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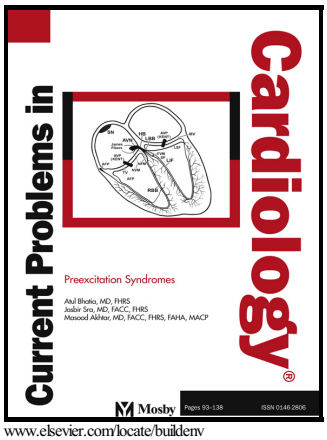

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Ahmet Afşin Oktay, Yvonne E. Gilliland, Carl J. Lavie, Stephen R. Ramee, Sangeeta Shah, Michael E. Cash, Homeyar Dinshaw, Salima Qamruddin

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Echocardiographic Assessment of Degenerative Mitral Stenosis: A Diagnostic Challenge of an Emerging Cardiac Disease

Authors: Ahmet Afşin Oktay, Yvonne E. Gilliland, Carl J. Lavie, Stephen R. Ramee, Sangeeta Shah, Michael E. Cash, Homeyar Dinshaw, Salima Qamruddin

Affiliations: Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute; Ochsner Clinical School - The University of Queensland School of Medicine, New Orleans, Louisiana

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Address for correspondence:

Salima Qamruddin, MD

Department of Cardiovascular Diseases
John Ochsner Heart and Vascular Institute
University of Queensland School of Medicine
1514 Jefferson Hwy., New Orleans, LA 70121

Phone: +1 (504) 842-2522; **Fax**: +1 (504) 842-5960

Email: salima.qamruddin@ochsner.org

ABBREVIATIONS AND ACRONYMS:

AF = Atrial fibrillation

AMC = Aortomitral curtain

AR = Aortic regurgitation

AS = Aortic stenosis

CAD= Coronary artery disease

CKD = Chronic kidney disease

CT = Computed tomography

CVD = Cardiovascular disease

CW= Continuous wave

DMS= Degenerative mitral stenosis

ESRD = End stage renal disease

HTN= Hypertension

LA = Left atrium / atrial

LV = Left ventricle / ventricular

LVOT = Left ventricular outflow tract

MAC = Mitral annular calcification

MR = Mitral regurgitation

MS = Mitral stenosis

MV = Mitral valve

MVA = Mitral valve area

PA = Pulmonary artery/arterial

PHT = Pressure half time

PISA = Proximal isovelocity surface area

PW= Pulse Wave

RMS = Rheumatic mitral stenosis

RVOT = Right ventricular outflow tract

TAVR = Transcatheter aortic valve replacement

TMPG =Transmitral pressure gradient

TMVR= Transcatheter MV replacement

TTE = Transthoracic echocardiography

TEE = Transesophageal echocardiography

VHD = Valvular heart disease

VTI = Velocity time integral

2D = Two-dimensional

3D = Three-dimensional

ABSTRACT:

Degenerative mitral stenosis (DMS) is characterized by decreased mitral valve (MV) orifice area and increased transmitral pressure gradient (TMPG) due to chronic non-inflammatory degeneration and subsequent calcification of the fibrous mitral annulus and the MV leaflets. The 'true' prevalence of DMS in the general population is not well known. DMS predominantly affects elderly individuals, many of whom have multiple other comorbidities. Transcatheter MV replacement techniques, although their long-term outcomes are to be tested, have been gaining popularity and may emerge as an optimal treatment options for patients with DMS.

Echocardiography is the primary imaging modality for evaluation of DMS and related hemodynamic abnormalities such as increased TMPG and PA pressure. Classic echocardiographic techniques used for evaluation of MS (PHT, PISA, Continuity equation, MVA planimetry) lack validation for DMS. Direct planimetry with 3D echocardiography and color flow Doppler is a reasonable technique for determining MVA in DMS. Cardiac computed tomography is an essential tool for planning potential interventions or surgeries for DMS.

This article reviews the current concepts on mitral annular calcification and its role in DMS. We then discuss the epidemiology, natural history, differential diagnosis, mechanisms and echocardiographic assessment of DMS.

"To raise new questions, new possibilities, to regard old problems from a new angle require creative imagination and marks real advance in science." Albert Einstein[1]

OVERVIEW AND BACKGROUND

Mitral stenosis (MS) is characterized by reduced valve orifice area and increased resistance to diastolic transmitral flow due to pathological changes in the structure and function of the mitral valve (MV). This process leads to a rise in the left atrial (LA) and pulmonary arterial (PA) pressures and eventually a reduction in cardiac output.[2] Rheumatic fever is the predominant cause of MS worldwide, although its frequency has significantly declined in the developed countries.[3]

The main pathological changes observed in rheumatic MS (RMS) are commissural fusion, thickening at the leaflet tips, chordal shortening and restricted mobility of the posterior MV leaflet (with preserved mobility of the anterior MV leaflet in earlier stages).[4] Historically, RMS has been extensively studied and this has led to broadened understanding of this disease. Several factors make RMS relatively easily recognizable in clinical practice. These include presentation at younger ages (symptoms are less likely to be confused with comorbidities), pathognomonic physical exam findings (opening snap with diastolic rumble, though it may not be heard in severe RMS) and easy recognition with echocardiography.

Contrary to RMS, non-rheumatic causes of MS, such as degenerative MS (DMS) have been considered to be rare. And they have received limited attention from clinicians and scientist up until recently. Significant improvements in longevity and aging of the general population have increased the prevalence of degenerative valvular heart disease (VHD). In contrast to the extensive knowledge on the natural history of degenerative aortic stenosis (AS), DMS remains a relatively ill-defined disease process.

In the literature, 'calcific MS' and 'MS due to mitral annular calcification (MAC)' have also been used to refer to DMS. DMS is usually characterized by MAC, and thickening and calcification of the MV leaflets. Contrary to RMS, DMS predominantly affects the base of the leaflets while the leaflets tips and commissures are usually spared.[4] The narrowest part of the orifice is often at the base of the leaflets instead of the tips. Recognition and diagnosis of DMS have been a challenge for clinicians mainly due to lack of validated echocardiographic parameters to quantify the degree of MS and the presentation of the disease usually in elderly patients who commonly have other symptomatic cardiac and non-cardiac conditions. Treatment of DMS has also been a challenge for several reasons such as the unavailability of medical therapies to prevent progression and delay the need for interventions and no benefit from percutaneous mitral balloon valvuloplasty or surgical commissurotomy. Moreover, surgical MV replacement have not been extensively used in this disease because of technical difficulties and high risk for complications of surgery in the presence of MAC and poor surgical candidacy of patients due to advanced age, debility and/or presence of multiple comorbidities.[5–7] Some innovative surgical techniques such as supra-annular insertion of a prosthesis or the use of a felt patch around the orifice as an anchor for prosthesis have been reported.[8,9] More recently, transcatheter MV replacement (TMVR) with "off-label" use of transchateter aortic valve replacement (TAVR) devices in DMS have been described **(Figure 1)**.[10]

Improvements in echocardiographic evaluation of DMS is essential for patient selection, timing of interventions, imaging guidance during procedures and post-procedure follow up. The revolutionary changes in the management of degenerative AS in the recent decade remind us that, superior interventional or surgical outcomes can only be achieved with parallel improvement in imaging modalities.

The aim of this review is to provide a comprehensive and contemporary update on DMS with a special focus on mechanisms, epidemiology, natural history and echocardiographic evaluation of DMS.

