New perspectives by imaging modalities for an old illness: Rheumatic mitral stenosis

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ABSTRACT

Mitral stenosis (MS) is a progressive and devastating disease and most often occurs among young women. Given its considerable prevalence in Mediterranean and Eastern European countries according to the Euro Heart Survey, new imaging modalities are warranted to improve the management of patients with this condition. A wide spectrum of abnormalities occurs involving all parts of this complex structure and causing different grades of MS and/or regurgitation as a consequence of rheumatic affection. Novel imaging modalities significantly improved the assessment of several aspects of this rheumatic destructive process including the morphological alterations of the mitral valve (MV) apparatus, left atrial (LA) function, LA appendage, right and left ventricular (LV) functions, and complications, namely, atrial fibrillation and thromboembolic events. Furthermore, new imaging modalities improved the prediction of outcome of patients who underwent percutaneous balloon mitral commissurotomy and changed the paradigm of patient selection for intervention and risk stratification. The present review aimed to summarize the role of new multimodality, multiparametric imaging approaches to assess the morphological characteristics of the rheumatic MS and its associated complications, and to guide patient management. (Anatol J Cardiol 2020; 23: 128-40)

Keywords: mitral stenosis, rheumatic heart disease, echocardiography, 3-D echocardiography, strain, multimodality imaging

Introduction

Rheumatic fever is the most important cause of mitral valve (MV) disease in low-income countries (1, 2); the prevalence of mitral stenosis (MS) remains high in Mediterranean and Eastern European countries according to the Euro Heart Survey, accounting for 12% of valvular diseases in Europe (3). The importance of this irreversible, progressive disease is severalfold: It usually affects young women, is a threat among women of childbearing age, and is associated with 1%-6% annual risk of thromboembolic events (4). MV has a complex structure with saddle shape annulus, two leaflets with six scallops, commissures, and two papillary muscles attached to both leaflets by numerous cordae tendineae. A wide spectrum of abnormalities occurs involving all parts of this complex structure and causing different grades of MS and/or regurgitation as a consequence of rheumatic affection. Novel imaging modalities significantly improved the assessment of several aspects of this rheumatic destructive process. The present review aimed to summarize the role of new multimodality, multiparametric imaging approaches to assess the morphological characteristics of rheumatic MS and its associated complications, and to guide patient management.

Morphological features

The hallmark of rheumatic MS is commissural fusion. Involvement of subvalvular apparatus with chordal fusion, thickening, and further shortening restricts mobility and increases rigidity of the leaflets. In the later stages of the disease, varying degrees of superimposed calcification worsens leaflet motion. The disease typically progresses from the commissures and the tips of the leaflets to the more proximal parts (body and base) and to the subvalvular apparatus (Fig. 1, Videos 1a-1c).

In degenerative MS, which occurs in older adults, the main mechanism is heavy calcification that starts from the annulus...
and extends toward the bases of the leaflets mostly affecting the posterior leaflet. In the absence of extreme leaflet calcification and thickening, annular calcification alone does not lead to severe hemodynamic consequences because the basal parts of the leaflets are affected more than the tips without commissural fusion (Fig. 2, Video 2).

Radiation-induced MS is a rare clinical condition. It is characterized by fibrosis and calcification of the valve usually extending from the anterior leaflet into the mitral-aortic fibrosa without commissural fusion. The posterior leaflet can be involved as well (Fig. 3, Videos 3a, 3b). After a long latent period following radiation exposure, significant valve dysfunction occurs in 1% of patients with radiation-induced MS at 10 years, in 4% at 15 years, and in 6% at 20 years (5).

Congenital MS is extremely rare and is characterized by supra- or subvalvular rings, annular hypoplasia, double orifice mitral valve (MV), hypoplastic papillary muscle, and parachute MV. Calcification does not usually occur in the valvular or subvalvular apparatus (Fig. 4, Videos 4a-4c) (6).

