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

Degenerative Mitral Regurgitation: Assessment, Physical Examination, and Imaging

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Abstract

Purpose of Review In this review, we provide a comprehensive approach to assess degenerative mitral regurgitation.

Recent Findings In the evaluation of MR, it is important to differentiate between primary (degenerative/organic) MR in which an intrinsic mitral valve lesion(s) is responsible for the occurrence of MR and secondary (functional) MR where the mitral valve is structurally normal, but alterations of the left ventricular geometry cause deterioration of the MV apparatus. Advanced imaging modalities, foremost two-dimensional and three-dimensional echocardiography, are essential for this determination.

Summary In the evaluation of degenerative MR, the exact mechanism, the extent of the disease, associated valve lesions, the grade of mitral regurgitation severity, and hemodynamic consequences require careful assessment in order to provide patients with appropriate monitoring and treatment.

Keywords Mitral regurgitation · Primary mitral regurgitation · Degenerative mitral regurgitation · Echocardiography · Mitral valve prolapse · Barlow's disease · Fibroelastic deficiency · Papillary muscle rupture

Introduction: Prevalence and Mechanisms of Mitral Regurgitation

Mitral regurgitation (MR) is *defined* as an abnormal retrograde blood flow from the left ventricle (LV) to the left atrium (LA) during left ventricular contraction. Trivial to mild mitral regurgitation is a common finding and is seen in nearly 50% of healthy people [1]. Severe MR is relatively uncommon in patients before the fifth decade, but the prevalence increases with age to 13.3% in patients ≥ 75 years of age [2].

For the evaluation of MR, it is essential to appreciate the complex structure of the mitral valve (MV). MV competence depends on several factors which include the mechanical and functional integrity of all components involved: the anterior and posterior mitral leaflets, the mitral annulus, the chordae tendinae, both papillary muscles, the left atrium, and the left ventricle. An anatomic abnormality or dysfunction of these components alone or in combination may lead to MV incompetence.

MR can be classified as primary (degenerative or organic) MR (DMR) (Fig. 1a and b) or as secondary (functional) MR (FMR) (Fig. 1c and d): With primary or degenerative MR, there is an intrinsic MV abnormality or lesion(s) responsible for the development of MR. With secondary or functional

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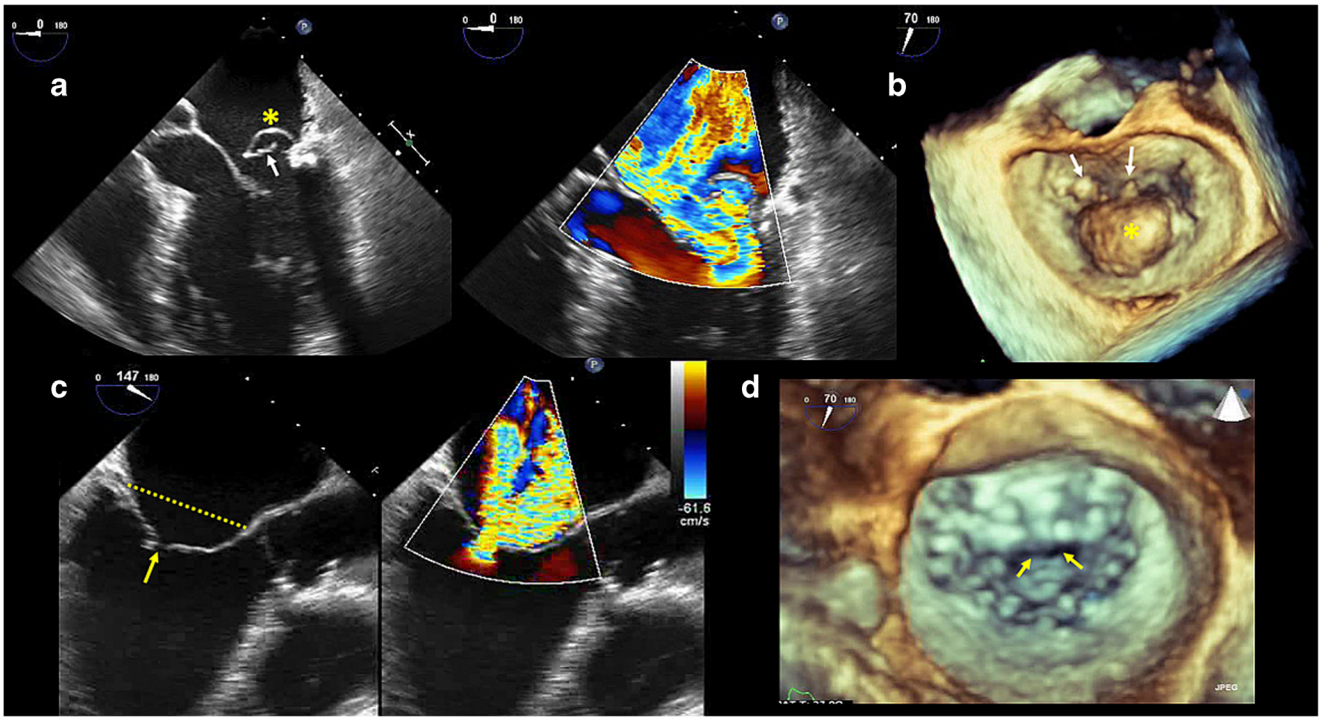