MITRAL VALVE ANATOMY

The MV apparatus consists of four key components: mitral annulus, MV leaflets, the chordae tendineae and papillary muscles. Abnormalities in any of these structures can lead to dysfunction of the MV. The mitral annulus is the anatomically ill-defined fibrous tissue at the juncture of the LA, left ventricle (LV) and MV leaflets. The mitral annulus resembles a kidney bean in two-dimensional (2D) images. In three-dimensional (3D) images, it has a saddle shape with anterior (aortic) and posterior aspects elevated compared to the medial and lateral (commissural) portions **(Figure 2)**.[11–13] This saddle shape of the annulus has been shown to reduce the mechanical stress exerted on the MV leaflets.[14] In adults, 3D area of the mitral annulus is approximately 10 cm^2 (range: 7 cm^2 – 12 cm^2).[15] The mitral annular area may change 20% to 42% between systole and diastole.[11]

The MV has anterior and posterior leaflets with the coaptation line from an anterolateral to posteromedial direction. The surface area of the MV leaflets is approximately 50% larger than the mitral annular area. This is essential for prevention of mitral regurgitation (MR). The anterior MV leaflet is usually larger than the posterior MV leaflet and has a traphezoid shape. The posterior MV leaflet is crescentic shaped and occupies two thirds of the annular circumference.[11]

Transthoracic echocardiography (TTE) is the primary imaging modality for evaluation of MV geometry, morphology and function. Transesophageal echocardiography (TEE), with the improved spatial resolution and lower rate of acoustic shadowing, provides a superior and more precise assessment of MV lesions.[16]

MITRAL ANNULAR CALCIFICATION

MAC is a chronic degenerative non-inflammatory process involving the fibrous mitral annulus and resulting in its progressive calcification.[17] MAC, by itself, does not cause any symptoms. Therefore, it is most commonly encountered as an incidental finding during evaluation of pulmonary diseases or other cardiovascular diseases (CVD).[18] Nevertheless, MAC has several prognostic clinical implications and it has been associated with increased risk of atherosclerosis,[19] coronary artery disease,[20] ischemic stroke,[21] atrial fibrillation (AF),[22] conduction system disorders[23] and mortality from CVD.[24]

The prevalence of MAC varies depending on the characteristics of the population studied and the diagnostic imaging modality utilized. The prevalence of MAC (computed tomography [CT] detected) was reported as 9% in the Multiethnic-Study of Atherosclerosis, a community based study of adults, ages 45–84 years old, without apparent CVD.[25] In elderly individuals (>65 years of age) its frequency increases to 42%.[26] Risk factors for MAC include older age, female gender, white race, chronic kidney disease (CKD), hypertension, diabetes mellitus, LV hypertrophy, increased body mass index, cigarette smoking and increased level of systemic inflammation.[25,27–29] Patients with CKD and particularly end-stage renal disease (ESRD) tend to develop MAC at younger ages and with a more rapid rate of progression compared to individuals with normal renal function.[24,30] The prevalence of MAC in dialyzed patients has been reported as 44% to 64%.[31,32]

Multiple pathophysiologic mechanisms play a role in the development of MAC. These include abnormalities in calcium and phosphorus metabolism, increased hemodynamic stress on the MV and atherosclerosis. [17–19] Increased prevalence of MAC in patients with MV prolapse have been attributed to the annular trauma secondary to the excess tension caused by redundant hypermobile MV leaflets.[33] A genetic contribution to the risk of MAC has also been described. A genome-wide association study

revealed an association between MAC and genetic polymorphisms near the pro-inflammatory gene IL1F9.[34]

Echocardiographic Evaluation of Mitral Annular Calcification

MAC is a common finding on echocardiography. There is no standardized echocardiographic definition of MAC or criteria to grade its severity. Parasternal long- and short-axes are the best views for detection of MAC, but it can also be visualized in apical views. On M-mode echocardiography, MAC is appreciated as an echo dense band beneath the posterior MV leaflet that moves in parallel with the LV posterior wall. On 2D echocardiography, it typically presents as a bright shelf-like irregular echodensity with associated acoustic shadowing at the angle of the posterior MV leaflet and atrio-ventricular groove **(Figure 3)**.[18]

In epidemiologic studies utilizing echocardiography, the severity of MAC was quantified based on either the maximal thickness of echodensity (>4 mm thickness defines severe MAC)[35] or the extent of mitral annular involvement on parasternal short-axis view (focal calcification in the mitral annulus defines mild MAC and marked calcification involving more than half of the circumference of the mitral annulus or intrusion of LV inflow tract with calcification defines severe MAC).[26]

Several limitations exist in the echocardiographic assessment of MAC. Echocardiography has relatively low specificity for distinguishing calcium from dense collagen[25] and its quantification of calcium is limited to visual scoring which is associated with significant variability due to reflection and diffraction of ultrasound waves.[36] In addition, the standard parasternal short-axis view, which is usually used to quantify the severity of MAC, does not visualize the anterior mitral annulus because it is not in the same plane with the posterior mitral annulus **(Figure 3-B)**. This may result in missing the anterior annular calcification and underestimating the severity of MAC.[32]

Cardiac CT Evaluation of Mitral Annular Calcification

CT is considered to be superior to echocardiography in demonstrating the location and extent of MAC.[18] It can provide better distinction of calcification and more complete visualization of the mitral annulus **(Figure 4)**. On CT, MAC is defined by an Agatston score (a standardized calcium quantification score on cardiac CT) > 0 at the LA and LV junction. Agatston score can also be used to quantify the severity of MAC, though there are no standardized cut-off values for grading.[37] MAC is usually detected as an incidental finding on CT scans of the abdomen or chest. More detailed evaluation of MAC can be achieved with dedicated electrocardiography-gated CT scans. Use of intravenous contrast material during CT scan can provide better visualization of the MV leaflets and myocardium.[38] Thus, CT with intravenous contrast can detect calcification of the MV leaflets and subvalvular apparatus and myocardial extension of calcification.[38] Estimation of mitral annular area is crucial for success of percutaneous MV interventions and this information can be obtained with CT **(Figure 4-B)**. Moreover, electrocardiography-gated contrast enhanced CT scan can provide reproducible estimates of the MV area (MVA) with use of a planimetry method. MVA obtained with CT-planimetry strongly correlates with the values obtained with cardiac catheterization (Gorlin formula)[39] or TTE using pressure half time (PHT)[39] or 2D planimetry methods.[40] It should be noted that CT slightly overestimates MVA (by ~0.15 cm^2) compared to echocardiographic planimetry or cardiac catheterization.[39] The superior imaging features makes CT an essential tool at the planning stage of potential interventions or surgeries for DMS.[17]

Distribution of Calcification

Epidemiologic studies utilizing M-mode or 2D echocardiography have traditionally suggested that, MAC predominantly affects the posterior annulus and involvement of the anterior annulus is extremely rare.[41] Data from more recent studies utilizing multimodality imaging have demonstrated that

involvement of the anterior annulus is not as rare as it was previously thought. A recent retrospective study on patients ≥ 65 years of age assessed the frequency of calcium deposits in different segments of the mitral annulus using non-contrast CT scan images performed for other clinical indications. The authors observed isolated posterior annulus calcification in 33%, isolated anterior annulus calcification in 5%, and both the anterior and posterior annulus calcification in 11% of the patients.[37] Detection of anterior MAC **(Figure 4-A)** carries significance in regards to risk of MS and presence of anterior MAC might be a better predictor of smaller MVA compared to posterior MAC.[36]

Mitral Annular Calcification and Mitral Valve Function

Recent studies, particularly with the help of multimodality imaging, have broadened the general understanding of mitral annular function and the impact of MAC on MV function and efficiency. Normally, all the components of the MV (the leaflets, annulus and subvalvular apparatus) function as a unit. The mitral annulus is a very dynamic structure and its shape changes throughout the cardiac cycle. In early systole, normally functioning mitral annulus contracts, particularly along the antero-posterior diameter, and accentuates its saddle shape due to descent and folding along the intercommissural diameter. These motions contribute to early approximation, coaptation and sealing of the MV leaflets and reduction of annular area and leaflet stress.[12,14,42]

Pressman et al. evaluated the mitral annular function using 3D echocardiography in individuals with varying degrees of MAC and age- and sex-matched controls.[12] The subjects were free of any other VHD. The study demonstrated that the behavior of the mitral annulus throughout the cardiac cycle was significantly different in patients with moderate and severe MAC compared to control subjects. MAC was found to be associated with impaired contraction of the annulus in systole and a mildly larger and flatter annulus throughout the cardiac cycle. The mild enlargement of the mitral annulus was mainly attributed to its decreased contraction during systole. Overall, the findings suggested that moderate and

severe MAC, by impairing annular dynamics, can cause inefficient blood flow through the LV. The results of the study also challenged the traditional assumption that mitral annular narrowing is the main cause of the increased pressure gradient across the MV in patients with MAC.