Assessment of rheumatic MS by 2D and Doppler echocardiography
Classically, the morphological characteristics of the MV can be defined by 2-D echocardiography (2DE) and the mitral valve area (MVA) by 2D planimetry and Doppler evaluation. These methods have several well-known limitations. Doppler evaluations based on mean and peak gradients and pressure half-time are affected by hemodynamic conditions including heart rate, transmitral flow volume, left ventricular (LV), and left atrial (LA) compliances (7). Within the first 48–72 hours following percutaneous balloon mitral commissurotomy (PBMC), pressure half-time and Gorlin calculations are unreliable due to the abrupt changes in mitral gradient and LA compliance. Although the assessment of MVA by 2D planimetry is not influenced by hemodynamic changes, determining

| Parasternal long axis | Basal short axis | Apical two-chamber |
|----------------------|-----------------|-------------------|
| ![Image](image1.png) | ![Image](image2.png) | ![Image](image3.png) |

**Figure 1.** (a–c) Typical features of rheumatic mitral stenosis by 2D transthoracic echocardiography. (a, b) Commissural fusion, leaflet thickening and rigidity and (c) involvement of subvalvular apparatus with chordal fusion, thickening, and shortening (Videos 1a–c)

| Basal short axis | Basal short axis | Apical two-chamber |
|-----------------|-----------------|-------------------|
| ![Image](image4.png) | ![Image](image5.png) | ![Image](image6.png) |

**Figure 2.** (a) Degenerative calcific MV. Note that the calcification mainly involves the annulus (arrow heads) extending toward the body of the leaflets. (b, c) The tips of the leaflets are relatively spared, (arrow) in contrast to rheumatic mitral stenosis, in which the calcification and thickening starts from the tips of the leaflets (Video 2)
the correct orifice cut plane from the LV short-axis view is difficult due to funnel-shaped narrowing (Fig. 5). Proximal isovelocity surface area (PISA) method is technically more demanding and recommended only if pressure half-time and planimetry are inconclusive (8). PISA method assumes that the flow convergence zone is hemispheric on the atrial side, which is not true for MS due to the limited opening angle of the leaflets (9). PISA method requires angle correction for the evaluation of MS, complicating its use. The use of continuity equation assuming that the transmitral flow is equal to the aortic stroke volume is cumbersome and only valid in the absence of significant valvular regurgitations (8).

**Assessment of rheumatic MS by three-dimensional (3D) echocardiography**

3-D echocardiography (3DE) allows detailed and accurate morphological analysis of the entire MV including the leaflets, commissures, annulus, and subvalvular apparatus. Commissural fusion is visualized by 3DE with more precision than 2DE (10), although calcifications are better characterized by 2DE (Fig. 6, Videos 5a, 5b). En face views of MV from either LA or LV perspectives are easily obtained. Both transthoracic and transesophageal (TOE) 3DE provide optimally oriented en face view of the stenotic orifice for planimetric measurement (Fig. 7, Videos 6a-6c) (11). This measurement provides the anatomic valve area, which is slightly higher than the Doppler-derived effective orifice area at the vena contracta level (12). Excellent intra- and interobserver correlations and higher interobserver agreement were found with 3D TOE measurements of MVA (13). 3DE facilitates communication with the operators. Yet, poor acoustic window, severe calcifications of the leaflet tips, inadequate gain settings, and technical expertise of the echocardiographer remain as limitations for planimetric evaluation of MVA by 3DE.
The calculation of the valve area of degenerative calcific MS is more challenging. The MV orifice is irregular, and the narrowest portion is not located at the tips of the leaflets but at the basal region. Therefore, selection of an accurate plane is more difficult than rheumatic MS and makes the use of 3DE crucial (14).

**Associated pathologies with MS**

**Left atrial remodeling**

LA dilatation reflects the hemodynamic burden of MS and is of prognostic importance. LA volume is independently associated with an increased risk for embolic cerebrovascular disease (15) and the development of atrial fibrillation (16), which play a key role in patient management. Linear measurements of the LA are outdated and insufficient because of the asymmetrical enlargement of the LA (17). LV and LA axes are not aligned. LA dilatation should be quantified using volumetric methods such as the modified Simpson’s biplane method of discs from LA focused views or by 3DE.

LA volumes derived from 2DE are typically smaller than the volumes derived from multidetector computed tomography (MDCT) or cardiac magnetic resonance (CMR) (18, 19). However, real-time 3DE measurements of LA volumes have been validated.