Fig. 1 Examples of degenerative and functional mitral regurgitation (**a**). A flail mitral valve prolapse (MVP) (*yellow star*) can be seen in a 0° transesophageal echocardiographic (TEE) view in 2D and 2D with color Doppler (**b**). The *white arrows* in **a** and **b** mark ruptured chords. The eccentricity of the MR jet can be appreciated in color Doppler. In **b**, a 3D TEE enface view shows the extent of the P2 flail and two ruptured chordae tendinae (*white arrows*). The prolapse is marked again with a *yellow star*. **c** An example of a patient with functional mitral regurgitation is given. The left ventricle is dilated, and the mitral leaflets are drawn into the left ventricle. The coaptation is below the annular plane (*yellow dotted line*). The mitral leaflets have a tent-like appearance ("tenting") as seen a 2D transesophageal echocardiographic (TEE). The lack of coaptation in **c** and in a 3D TEE enface view (**d**) is marked with *yellow arrows*

MR, the MV is structurally/anatomically normal. MR is the result of MV deformation due to an abnormal LV geometry and LV dysfunction. Both DMR and FMR can occur in the same patient (mixed disease).

The Carpentier classification [3] allows for a further subclassification of MR by focusing on mitral leaflet motion to describe specific types of MV dysfunction: Type I is characterized by normal leaflet motion. In these cases, MR is caused by mitral annular dilation or calcification, MV clefts, or MV perforations. Type II describes cases with excessive leaflet mobility as seen in patients with MV prolapse(s) or flail leaflets, and type III describes cases in which there is restricted motion of the leaflets. This is present either in diastole (type IIIa) as it is typically seen in rheumatic MV disease or in systole (type IIIb) as it is characteristic for ischemic MR. Table 1 gives an overview of mechanisms, causes, and types of dysfunction according to the Carpentier classification.

In the industrialized world, 60–70% of MR patients undergoing surgery have DMR caused by primary myxomatous disease, primary flail leaflets or annular calcification, followed by ischemic MR (representing 20% of cases), infective endocarditis, and rheumatic MR (each with representing 2–5% of cases), and some rare causes including cardiomyopathies, cleft mitral valve, traumatic rupture of chordae or papillary muscles, radiation heart disease, drug-induced, and inflammatory diseases [4, 5].