The calcification in the mitral annulus does not respect the annular boundaries and it usually extends into the LV myocardium, LA and/or onto the MV leaflets.[43] Involvement of the MV leaflets appear to contribute to MS and valve dysfunction observed in patients with MAC. Movva et al. assessed the relationship of MAC with leaflet motion and trans-mitral pressure gradients (TMPG) in a cohort of 75 patients with ESRD.[32] The authors determined the degree of MS based on TMPG which was estimated using mitral inflow spectral Doppler. Sixty-four percent of the study participants were found to have some degree of MAC. Among the patients with MAC, 75% had moderate to severe calcification, 58% had extension of calcification more than halfway onto at least one of the leaflets and 62% had protrusion of calcification beyond the mitral annulus. None of the patients with mild MAC were found to have pressure gradient across the MV, while 58% of the patients with moderate and severe MAC did. MS was found to be significantly associated with the severity of calcification and extension of calcification beyond the mitral annulus or onto the MV leaflets. Extension of calcification more than halfway onto the MV leaflet(s) was the strongest predictor of restricted leaflet motion. In addition, presence of calcium in an annular segment was associated with a reduced opening angle of the attached leaflet segment.

RADIOTHERAPY INDUCED MITRAL VALVE DISEASE

Radiotherapy induced MV disease is a form of VHD with distinct pathophysiologic and imaging features and it shares some common features with degenerative MV disease. A good grasp of some general features of this condition is crucial in approaching patients with suspected degenerative MV disease.

Radiotherapy induced VHD is a dose-dependent late complication of radiation for thoracic malignancies such as lung cancer or Hodgkin's disease. Clinically significant VHD manifest >20 years after exposure to radiation and predominantly affects left sided valves.[44] Valvular regurgitation is more frequently seen with radiation induced VHD, although AS and MS have also been reported. The hallmark findings of radiation induced MS are severe MAC (predominantly the anterior annulus), thickening and calcification of the aortomitral curtain (AMC), anterior MV leaflet and aortic valve.[4, 30] The poster MV leaflet has been reported to remain mobile in some cases. Radiation-induced MS typically also differs from RMS. It typically affects the base or mid-body of the MV leaflets and does not affect the subvalvular apparatus or cause commissural fusion.[45] It should be kept in mind that restrictive cardiomyopathy may accompany radiation induced VHD in severe forms.[38]

AORTOMITRAL CURTAIN AND MITRAL VALVE FUNCTION

The AMC is defined as the fibrous tissue between the anterior mitral annulus and aortic valve annulus at the level of left and non-coronary cusps. There is now growing evidence that the dynamics of aortic and mitral annuli are interdependent throughout the cardiac cycle and the mitral and aortic coupling is an essential component of the normal cardiac physiology. The AMC, as an anchor affecting the function of both valves, plays a critical role in mitral-aortic valvular coupling. The dynamic nature of the angle between aortic valve and MV appears to contribute to the blood flow through the LV outflow tract (LVOT).[46] Structural abnormalities in the AMC appear to have prognostic consequences. In fact, a retrospective study on a patient population with radiation induced cardiac disease who underwent cardiothoracic surgery identified increased thickness of AMC as an independent predictor of mortality.[47] Two possible explanations for this association were as follows. The thicker AMC may reflect overall advanced CVD or it may signify a causative relationship between thickened AMC and adverse surgical outcomes.

The relationship between MAC and structure and function of the AMC has not been studied. A recent study reported the frequency of AMC calcification as 15.8% among AS patients who were referred for TAVR.[48] These results suggest that AMC thickening and calcification may not be limited to the patients with radiation induced heart disease but can be seen as a part of age-related degenerative process. We need further research to determine the extent of AMC involvement in patients with anterior MAC and to explore the possible contribution of AMC calcification and dysfunction in DMS.

DEFINING SEVERE MITRAL STENOSIS

In simple terms, severe MS is defined as the degree of stenosis at which MS symptoms (exertional dyspnea and decreased exercise tolerance being the most common) would occur and an intervention for the MV would improve these symptoms.[5] Worsening degrees of MS result in a cardiac output level which is subnormal at rest and fails to increase during exercise.

The normal MVA at the tips is 4.0 to 5.0 cm^2. Individuals with an MVA >1.5 cm^2 usually do not have any symptoms due to MS.[49] The current VHD management guidelines define severe MS as a MVA of ≤1.5 cm^2. This generally corresponds with a mean TMPG of 5 to 10 mmHg across the MV at a normal heart rate **(Table 1)**.[5] The current guidelines do not recommend indexing the valve area based on gender or body size. It remains unclear how to define severe MS based on MVA values determined by CT-planimetry. An investigation by Lebcke et al suggested that a CT-determined MVA of 1.7 cm^2 is the best cut-off to distinguish mild MS from moderate to severe MS.[39]

The values for quantification of MS severity were defined based on research studies involving patients with RMS. These definitions have not been validated in patients with DMS.

Another potential challenge exists in assessment of MVA in patients with DMS. It remains unclear whether it is reliable to use the same MVA threshold values in both RMS and DMS. Some

previous studies have suggested that same stenotic orifice area may lead to different gradients across the valve in RMS and DMS because of differences in the geometry of the orifice and mobility of the leaflets.[50] Gilon et al., using 3D echocardiographic laser stereolitography, have tested the hypothesis that 3D geometry proximal to the stenotic orifice significantly impacts the pressure loss across a stenotic valve.[51] The study revealed that for the same anatomic MVA, mobile dome shaped MV geometry (such as in RMS) is associated with larger effective orifice area and smaller TMPG when compared to funnel shaped or flat immobile MV geometry (such as in DMS). These results suggested that at a given anatomic orifice area DMS can result in more significant hemodynamic impact on the flow. The hemodynamic differences between distinct valve morphologies were attributed to the fact that a dome shaped stenosis would permit more gradual convergence of flow proximal and distal to the stenosis.

EPIDEMIOLOGY OF DEGENERATIVE MITRAL STENOSIS

Because of lack of a standardized definition of DMS, there is a great variability among epidemiologic studies in terms of how DMS is defined and its severity is quantified. Some of the methods used to diagnose DMS were as follow: hearing a 'MS' murmur in the presence of MAC, elevated TMPG determined by echocardiography or MVA determined by different algorithms such as planimetry, PHT or continuity equation. The cut-off levels for these parameters also differed from study to study. Due to the variability among studies and the use of non-validated techniques (as will be discussed below), the results of epidemiologic studies should be interpreted with caution. Most epidemiologic studies on DMS are either single-center studies with relatively small patient numbers or date back to 3-4 decades ago. Therefore, our knowledge on the contemporary epidemiology and natural history of DMS is limited.