**Figure 5.** Imprecise stenotic MVA depending on the 2D transverse cut plane due to a funnel-shaped stenotic orifice

**Figure 6.** Commissural (a) fusion and (b) calcification by 2DE versus 3DE. Note that commissural fusion is more precisely appreciated by 3DE; however, calcifications are more easily appreciated by 2DE (Videos 5a, 5b)

**Figure 7.** Stenotic MV (a) from the LA surgeon’s view, (b) from the ventricular perspective, (c) 3D parasternal long axis cut plane showing chordal thickening and fusion, and (d) flexislice from 3D dataset to obtain the optimal en face view of the MVA for measurement by planimetry (Videos 6a-6c)

AML - anterior mitral leaflet, PML - posterior mitral leaflet
against MDCT and CMR (20, 21) and are more accurate and reproducible than 2DE (19). LA phasic function can be assessed by means of volume changes over the cardiac cycle or strain and strain rate by quantifying LA reservoir, conduit, and booster pump functions (Fig. 8, 9). Early alterations in LA phasic function can increase the hemodynamic burden and risk imposed by MS. The LA function deteriorates before an overt LA dilatation occurs (22). LA remodeling also includes interstitial fibrosis, which correlates with LA dilatation, and decreases LA reservoir function (23). Such structural and functional changes of the LA can lead to a reduction in LA flow dynamics and blood stagnation and trigger atrial fibrillation and thrombus formation (16, 24, 25).

**Left atrial appendage morphology and function**

LA enlargement in association with MS causes blood stasis and thrombus formation not only in the LA but also in the LA appendage (26). In those with rheumatic MS, thrombi develop more frequently in patients with LA than those with nonvalvular atrial fibrillation. LA appendage is best visualized with TOE to exclude thrombus upon suspicion or before PMBC. Although 3DE is sometimes helpful in diagnosing thrombus, it cannot provide a precise description of the tissue properties and is not reliable for differentiating pectinate muscles from thrombi. The most valuable approach is to use multiplane images extracted from the 3D TOE dataset. This approach allows visualization of all parts of an irregular appendage (Fig. 10). If the spontaneous echocontrast in the LA appendage is extremely dense, it may obscure a threatening thrombus. In such instances, contrast agents or MDCT should be used to exclude thrombus (27).

3D TOE is also crucial for the assessment of the LA appendage orifice with clear delineation of its shape, dimensions, and surrounding structures like pulmonary vein, MV, and circumflex artery whenever LA appendage occlusion is planned (Fig. 11).

**Left ventricular dysfunction**

LV dysfunction occurs in patients with MS due to the chronic reduction in preload (28). Even with preserved EF, subclinical LV systolic dysfunction can be detected by strain imaging and 3D methods (29). Favorable changes after successful PBMC can also be tracked by strain imaging, which can accurately determine a reduction in LV diastolic filling rather than irreversible structural abnormality and can help decrease LV mechanical performance in patients with severe MS (Fig. 12) (30).

**Tricuspid valve (TV) dysfunction and right ventricular (RV) dilatation**

Severe MS can lead to secondary pulmonary hypertension (PHT). Long-standing PHT causes tricuspid annular dilatation...
and right ventricular (RV) remodeling, which in turn beget tricuspid regurgitation (TR) by causing papillary muscle displacement and tethering of the tricuspid valve (TV) leaflets (Fig. 13a-13d, Video 7) (31). In patients with rheumatic MS, TR is usually secondary to PHT. TV is rarely affected by the rheumatic process. However, multivalvular rheumatic process may occur and should be carefully described and quantified to optimize the patient outcome. Commissural fusion, leaflet thickening, and chordae thickening and fusion can be visualized to confirm the rheumatic process affecting the TV, even more frequently than previously thought by means of 3DE (Fig. 14, Video 8). 3DE can be used for quantifying the stenotic TV area by direct planimetry from an optimally oriented perpendicular cut plane obtained by multiplanar reconstruction (Fig. 14).

By contrast, functional TR requires a comprehensive assessment of tricuspid annulus, papillary muscle displacement, leaflet tethering, tenting, and RV remodeling. Tricuspid annular dilatation, as measured by 2DE from the apical four-chamber view in everyday clinical practice, does not quantify the correct dilatation that typically occurs from the anteroseptal commissure to the anterolateral commissure. With 3DE, one can correctly quantify the tricuspid annular dilatation from the surgical view (Fig. 13b). Diagnosis of rheumatic TV involvement and correct measurement of the tricuspid annular dilatation are both important to guide the surgeons and to plan timely interventions addressing the underlying TV pathology in order to prevent clinical deterioration during follow up, because many of these patients develop severe TV dysfunction and intractable right heart failure despite the normal functioning of mitral prostheses later in the disease course.

