recently, RT3DE has been shown to enhance the visualization of the interatrial septum and the assessment of optimal location for puncture, as well as to assess degree of post PBV commissurotomy splitting, leaflet tears, and more accurate assessment of new or worsening MR[35]. Intracardiac ECHO (ICE) is another useful imaging modality that can identify the fossa ovalis, guide placement of

the transseptal puncture sight at the limbus, and assess the left atrial appendage. The ICE catheter can also provide RT3DE images of the structures surrounding the catheter tip, resulting in improved imaging, and excellent spatial resolution[45, 46, 47].

The Inoue balloon technique has been the most commonly employed. After transseptal catheterization, a balloon-tipped catheter is advanced into the left ventricle. One or two exchange guide wires are advanced through the lumen of the balloon-tipped catheter and positioned at the apex of the left ventricle or, less frequently, in the ascending aorta. The balloon-tipped catheter is withdrawn over the guide wires, and the interatrial septum is dilated with the use of a peripheral angioplasty balloon. Finally, the valvotomy balloons are advanced over the guide wires and positioned across the mitral valve (Figure 9).

RESULTS / OUTCOMES

The criteria for the desired end point of PBV includes: MVA >1cm2/m2; complete opening of at least 1 commissure; appearance of increment of MR>1 in a 4 grade system; and the prediction of PBV success related to patient status, anatomy, and team experience[13]. Mortality of PBV is <1%. The complications of PBV requiring urgent surgery or repeat PBV include acute cardiac tamponade, acute or worsening mitral regurgitation, or restenosis, whereas chronic progressive increases in mitral regurgitation requires consideration for elective surgical repair or replacement in 2.5% of cases [34,45,46]. Other complications related to PBV include atrial septal shunting in <2%, and cardiac perforation with tamponade in <1%.The failure rates range from 1% to 17%. This usually results from unfavorable anatomy (e.g., severe atrial enlargement, subvalvular stenosis, or heavy calcification), but most failures occur as a consequence of an unsuccessful transseptal puncture or inability to position the balloon correctly across the mitral valve.

Restenosis after percutaneous mitral valvuloplasty is generally defined as a loss of more than 50% of the initial gain, with a valve area less than 1.5 cm2. The incidence of restenosis after a successful procedure ranges from 2% to 40% at time intervals ranging from 3 to 10 years.

Recent studies have been encouraging, though there remains debate in terms of long-term results when compared to surgery. A reasonable approach to select either PBV or surgery is presented in Table 12[16].

Table 12[16]

Patient Selection in the Choice of Intervention for Relief of Mitral Stenosis

Procedure	*MV Morphology Score*	*Severity of MR*	*Other Valve Lesions*	*Pulmonary Hypertension*
Balloon mitral commissurotomy	<8 ideal <10 acceptable	≤2+	No other valve procedure needed	PA pressures improve postprocedure, even when severely elevated
Open surgical commissurotomy	<8 ideal <10 acceptable	≤2+*	May have other valve procedures or CABG	
Mitral valve replacement	Valve may be calcified and deformed; score not predictive of outcome	MR may be severe	May have other valve procedures or CABG	Higher risk with PA systolic pressure >60 mm Hg

CABG, coronary artery bypass grafting; MR, mitral regurgitation; PA, pulmonary artery.
*Or annuloplasty ring if >2+.

The immediate or early, mid-term, and long-term results or outcomes for PBV have been well recorded[13,26,35,46]. The National Heart, Lung, and Blood Institute (NHLBI) PBV registry report,in 1992, noted the results in 738 patients that underwent PBV. At 30 day follow-up 4% of the patients required mitral valve surgery, 3% died, and 83% were clinically improved. Yet, fewer patients with multivalve disease became asymptomatic. In other studies, the immediate or early results have shown that the MVA increases from a stenotic MVA of 0.7 to 1.1, to a MVA of 1.9 to 2 cm2[32,35]. Vahanian et al.[46] reported 2,773 patients with a mean age of 47 +/- 15 (range 9-86 years). 71% were NYHA class III or IV, and 41% had AF. MR was mild in 39% and moderate in 2%. 27% had calcified leaflets. All underwent the antegrade approach. The MVA increased from 1.0 to 1.9cm2. MVA <1.5cm2 or MR >2 occurred in 11.5%. Technical failure occurred in 1.2%. Mortality was 0.4%. MR>3 occurred in 4.7% with 84% of them requiring subsequent surgery (0.7% urgently). Results at 10 years were: 85% alive, 61% no further procedures, and 56% good functional condition (NYHA I/II). Lung et al.[48], in 1996, reported five-year actuarial rates for global survival with no cardiac-related deaths, and no need for surgery or repeat dilation. The composite endpoint of good functional results were: 93 +/- 4%, 97 +/- 3%, 84 +/- 6%, and 76 +/- 6% respectively. Fawzy et al.[49,] in 2009, noted event free survival: 10 years 88%; 15 years 60%; and 19 years 28%. Multivariate analysis identified ECHO scores <8, and post MVA <1.8 as predictors of restenosis, and ECHO scores >8, with preexisting AF as predictors of combined events.

Palacios et al. (50) observed the predictors of unfavorable PBV long-term outcomes to include: ECHO scores >8; increasing age; prior surgical commissurotomy; NYHA functional class IV; higher post PBV PAP; pre-procedure MR>2; or postprocedure MR >3. Zimmet et al. (51), in 2006, also noted severe MR, and higher ECHO scores as independent predictors of failed PBV, and requiring surgery. Bouleti et al.[52] developed a 13 predictive point score system to assess late functional results up to 20 years after a good immediate result. The factors included age, sex, hear rhythm, valve anatomy, and final mean mitral gradient (mm Hg). The lower the score the better the result.

Song et al.[53], in 2010, looked at long-term outcomes of open cardiac surgery versus PBV. Over a median follow-up of 109 months the observed (unadjusted) event-free was similar in both groups (OHS-159 patients/ 402- PBV patients). The long-term event-free adjusted survivals were better with OHS, especially with ECHO scores >8 [54-56].

Repeat PBV or PBV after previous surgical commissurotomy requires an individualized approach since the anatomic morphology varies[45]. Turgeman et al.[57] reported that patients with mitral restenosis caused by symmetrical commissural refusion obtain better results from repeat procedures compared with patients with restenosis secondary to subvalvular abnormalities, unilateral commissure fusion or bilaterally split commissures.

In summary, PBV is the preferred procedure for patients with moderate to severe MS, non-calcified mitral leaflets, symptomatic or asymptomatic with PAH, and no LA appendage thrombus, scores <8, and no MR >2.The RT3DE score may well be the most predictive modality to employ for valve and subvalvular morphology, residual or worsening MR or overall outcome. Ultimately surgical procedures may be indicated since PBV is primarily a bridge procedure, especially in younger patients with ongoing rheumatic activity and subsequent fibrosis and calcification of the mitral valve leaflets and subvalvular apparatus. The innovative interventional and surgical advances for valve repair and replacement for MR will be discussed further in parts 3 and 4, as well as surgery for the other valve conditions [58].

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