A prospective survey which was published in the early 2000's and included 5,000 patients with moderate-to-severe native VHD from 25 different European countries reported the frequency of DMS as

12.5% among all MS cases.[52] The proportion of patients with DMS was significantly higher in advanced age groups. For instance, DMS accounted for 60% of all MS cases in patients >80 years of age. In a retrospective study on a cohort of unselected individuals (n=4270) who were referred for outpatient echocardiograms, 0.5% of the individual were found to have severe MAC and increased pressure gradients across the MV at rest.[41]

MAC shows significant association with MR. In a retrospective study, presence of MAC was associated with a 2-fold increased risk of MR.[53] The epidemiologic characteristics of concomitant DMS and MR have not been defined. DMS show significant association with degenerative involvement of other valves. Iwataki et al. reported the frequency of severe DMS (defined as MVA <1.5 cm^2 by continuity equation) as 24% among patients with degenerative AS.[54] Another recent study assessed the frequency of MV pathologies detected with CT among 394 severe AS patients referred for TAVR.[36] In this cohort, 50% of the subjects were found to have MAC. In addition, 32% of subjects with MAC were found to have a MVA < 2 cm^2 based on MV planimetry with CT. Severe degenerative AS has also been associated with increased TMPG. Yong et al. reported the frequency of subjects with increased TMPG (invasively determined TMPG of ≥5 mm Hg) as 55% in a cohort of patients with severe degenerative AS who were referred for balloon aortic valvuloplasty.[55]

NATURAL HISTORY OF DEGENERATIVE MITRAL STENOSIS

Pasca et al. have recently shed some light on the natural history of DMS.[56] Their single-center study was conducted on a cohort of 1004 DMS patients with a mean follow-up period of 3.5±2.8 years. In the study, DMS was defined as increased mean TMPG (>2 mm Hg) in the presence of severe MAC without commissural fusion. MS grading was performed based on the mean pressure gradients estimated by echocardiography. In the cohort, 78% of the patients had mild MS, 14% moderate and 8% severe. DMS was associated with very poor survival with 1-, 5- and 10-year mortality rates of 32%, 53%,

75%, respectively. When compared to the US general population (similar age- and sex-distribution), 5-year mortality was almost 3 times higher in patients with DMS **(Figure 5)**. The predictors of poor survival in patients with DMS were; advanced age, AF, renal failure, other valvular abnormalities (AS, MR or tricuspid regurgitation), increased right sided filling pressures, low albumin and use of digoxin. Higher grade of DMS was a predictor of mortality in their multivariate analysis. Its effect did not remain significant in the comprehensive model, which included clinical biochemical, and pharmacologic data. These results suggest that DMS is a marker of poor survival. However, further research is needed to investigate whether DMS has a direct impact on mortality.

The data on natural course of progression of DMS is also limited. Tiyagi et al. assessed the characteristics of progression of DMS in a cohort of 254 patients. The authors observed that, in patients with DMS, TMPG progressively increases with a rate of 0.8±2.4 mm Hg per year.[57]

ECHOCARDIOGRAPHIC QUANTIFICATION OF DEGENERATIVE MITRAL STENOSIS

Reliable estimation of MVA and mean TMPG are the main components of echocardiographic assessment of MS. There exist several echocardiographic techniques for assessment of MVA and mean TMPG. Strengths, weaknesses and applicability of these techniques in patients with DMS are given in **Table 2** and discussed below. The validity of these techniques has mainly been tested in patients with RMS. There have been no well-designed studies in patients with DMS comparing the echocardiography defined MVA and TMPG values with those obtained from invasive hemodynamic studies or surgically removed valves.

Echocardiographic Warning Signs

Since DMS is not a commonly encountered clinical entity, a high index of suspicion is essential for early diagnosis of this condition. Cardiologists and sonographers should be aware of

echocardiographic warning signs of DMS **(Table 3)**. Presence of these warning signs should trigger detailed echocardiographic evaluation (including 3D) of the entire MV apparatus. It should be noted that in patients with DMS, calcification occurs at the base of the leaflets while the leaflet tips are usually spared. Thus, pliable and thin leaflet tips appearing on echocardiography images should not be interpreted as a finding against the presence of MS.

Mitral Valve Area by Planimetry

Direct planimetry is considered as the most reliable echocardiographic method to determine MVA in patients with RMS. 2D planimetry involves direct visualization of the MV leaflets in the parasternal short-axis view in mid-diastole and tracing of the inner rim of the orifice, including opened commissures, to calculate MVA.[2] Direct planimetry requires careful scanning across the MV and optimum beam position and angulation to determine and intersect the limiting orifice which in RMS is usually at the tips of the leaflets. Averaging of several measurements is recommended in the presence of AF or heart rate variability. A major advantage of direct planimetry is that, unlike other echocardiographic methods to assess MS, planimetry is not affected by cardiac chamber compliance, flow conditions or other valvular abnormalities such as MR or aortic regurgitation (AR).[16] Multiple studies in patients with RMS have confirmed that MVA determined by 2D direct planimetry strongly correlates with direct sizing during surgery and invasively derived MVA by Gorlin formula.[58,59] 3D echocardiography, which can provide simultaneous display of orthogonal views, can enhance accuracy of MVA measurements. Direct planimetry with 3D echocardiography is a reliable and reproducible method in RMS. And it was shown to be superior to 2D echocardiography in assessment of MVA in patients with RMS.[60,61] 3D echocardiography can be performed with both transthoracic and transesophageal echocardiographic techniques.

Planimetry of MVA with 2D echocardiography is challenging and unreliable in patients with DMS. The limiting orifice of mitral inflow in DMS is usually located at the base of MV leaflets. Thus, planimetry at the level of leaflet tips does not represent the true limiting orifice. Moreover, the acoustic shadowing from the calcification of the annulus and leaflets prevents 2D visualization of the orifice at the base.[16] 3D echocardiography (with TTE or TEE) have been suggested to overcome these limitations. It may provide more accurate quantification of limiting orifice in DMS due to its ability to demonstrate en-face views of the MV structure.[30] 3D echocardiography can also be helpful in confirming the absence of commissural fusion. Severe calcification and blooming artifact may represent a challenge for visualization of limiting orifice and leaflet tips in some cases.

Chu et al. described a color-flow guided real time 3D echocardiographic planimetry method for determining the limiting mitral orifice in a cohort of 34 patients with suspected DMS.[50] The investigators excluded patients with significant MR or AR and used MVA obtained by continuity equation with continuous wave (CW) Doppler as the independent standard of effective MVA. The study demonstrated that MV orifice area calculated by 3D echocardiography strongly correlates with the independent standard (continuity equation). Interestingly the stenotic orifice in DMS was found to have a tubular geometry which is different from doming pattern seen with RMS. MVA calculation by 3D echocardiography has not been validated using invasive evaluations.

In conclusion, planimetry with 3D echocardiography (particularly with TEE approach) is most useful echocardiographic modality to confirm diagnosis and quantify the orifice area in patients with DMS.

Pressure Half Time Method

The PHT refers to the time interval it takes for the TMPG to decay to the half of peak value observed in diastole.[2] The PHT method for estimation of MVA is based on the concept that the duration

of pressure drop from LA to LV inversely correlates with the mitral orifice area.[16] The PHT is calculated with CW Doppler of mitral inflow obtained from apical four chamber view. The significant correlation between PHT and invasively determined MVA was first described by Hatle et al. in 19 patients with MS.[62] Based on this correlation, an empiric formula of MVA=220/PHT was subsequently derived. The original report by Hatle et al. did not specify the etiology of MS in the patients included in their study. Later studies which specifically included RMS patients confirmed the association between PHT and invasively (with Gorlin formula) or surgically determined MVA in this patient population.[59,63]. PHT is easy to perform and less time consuming.