Figure 10. LA appendage by 3D TOE. Note the thrombus captured on the flexislice display (arrow), which was not visible on conventional cut planes.

Figure 11. Optimal en face view of LA appendage orifice on 3D volume rendered display and correct measurement planes by flexislice.

Figure 12. LV function by longitudinal strain before and after percutaneous balloon mitral commissurotomy. Note the improvement in strain from $-17.6\%$ to $-21.2\%$ despite normal ejection fraction before and after the procedure.
RV dilatation is best assessed by 3D volume quantification due to the peculiar shape of this chamber wrapping around the LV. The assessment of RV volumes by 3DE has been tested against CMR. 3DE tends to underestimate RV volumes compared with CMR. However, its reproducibility was validated and serves as an accurate means of assessing RV volumes and functions (32). Subclinical RV dysfunction occurs in the early stages of MS and can be detected by strain quantification at rest (33). Quantification of RV dysfunction, before significant dilatation occurs, has potential implications for patient management as it is not a simple bystander of MS but reflects the hemodynamic burden and impacts the prognosis of patients with rheumatic MS (34).

**Role of transoesophageal echocardiography**

The use of TOE is recommended for the assessment of MS in patients with poor transthoracic acoustic windows, for pre-procedural assessment of MV morphology before PBMC, and to rule out thrombi in the LA and/or LA appendage (35). TOE with or without 3DE is definitely superior to transthoracic echocardiography in terms of visualizing morphological abnormalities. 3D TOE allows excellent evaluation of commissural fusion and MVA by planimetry (Fig. 7) (36).

3D TOE is useful in visualizing the full delineation of LA appendage and interatrial septum morphology for planning PBMC. Guidance of PMBC by 3D TOE secures and facilitates safe trans-septal puncture, helps to orient the balloon to the stenotic orifice, and decreases or even prevents radiation exposure during the procedure, which is very important considering the patients’ young age and female gender preponderance with possible late diagnoses during pregnancy (Fig. 15) (37, 38).

**Role of stress echocardiography**

In some patients, symptoms may be discordant with the severity of MS. Stress echocardiography is mainly useful for (1) asymptomatic patients with echocardiography findings of severe MS or (2) symptomatic patients with echocardiography findings of mild or moderate MS. Stress echocardiography helps evaluate the true hemodynamic burden of MS. The estimation of pulmonary artery pressure during stress echocardiography (exercise or dobutamine) helps clinicians decide whether other types of interventions or medical therapy should be provided (35, 39, 40). As the heart rate increases with exercise, the diastolic transmural gradient increases exponentially as well as the LA pressure; consequently, pulmonary capillary wedge pressure increases due to the fixed stenotic mitral orifice. Exercise stress echocardiography (preferentially supine bicycle) is more conclusive from a pathophysiologic standpoint than pharmacological stress echocardiography for the assessment of MS severity and its hemodynamic burden; it is the preferred modality and uncovers symptoms in almost 50% of patients with moderate-to-severe MS who are asymptomatic at rest (41). Dobutamine stress echocardiography is an alternative only if the patient is unable to perform exercise (40). If the MV morphology is suitable for PBMC procedure, patients without symptoms but with objective significant limitation on exercise may be considered for PBMC (40). PBMC can be considered in patients with a valve area of more than 1.5 cm$^2$ who show a transmitral mean gradient of >15 mm Hg, pulmonary artery wedge pressure of $>25$ mm Hg, or pulmonary artery systolic pressure of >60 mm Hg during exercise (35). When a dobutamine stress test is performed, the evaluation of pulmonary pressure is not helpful. A mean transmural gradient more than 18 mm Hg during the stress test shows the high probability of clinical deterioration or the need for surgery (42).
Echocardiography for percutaneous mitral balloon commissurotomy