Mitral valve prolapse (MVP) which has a wide spectrum of etiologies and clinical presentations as outlined in Table 2 is the most common cause of primary MR in developed countries [6]. Two main phenotypes of MVP have been described [7]: Patients may present with severe diffuse myxomatous degeneration of the entire MV with thickened and redundant leaflets, excessive leaflet tissue, elongated chordae tendinae, and sometimes translocation of the posterior mitral annulus into the LA (this is often described as "Barlow's disease") (Fig. 2). In other patients who may present at an older age, the leaflets have been described by some surgeons as being thin and somewhat delicate, and suggesting that the lack of adequate connective tissue leads to chordal rupture and a flail mitral leaflet. Several reports have attributed this finding to fibroelastic deficiency disease. However, pathologic studies show that fibroelastic deficiency cannot be reliably differentiated from MVP or Barlow syndrome by gross inspection but only by quantitative histologic evaluation. Qualitative histology is not sufficient to distinguish these two entities. It is therefore not surprising that the terms mitral valve prolapse and myxomatous degeneration due to fibroelastic deficiency disease have been used as synonyms [7].

Table 1 Mechanisms, causes, and type of mitral valve dysfunction in patients with primary and secondary mitral regurgitation

	Primary (degenerative/organic) MR			Secondary (functional) MR
Mechanism	Intrinsic valve lesion			Structural normal valve, MV deterioration due to geometrical LV abnormalities
Causes		Non-ischemic		
	Endocarditis (perforation)	Degenerative (billowing/ prolapse/ flail)	Rheumatic (chronic rheumatic MV disease)	Cardiomyopathy
	Annular dilation (rarely isolated)			Myocarditis
	Degenerative (annular calcification)	Endocarditis (ruptured chordae)	Iatrogenic (post-radiation, toxic, drug-induced)	LV dysfunction of any cause
	Congenital (cleft)	Traumatic (ruptured chordae/PM)		
		Rheumatic (acute RF)	Inflammatory diseases (lupus erythomatodes/anticardiolipin, eosinophilic endocardial disease, endomyocardial fibrosis)	
		Ischemic		
	–	Ruptured PM	–	Functional ischemic
Type of dysfunction (Carpentier classification)	Type I (normal leaflet motion)	Type II (excessive leaflet motion)	Type IIIa (restricted leaflet motion in diastole)	Type I (normal leaflet motion) Type IIIb (restricted leaflet motion in systole)

MV mitral valve, *LV* left ventricle, *PM* papillary muscle, *RF* rheumatic fever

This finding also suggest that when describing the MV, fibroelastic deficiency disease is a term that should be reserved for pathologists performing quantitative histology rather than the clinician or surgeon. When a flail mitral leaflet occurs, it affects the posterior leaflet in approximately 70% of cases. The myxomatous degeneration is most likely localized to the flail segment whereas the MV has a normal morphology elsewhere [8] (primary flail leaflet).

Other less common causes or associations of MVP are listed in Table 2 and include acute rheumatic MV disease, Marfan's syndrome, infective endocarditis, acute rupture of a papillary muscle, or acute myocardial ischemia which involves a papillary muscle.

Severe MR has significant impact on functional capacity and mortality [2], and the correction of degenerative MR is curative in most cases as the MV itself is "the disease." As moderate and severe MR are often progressive over time, it is important to detect and appropriately quantify MR severity as well as understand the MV anatomy and pathologic abnormality in order to offer appropriate monitoring and treatment.

Natural History and Predictors of Complications

One important part of the clinical assessment and treatment decisions is knowledge of the natural history of DMR to predict the clinical course and to optimize outcomes. Unfortunately, the clinical course is variable and oftentimes unpredictable, making diligent clinical follow-up essential to avoid complications from chronic LV volume overload. Data from longitudinal follow-up to estimate complication rates are available for MVP but not for other etiologies, such as rheumatic MR, or MR from a flail leaflet. In MVP, posterior leaflet involvement had a much higher rate of severe MR and related complications such as atrial fibrillation, congestive heart failure, or chordal rupture. Baseline severity and worsening of severity of MR during follow-up was the most important predictor of complications [9]. In another study of asymptomatic MVP, 10-year mortality was 19% and mitral valve prolapse-related events were 20% at 10 years (i.e., stroke, heart failure, endocarditis, and mitral valve surgery). The most important predictors of complications were a LV ejection fraction < 50%, more severe MR, flail leaflet, atrial fibrillation, left atrial size > 40 mm, and age > 50 years [10]. These data underscore the importance of clinical follow-up with serial echocardiograms to detect progression of MR and associated structural changes. The progression of MR in MVP has been estimated as 5.9 ml increase in regurgitant volume per year (10 of 64 patients with prolapse developed new flail leaflet during follow-up) [4]. The natural history of flail mitral leaflet is very different compared with prolapse as progression of regurgitation severity and signs of LV volume