The PHT method is dependent on the compliance of LV and LA. Decreased LV compliance, a cardinal finding of diastolic dysfunction, commonly coexist with severe MAC (seen in the older population). In the presence of decreased LV compliance PHT may shorten due to rapid equilibration of TMPG and this may result in overestimation of derived MVA.[50,64] A study by Karp et al. compared the PHT-derived and Gorlin equation-derived MVA in individuals with normal and decreased LV compliance.[65] In individuals with stiff LV (decreased LV compliance), the PHT method overestimated the invasively derived MVA by 72%. Overestimation was only 10% for individuals with normal LV compliance.

PHT is inversely related to MVA, and directly to LA compliance and square root of peak transmitral gradient.[64] Computer generated models of this relationship have shown that for a fixed MVA and a fixed initial LA pressure, decreasing LA compliance (or increasing stiffness) may shorten PHT and lead to overestimation of MVA by this method.[64] Decreased LA compliance is an important cause of increased LA pressure and have been associated with poor prognosis in patients with RMS.[66] Further research is needed on patients with DMS to investigate the characteristics of LA compliance and the impact of LA compliance on MV hemodynamics and PHT in this patient population.

The PHT is considered to be unreliable in patients with tachycardia or AF.[2] Concomitant AR and/or AS may also shorten PHT by affecting LV filling time or compliance.[67] Consistent with the limitations listed above, a retrospective study on patients with MS who underwent echocardiography and cardiac catheterization demonstrated that PHT method significantly overestimates MVA in patients age 65 years or older.[68] Because of the high likelihood of inaccurate estimation of MVA, valve stenosis guidelines recommended against use of PHT in assessment of DMS.[49]

Proximal Isovelocity Surface Area Method

The proximal isovelocity surface area (PISA) method relies on the principal that flow converges and accelerates towards an orifice, and that results in formation of shells with increasing velocity and decreasing radius. And based on the low of conservation of mass, the flow rate through a stenotic MV must be equal to the flow rate at a given hemispheric shell.[2] The PISA for MVA is obtained with color flow Doppler in apical four chamber view. The calculation of PISA requires the measurement of several different parameters: the aliasing velocity, radius of the convergence hemisphere, the peak mitral inflow velocity and the opening angle of the leaflets relative to flow direction.[30] The PISA method for estimation of MVA has been validated in patients with RMS.[69] The PISA method appears to have several advantages compared to the PHT method. It has been shown to be less or not affected by MR,[69] AF,[70] AR,[71] and changes in atrio-ventricular compliance.[72] However the PISA method is technically difficult, more time consuming and susceptible to measurement errors.[49] De Agustin et al. tested the validity of 3D echocardiography PISA for estimation of MVA in patients with RMS.[73] The study demonstrated that, compared to the traditional 2D PISA method, the novel 3D PISA method better correlates with the other reference techniques (planimetry and PHT) used to determine MVA.

To our knowledge, there has been no study assessing the use of PISA method in patients with DMS. Its validity in this patient population has not been determined. The PISA method is particularly

challenging in evaluation of DMS because of difficulty of determining the location of flow limiting orifice and calculation of opening angle relative to the direction of flow.

Continuity Equation Method

The continuity equation method relies on the law of conservation of mass. This method requires that, in the absence of valvular regurgitation or intra-cardiac shunting, the transmitral stroke volume is equal to the stroke volume obtained from right ventricular outflow tract (RVOT) or LVOT.[2] Based on the Doppler-derived continuity equation, the MVA can be calculated with the following formula: MVA=Stroke Volume/Mitral Velocity Time Integral (VTI).[49] Some studies have demonstrated that the MVA determined by continuity equation correlates with the values obtained from cardiac catheterization (by Gorlin formula) in patients with RMS (correlation coefficient of 0.64).[63] The continuity equation was used as one of the reference methods to determine the MVA in the study by Chu et al. which tested the validity of planimetry by 3D echocardiography in patients with DMS.[50] That study demonstrated a strong correlation with MVA values determined by Doppler-derived continuity equation and 3D planimetry.

There are several limitations for use of continuity equation method for assessment MVA. 1) Like the PISA method, continuity equitation requires multiple independent measurements which make this test susceptible to manual measurement errors. 2) It is generally difficult to reliably obtain RVOT stroke volume because of poor acoustic windows. 3) The continuity equation for MVA becomes invalid in the setting of significant MR, AR (if LVOT stroke volume is used as reference) or pulmonary regurgitation (if RVOT stroke volume is used as reference). 4) AF or other irregular heart rhythms result in beat-to-beat variability in stroke volume and make continuity equation unreliable.[49]

In conclusion, the continuity equation is not an ideal method for calculation of MVA in patients with DMS because of the possible impact of measurement errors and high prevalence of concomitant irregular heart rhythm or valvular regurgitation in this patient population.

Doppler-derived Transmitral Pressure Gradient

The TMPG is considered the main supportive criterion in the assessment of MS.[49] The echocardiographic TMPG is obtained from apical 4-chamber view with use of CW Doppler and application of simplified Bernoulli equation (4 x [velocity]^2). The peak Doppler velocity is used to calculate the peak TMPG, whereas the average of instantaneous gradients enveloped in the CW Doppler signal is used to calculate the mean TMPG.[2] In order to obtain the maximum gradient, the Doppler beam needs to be aligned parallel to flow.[16] The mean TMPG is considered to be a more reliable hemodynamic parameter because the peak TMPG is highly variable and more influenced by LA compliance and LV diastolic dysfunction.[74] In patients with RMS, Doppler-derived mean TMPG values correlate well with invasive measurements obtained with trans-septal catheterization.[75] Such validation studies are lacking for patients with DMS. A study by Hermann et al. utilized an in-vitro simulator and MV models and revealed a good correlation between Doppler-derived and invasively measured TMPG values in the presence of severe MAC, but the Doppler method slightly overestimated the pressure gradient.[76]

In patients with AF, it is recommended to take the average of multiple heart cycles in order to accurately obtain the mean TMPG.[2] In patients with RMS, a mean TMPG of <5 mm Hg is suggestive of mild MS while a mean TMPG >10 mm Hg supports the diagnosis of severe MS.[49] Because of lack of a standardized definition and grading algorithm for DMS, Doppler-derived mean TMPG has commonly been used as the only criterion to grade MS in the epidemiologic studies in these patients.[56, 57] Although the TMPG can be accurately measured with Doppler, several limitations impair its reliability as a marker

or severity of MS. The TMPG is highly dependent on the heart rate, flow across the MV and atrio-ventricular compliance.[49] Of note, high cardiac output states and significant MR can increase the TMPG.

Other Echocardiographic Parameters

Enlarged LA and increased PA pressure are the major consequences of MS and increased TMPG. And concomitant severe pulmonary hypertension (resting PA systolic pressure >60 mm Hg) have been demonstrated to be a predictor of poor prognosis in patients with RMS.[77] Careful evaluation of LA volume and PA systolic pressure is essential in assessment of MS. DMS predominantly affects elderly patient population with multiple comorbidities influencing LA size and PA pressure. Thus, LA enlargement or increased PA systolic pressure is unlikely to be specific for diagnosis of DMS when used alone.

Stress Echocardiography

The current guidelines recommend hemodynamic exercise testing with Doppler echocardiography or invasive hemodynamic measurements to determine exercise response of mean TMPG and PA pressure in patients with MS whose clinical signs or symptoms don't correlate with resting Doppler echocardiography measurements.[5] In simple term, two potential case scenarios which can benefit from evaluation of MS with stress echocardiography are; 1) asymptomatic patients with echocardiography findings of severe MS or 2) symptomatic patients with echocardiography findings of only mild/moderate MS.