The major goal of PBMC is to achieve a complete bilateral commissural opening. Therefore, commissural fusion is a prerequisite for PBMC. Wilkins score has been the most widely used scoring system until recently to assess the anatomical suitability of the valve for PBMC (43). Wilkins score takes into account leaflet mobility, thickness, calcification, and involvement of subvalvular apparatus; it is used to grade each of these components from 1 to 4. From each of the components of the Wilkins score system, valvular thickening has the highest correlation with changes in MV area. An echo score of less than 8 is associated with lower rates of restenosis and better survival from redo PBMC and MV replacement. However, patients with a score of more than 12 are less likely to have a satisfactory result and are referred for surgery. Patients with an echo score ranging from 8 to 12 need more detailed morphological and clinical evaluation (44). Despite a significant negative correlation between the absolute change in MV area achieved after PBMC and the total echo score, the relationship is scattered and the score remains relatively imprecise for predicting the final result from PBMC. Approximately 40% of patients with an echo score of more than 8 demonstrated a good outcome (45). Wilkins score has additional limitations: lack of precise delineation of commissural involvement, localization of calcium deposition (valvular or commissural), uneven distribution of pathologic abnormalities, discrimination of relative contribution of each variable (no weighting of variables), and lack of inclusion of TOE and 3DE findings. These morphological parameters impact the success of PBMC (46). PBMC is unlikely to increase the MV area if commissural fusion is absent or the commissures resist splitting due to the presence of calcification (Fig. 16). Not only the extent of calcification, but also the localization of calcification at the commissures, uneven distribution of commissural fusion, and irregular distribution of calcification on the leaflets are important for the success of PBMC (46-48). Because irregular calcifications may cause tears on the leaflet, the instability of the balloon during inflation and asymmetrical commissural involvement may result in excessive splitting of the less or noncalcified commissure. Patients with low Wilkins score but unfavorable calcifications have significantly lower rates of success; however, a high Wilkins score does not preclude the possibility of a satisfactory result. PBMC can be an option if there is no commissural calcification, despite relatively high Wilkins scores (47, 49).

Consequently, other scoring systems have been proposed to improve patient selection for PBMC. Cormier score divides the patients into three groups depending on leaflet mobility, calcification, and affection of subvalvular apparatus: group 1, pliable leaflets and mild chordal thickening (chordae >10 mm long); group 2, pliable mitral leaflets and extensive subvalvular disease (thickened chordae <10 mm); and group 3, calcified valves confirmed by fluoroscopy (50). Many other 2DE scoring systems have been proposed, but none of them was shown to be superior to other scoring systems except Nune’s and Anwar’s scoring systems (51, 52).

In Nune’s scoring system (51), the quantification is based on the assessment of commissural (a)symmetry as the ratio of leaflet area on either side of the minor dimension of the valve in the short-axis view and the leaflet displacement by measuring the maximum apical displacement of the leaflets relative to the annulus in the apical four-chamber view in addition to the assessment of subvalvular involvement (Fig. 17): MVA ≤1 cm² is assigned 2 points, maximum displacement of leaflets ≤12 mm is assigned 3 points, commissural area ratio ≥1.25 is assigned 3 points, and finally subvalvular involvement 3 points. Three risk groups are defined based on the following scores: 0–3 (low), 4–5 (intermediate), and 6–11 (high) and with observed suboptimal PBMC results of 16.9%, 56.3%, and 73.8%, respectively. A net reclassification improvement of 45% over Wilkins score has been reported with this scoring system, which was found particularly valuable in patients who were in the intermediate-risk group (score, 8–12) by Wilkins score.
The new scoring system proposed by Anwar et al. (52) includes a morphologic evaluation of the MV by 3DE with a more detailed anatomical approach. Each scallop is scored separately for calcification, thickness, and mobility as 0 or 1. Importantly, calcifications of A1, A3, P1, and P3 (next to comissures) are given a score of 2 as commissural calcification affects commissural splitting and

**Figure 16.** Calcification patterns: (a, b) Asymmetric commissural calcification, (c) asymmetrical bi-commissural and irregular leaflet calcification, (d) diffuse leaflet calcification with commissural sparing, and (e) diffuse severe calcification of leaflets and commissures

**Figure 17.** Assessment of the asymmetry of commissural involvement and maximum displacement of leaflets according to Nune’s scoring system (53). Symmetry denotes commissural area ratio.