Table 2 Etiologies of mitral valve prolapse (MVP)

Degenerative (myxomatous/idiopatic/-primary)	Most common etiology of MVP occurs in adolescence or young adulthood but is more frequent in older adults.
	The classic form (Barlow's disease/"classic" MVP syndrome) is characterized by involvement of both mitral leaflets, excessive leaflet tissue, redundant leaflets, elongated and thickened chordae tendinae, and annular dilation
	Thickening of the leaflets to 5 mm or greater
	Only focal myxomatous changes may be present
	MR is usually trivial or mild in early stages of the disease
	In the more advanced stages, MR becomes typically progressive with enlargement of left-sided chambers
Fibroelastic deficiency	Less common etiology of MVP
	More frequent in the elderly (> 70 years)
	MV involvement is more focal
	The leaflets are usually very thin and delicate, and the chordae tendinae are thin and friable
	Fibroelastic deficiency as well as focal myxomatous changes may be present in different areas of the MV at the same time
Acute rheumatic valve disease	Acute rheumatic valvulitis may be associated with typical MVP with diffuse degenerative changes
	Chronic rheumatic MV disease is typically not associated with MVP
Marfan's syndrome	The appearance of generalized MV degeneration associated with mitral annular dilation may simulate Barlow's disease
	The aortic root and aorta are typically involved, and other systemic abnormalities are present
Infective endocarditis (IE)	Acute and subacute IE may lead to ruptured chordae tendinae and flail leaflets
	Vegetations, destructive lesions, and complications of IE (e.g., annular abscess) may be seen
	A clinical correlation and positive blood culture help to diagnose this condition
Acute papillary muscle rupture	PM rupture may be a consequence of acute myocardial infarction resulting in severe MR and acute pulmonary edema
	Rupture of the tip of one head of PM may present as flail leaflet with severe MR
	Echocardiography typically reveals a ruptured PM head at tip of the flail chord
Acute myocardial ischemia	If myocardial ischemia involves a PM, a MVP may occur
	In chronic ischemic MR, leaflet tethering rather than MVP is present

MR mitral regurgitation, *MV* mitral valve, *IE* infective endocarditis, *PM* papillary muscle

overload occur at a much faster pace. Of note, many authors use the presence of flail mitral leaflet as an indication of severe MR, though several cases of non-severe regurgitant flail mitral valves have been reported. Further, chronic less than severe MR from MVP may turn into very severe MR from an acutely ruptured chordae. Sudden cardiac death is a rare occurrence in degenerative MR. However, observational studies (from autopsy and ICD studies) have demonstrated a link between sudden cardiac death from ventricular arrhythmias and MVP and flail mitral leaflet [11–13]. Although the mechanism is unclear, it may be related to the severity of MR and thromboembolic events and possibly related to a genetic predisposition of sudden cardiac death in connective tissue disorders that can lead to degenerative mitral disease as well [14]. Evidence for the former is that arrhythmic risk reportedly decreases after surgical repair [15].

Assessment of Patients with Degenerative MR

Clinical Presentation

Acute Degenerative Mitral Regurgitation

Acute severe degenerative MR is mainly caused by anatomic disruption of the MV—most commonly due to flail