It has long been known from the invasive hemodynamics studies (mainly by Gorlin et al.) that exercise leads to elevated LA and PA pressures in patients with MS because of fixed MV orifice despite increased cardiac output.[78] Studies using Doppler echocardiography have also demonstrated that mean and peak TMPG and PA systolic pressure significantly increase with exercise in patients with MS.[79]

Dobutamine stress echocardiography has also been confirmed as an effective and safe modality for assessment of severity of RMS.[80] Reis et al. found that a TMPG cut-off value of ≥ 18 mmHg during exercise is a predictor of future adverse clinical events in patients with RMS.[80]

Because exercise is more physiologic, it is the recommended way of stress for evaluation of MS.[5] It is not uncommon that patients with VHD report no symptoms because of intentional or unintentional limitation of activities. Exercise stress testing may help with determining the functional capacity and exercise induced symptoms in patients with MS. A prospective study revealed that almost 50% of individuals with MS (MVA ≤ 1.5 cm^2) who claim to be asymptomatic with daily activities would develop dyspnea during a stress test.[81]

Contrary to the previous guidelines,[82] current VHD guidelines do not include PA systolic pressure (peak exercise) as a criterion for diagnosis of severe MS. However a rise in PA systolic pressure to >60 mmHg to 70 mmHg with exercise should warrant more detailed evaluation for MS.[5] Serial evaluation of PA systolic pressure during exercise carries importance as well. Brochet et al. demonstrated that the rapid and high progression of TMPG and PA systolic pressure at early exercise (compared to peak) is a strong predictor of dyspnea during a stress test in patients with MS.[81] Conversely, PA systolic pressures at peak exercise was not a predictor of exercise limiting symptoms.

It should be noted that, previous studies on use of stress echocardiography in MS have been performed on patients with RMS or non-specified MS. Therefore, we are still in need of further research to determine the utility of exercise or dobutamine stress echocardiography in evaluation of DMS. Although supportive evidence is still lacking, stress echocardiography may provide significant help in approach to patients with DMS, especially if there is discordance between symptoms and resting echocardiography findings. In addition, cardiopulmonary stress testing can provide further help in non-invasive determination of the mechanisms underlying exercise intolerance in patients with DMS. The

clinical utility of this combined stress echocardiography and cardiopulmonary stress testing approach was recently demonstrated in a group of patients with RMS.[83]

CONCLUSIONS AND CLINICAL PERSPECTIVES

DMS is characterized by decreased MV orifice area and increased TMPG due to chronic non-inflammatory degeneration and subsequent calcification of the fibrous mitral annulus and the MV leaflets. DMS has been a challenge for clinicians from diagnostic and therapeutic perspectives. And it has received limited attention from researchers up until recent years. Thus, the natural course of DMS is still poorly understood.

The 'true' prevalence of DMS in the general population is not well. DMS predominantly affects the elderly individuals. It is seen in younger individuals in the setting of ESRD. Radiation induced MS resembles DMS and may occur >20 years after thoracic radiation exposure. Recent studies utilizing multimodality imaging techniques have broadened the understanding on MV function and the underlying mechanisms of DMS. Furthermore, recent advances in transcatheter valve interventions have brought hope for more effective and possibly less risky options for treatment of DMS.

Echocardiography is the primary imaging modality for evaluation of DMS and related hemodynamic abnormalities such as increased TMPG and PA pressure. Classic echocardiographic techniques used for evaluation of MS (PHT, PISA, Continuity equation, MVA planimetry) lack validation for DMS. Direct planimetry with 3D echocardiography and color flow Doppler is a reasonable technique for determining MVA in DMS.

Cardiac CT is superior to echocardiography in evaluation of MAC. It can be very helpful for evaluation of DMS, especially in the planning stages of future MV interventions. Stress echocardiography, preferably with exercise, may be considered in evaluation of patients with DMS

especially when echocardiography findings are equivocal or discordant with symptoms. Concomitant use of cardiopulmonary stress testing may provide further valuable information regarding the mechanisms underlying exercise intolerance in patients with DMS.

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FIGURE/TABLE LEGENDS

Figure 1:

Title: Degenerative mitral stenosis and transcatheter mitral valve replacement.

Caption: TEE views of a 56 year-old male with h/o ESRD, cirrhosis, CAD and HTN who presented with exertional dyspnea. 3D zoom view of the MV shows severe MAC sparing the leaflets (A). 3D Planimetry of MV revealed an area of 1 cm^2 (B). Peak and mean TMPG was 11 to 13 mmHg at a heart rate of 85 beats per minute (C). Simultaneous right and left heart catheterization demonstrated a mean TMPG of 14 mmHg at a heart rate of 90 beats per minute (image not shown). He was diagnosed with severe DMS. He successfully underwent TMVR with balloon-expandable Sapien 3 (26 mm; Edwards Life Sciences, Irvine, CA) valve with a transapical approach (D).

Figure 2:

Title: Saddle shaped mitral annulus.

Caption: Three-dimensional illustration of the mitral annulus from left antero-lateral (2-A) and anterior (2-B) views. A, anterior annulus; AL, antero-lateral; Ao, aortic valve; P, posterior annulus; PM, postero-medial; TPM, tips of papillary muscles. 3D image was reconstructed by the mitral valve quantification software of Phillips. Revised reprint, with permission, from Garbi et al.[13]

Figure 3:

Title: Echocardiography of mitral annular calcification.

Caption: (A) Parasternal long axis view demonstrating a bar of calcium seen in the posterior mitral annulus (arrow) with flow acceleration across the mitral valve. (B) Crescent shaped appearance of the posterior mitral annulus with severe calcification (arrow) in the parasternal short axis view. The anterior annulus is not seen in this view. (C) Apical four chamber view showing anterior and posterior mitral

annular calcification (arrow heads). (D) CW Doppler of mitral inflow showing a mean TMPG of 12 mmHg at a heart rate of 76 beats per minute.

Figure 4:

Title: Cardiac computed tomography of mitral annulus calcification.

Caption: (2-A) Dense calcification of the anterior and posterior mitral annulus on coronal section. (2-B) Dense circular mitral annular calcification on oblique axial view. Mitral annular area is calculated as 4.0 cm^2.

Figure 5:

Caption: Survival in degenerative mitral stenosis

Title: Kaplan-Meier survival curves of patients with mild, moderate or severe degenerative mitral stenosis compared with expected survival of age- and sex-matched population from US. Revised reprint, with permission, from Pasca et al.[56]

Table 1:

Title: Stages of Mitral Stenosis

Caption: Adapted from the 2014 American Heart Association / American College of Cardiology valvular heart disease guideline.[5] LA, left atrium; MVA, mitral valve area; MS, mitral stenosis; PA, pulmonary artery.

Table 2:

Title: Echocardiographic techniques for quantification of severity of DMS.