| Commissural area ratio | Leaflet displacement |
|------------------------|----------------------|
| Perpendicular bisector of intercommissural line |
| Symmetry = \( \frac{\text{Area max}}{\text{Area min}} \) |
is a strong predictor of grade >2 mitral regurgitation after PBMC (47, 53). The subvalvular apparatus is also divided into the following three levels: proximal, middle, and distal segments, each being scored for thickness (0, 1) and separation (0, 1, 2). Total 3D score ranges from 0 to 31 points. Mild involvement is scored with <8 points, moderate with 8–13 points, and severe with ≥14 points (52). The strengths of the latter two scoring systems to predict immediate results from PBMC and long-term outcome over Wilkins score relies on the incorporation of commissural morphology and better definition of chordal thickening and fusion, which are best assessed with 3D TOE and clearly underestimated by Wilkins score.

Finally, due to the rapid changes in loading conditions and atrial septal defect immediately following the PBMC, pressure half-time evaluation is prone to errors. 3DE facilitates immediate evaluation of the MVA by planimetry and assessment of commissural splitting, leaflet tears, the site, and degree of new mitral regurgitation in the catheterization laboratory more precisely and accurately than 2DE.

**Multidetector computerized tomography (MDCT)**

High resolution of MDCT favors its use as an alternative or complementary method to evaluate the morphological properties of rheumatic MS in patients with poor acoustic windows (54). One can utilize different views of ECG-gated MDCT in contrast to the delineate characteristics of the MV apparatus and to measure the MVA accurately (55). MDCT provides a 3D acquisition of the whole heart and multiplane reconstructions as well; thus, a parasternal short-axis view of the MV orifice at the tips of the leaflets can be obtained for direct planimetric measurement of the MVA (54). A short-axis diastolic view can nicely show the thickening of the MV leaflets with commissural fusion and calcification. A two-chamber view displays the valve with the characteristic hockey-stick appearance. MDCT is sensitive and can accurately identify calcifications in the leaflets and commissures (56). Moreover, MDCT can show the typical secondary signs of MS including LA enlargement with an anatomically normal left ventricle, pulmonary vein dilatation, pulmonary venous hypertension, and RV dilatation (56). Additionally, MDCT accurately detects thrombus in the LA or LA appendage by late contrast images (Fig. 18). In addition, LA appendage morphology, the angle of the LA appendage bending, and the diameter of the orifice can be accurately measured by MDCT (57).

**Cardiac magnetic resonance**

If transthoracic echocardiography is suboptimal or inconclusive and TOE is contraindicated, CMR can be useful. Good demonstration of the restricted MV leaflets can be achieved particularly on the LV outflow tract view. Direct planimetric measurement of the stenotic orifice area by CMR correlates strongly with the pressure half-time method (58). For an accurate measurement of the MVA, the image plane should be positioned at the tips of the MV and multiple parallel thin slices should be taken; otherwise, misalignment may result in significant overestimation (59). CMR also enables visualization of LA appendage morphology and thrombus based on intrinsic tissue characteristics and anatomic appearance. Contrast-enhanced CMR is helpful for assessing thrombus composition and chronicity as a complementary technique to TOE and MDCT (60). Another futuristic approach applied is the phase-contrast imaging to derive velocities, pressure half-time, and definition of the MVA; however, it has to be carefully

![Figure 18. LA appendage by MDCT. (a) No thrombus and (b) presence of thrombus within the LA appendage seen on late phase contrast (Asterix) (Courtesy of Dr. Tuncay Hazirolan)](image)
performed, because low temporal resolution of CMR may cause underestimation of peak velocities (58, 61). RV and LA remodeling is optimally measured by CMR. CMR is also useful for detecting LA fibrosis (Fig. 19) (25). However, CMR remains the third choice if echo and MDCT are inconclusive.

**Conclusion**

In conclusion, state of the art approach to the management of patients with rheumatic MS and the new scoring systems requires the use 3DE and multimodality imaging to ensure a thorough assessment of the MV morphology and MS severity. TOE is an integral part of the assessment of rheumatic MS. Stress echocardiography, MDCT, and CMR are complementary tools for the assessment of morphological characteristics of the stenotic MV and their associated structural abnormalities.

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