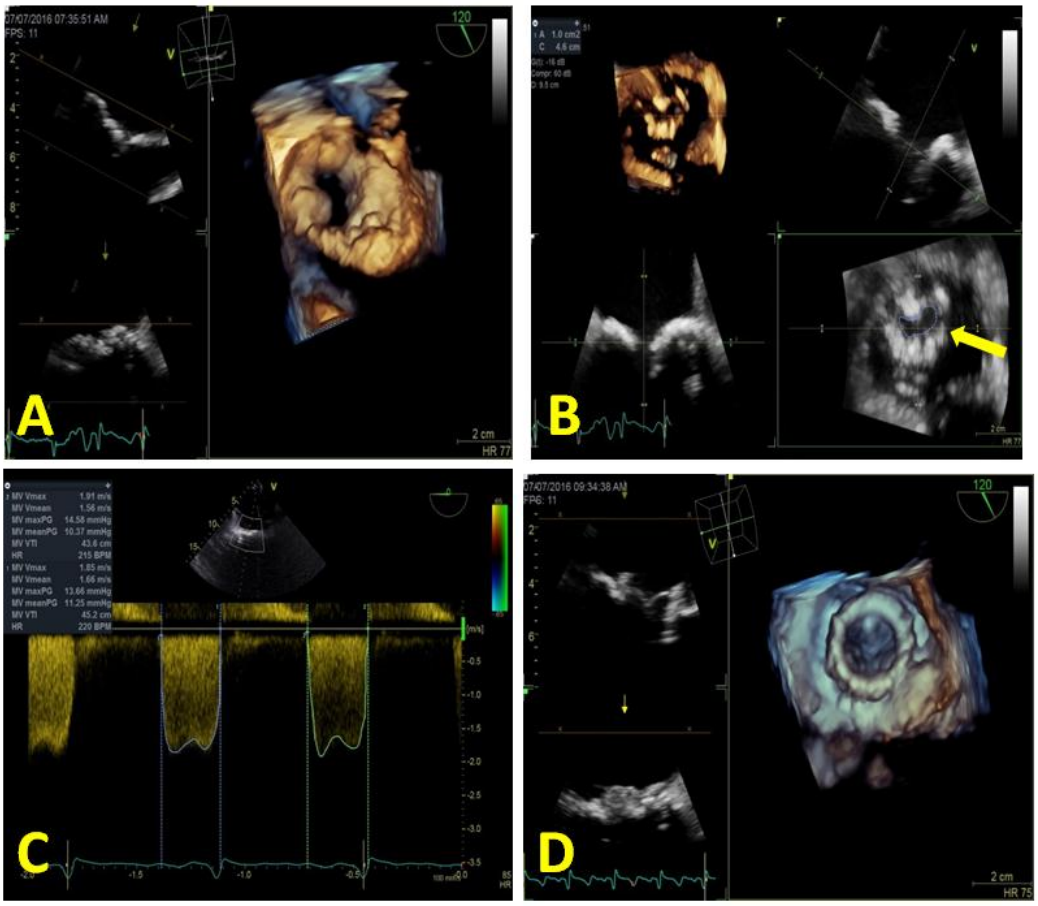
Caption: CW, continuous wave; DMS, degenerative mitral stenosis; LVOT, left ventricular outflow tract; PISA, proximal isovelocity surface area; PW, pulse wave; RMS, rheumatic mitral stenosis; RVOT, right

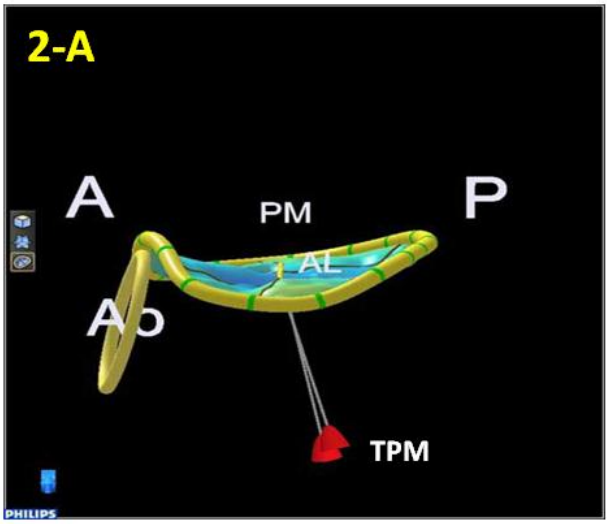
ventricular outflow tract; TMPG, transmitral pressure gradient; 2D, two-dimensional; 3D, three-dimensional.

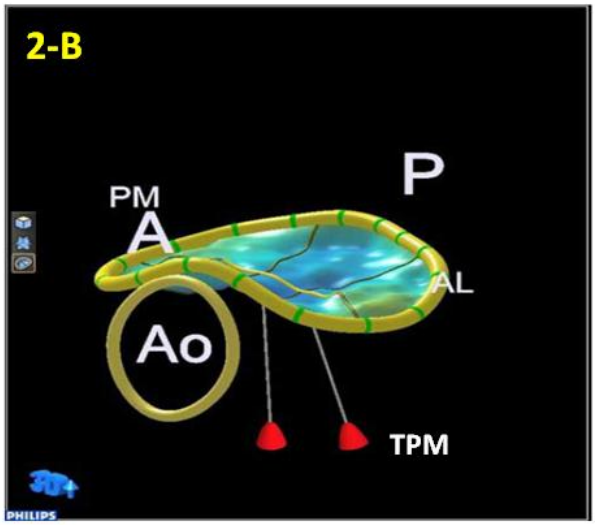
Table 3:

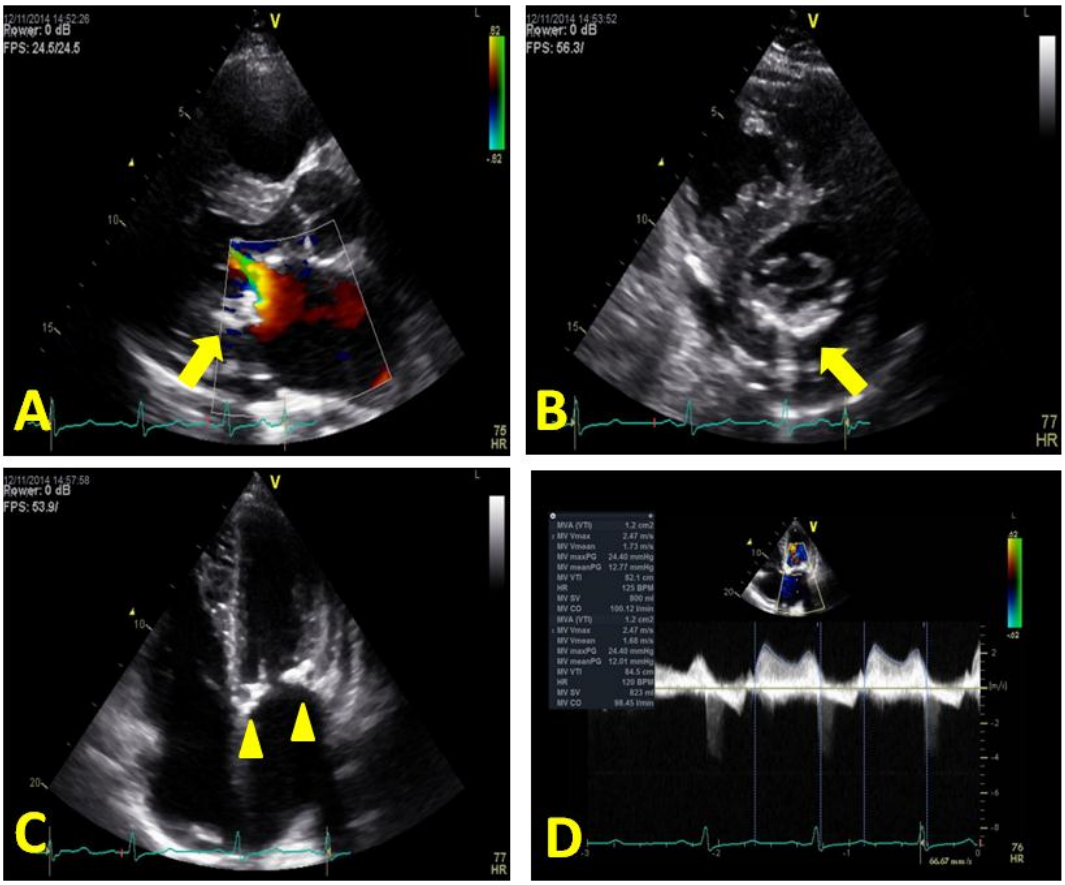
Title: Echocardiographic signs for degenerative mitral stenosis.

Caption: MAC, mitral annular calcification, MV, mitral valve.

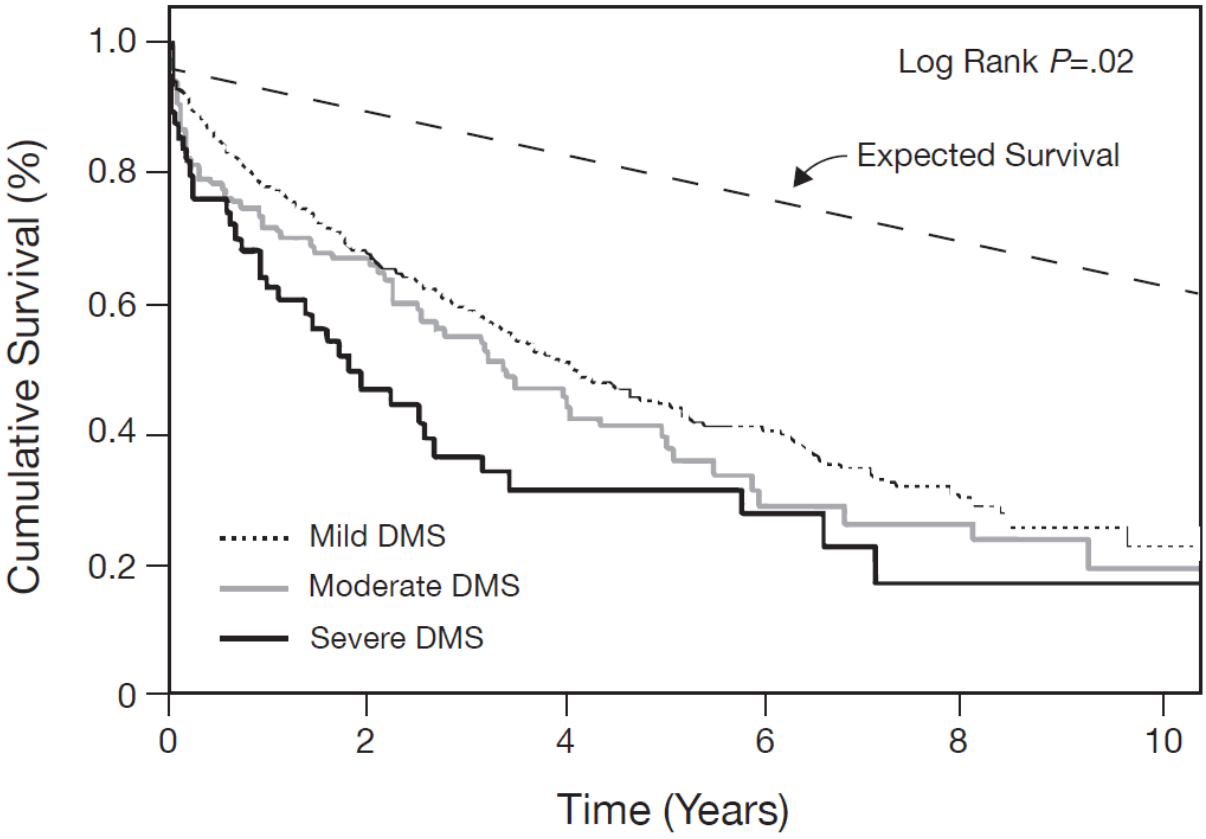









A
24.6 mm
8.67 mm
9.52 mm
R
L
F
%R-R:30
FOV:250.00 mm
HELICAL MODE
120 kV
232 mA
Tilt:0.00
RAO 33: CRA 8
No: 1
TERARECON
W:1000 L:300
B
Distance: 26.9 mm x 19.4
Area: 4.00 cm²
Avg. Diameter: 22.6 mm
Perimeter: 74.7 mm
F
H
P
%R-R:30
FOV:250.00 mm
HELICAL MODE
120 kV
232 mA
Tilt:0.00
LAO 55: CAU 17
No: 2
TERARECON
W:1000 L:300


Log Rank P=.02
Expected Survival
Mild DMS
Moderate DMS
Severe DMS
Cumulative Survival (%)
1.0
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Time (Years)

Stage	Definition	Mitral Valve Area	Hemodynamic Consequences	Symptoms
A	At risk of MS	➢ MVA > 1.5 cm^2	➢ Normal transmitral flow velocities ➢ Normal PA pressures at rest ➢ Normal LA volumes ➢ ↑ transmitral flow velocities	➢ None
B	Progressive MS	➢ MVA > 1.5 cm^2	➢ Normal PA pressures at rest ➢ Mild-to-moderate LA enlargement ➢ ↑ transmitral flow velocities	➢ None
C	Asymptomatic Severe MS	➢ MVA ≤ 1.5 cm^2 ➢ MVA ≤ 1.0 cm^2 (very severe MS)	➢ PA systolic pressure > 30 mm Hg ➢ Severe LA enlargement ➢ ↑ transmitral flow velocities	➢ None
D	Symptomatic Severe MS	➢ MVA ≤ 1.5 cm^2 ➢ MVA ≤ 1.0 cm^2 (very severe MS)	➢ PA systolic pressure > 30 mm Hg ➢ Severe LA enlargement	➢ ↓ exercise tolerance ➢ Exertional dyspnea

	Echocardiographic Modality	Tomographic View	Strengths	Limitations	Applicability
2D Planimetry	2D echocardiography	Parasternal short-axis	Not affected by; •Level of transmitral flow •Atrioventricular compliance •Concomitant aortic or mitral regurgitation	•Acoustic shadowing from calcification of aortic valve, aortic root or mitral annulus. •Inability to visualize flow limiting orifice	•Not useful in DMS because of its limitations
3D Planimetry	3D echocardiography with color flow Doppler	N/A	•More accurate visualization of the flow limiting orifice	•Requires expertise	•Can be useful in evaluation of DMS •Not validated

					with "gold-standard" methods
Pressure Half Time	CW Doppler	Apical four chamber	•Easy to obtain and less time consuming	Affected by; •Atrioventricular compliance •Atrial fibrillation or tachycardia •Concomitant aortic regurgitation or stenosis	•Not reliable in DMS because of high risk of inaccurate estimation of MVA

PISA Method	•Color Doppler •CW Doppler •2D echocardiography	Apical four chamber	Not or minimally affected by; •Mitral or aortic regurgitation •Atrial fibrillation •Atrioventricular compliance	•Technically difficult •Time consuming •Risk of manual measurement errors	•Validity is unknown in DMS
Continuity Equation	PW Doppler CW Doppler	•Apical four chamber view for the mitral inflow •Different views for LVOT or RVOT stroke volumes	•Easy to obtain	Unreliable in the setting of; •Mitral regurgitation •Aortic or pulmonary regurgitation (for LVOT or RVOT stroke volumes, respectively) •Atrial fibrillation Risk of; •Manual measurement errors	•Not reliable because of its limitations and high risk of measurement errors

Doppler-derived Mean TMPG	CW Doppler	Parasternal four chamber	•Easy to obtain •Good correlation with invasively obtained gradients (in patients with RMS)	Affected by; •Heart rate •Level of transmitral flow and mitral regurgitation •Atrioventricular compliance	•Can be useful as a screening or confirmatory parameter

Moderate or severe MAC
Calcification protrusion beyond mitral annulus
Calcification of MV leaflet(s)
Restricted motion or decreased opening angle of MV leaflet(s)
Concomitant anterior and posterior MAC
Increased transmitral pressure gradient
Turbulent transmitral flow on color flow Doppler
Left atrial enlargement
Elevated pulmonary artery systolic pressure