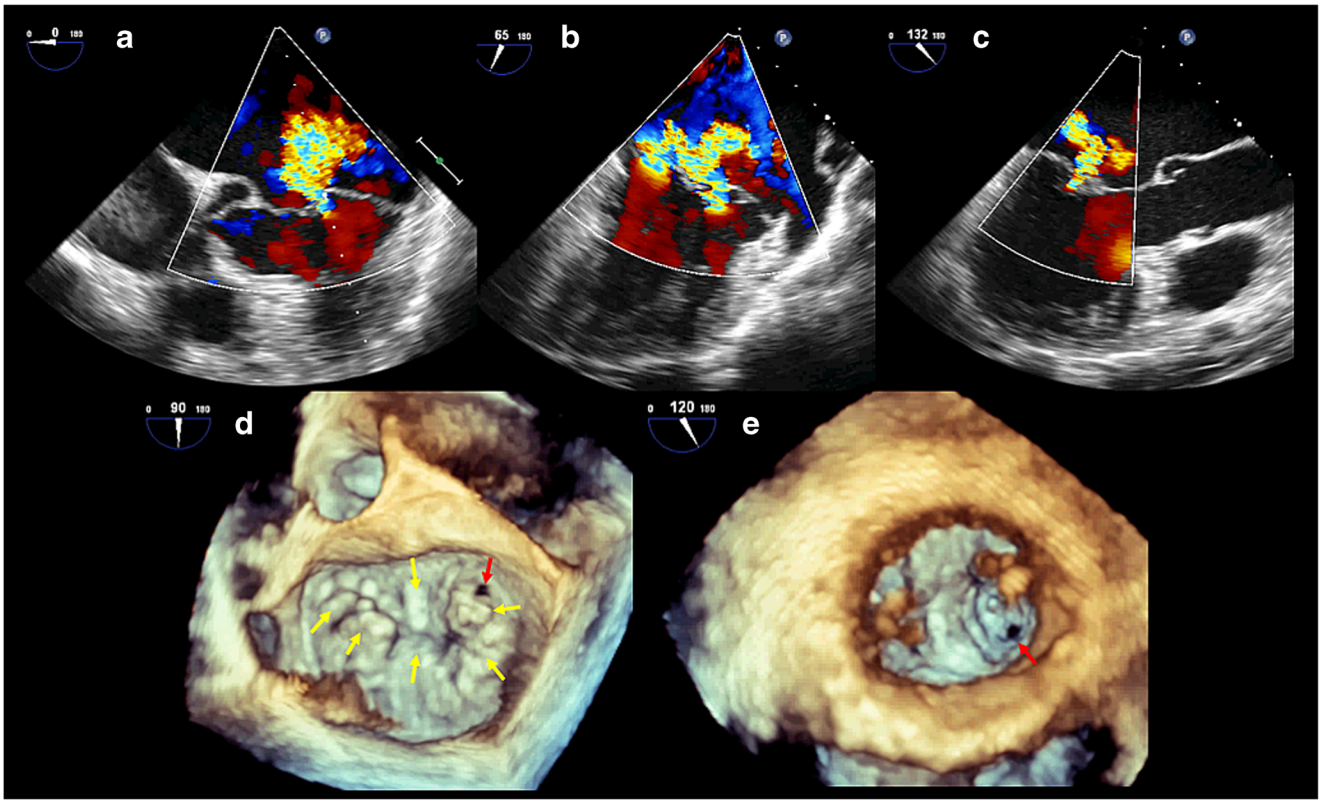

Fig. 2 Typical example of Barlow's disease. Multiple MR jets are visible in different TEE views (**a** = 0; **b** = 65°; **c** = 132°). An enface 3D TEE view from the left atrial side (**d**) reveals redundant tissue and multiple prolapses in multiple segments of the mitral valve (*yellow arrows*). An additional perforation of the anterior leaflet is marked with a *red arrow* in **d** and **e** that shows the mitral valve from the left ventricular side

MV leaflet(s) or papillary muscle rupture. Flail MV leaflet maybe spontaneous due to the inherent abnormal tensile strength of the chordae or the consequence of infective endocarditis or trauma. Papillary muscle rupture is most often due to acute myocardial infarction and rarely caused by trauma. Patients with flail MV leaflet(s) typically present with acute or worsening shortness of breath and may also have pulmonary edema. Patients with papillary muscle rupture present with more profound signs and symptoms including acute shortness of breath, pulmonary edema, and/or shock. In the setting of papillary muscle rupture, physical examination may be deceptive as there is wide open MR, and consequently, there is often very little turbulence because of the size of the regurgitant mitral orifice—thus, the murmur may be soft or even not audible. When a murmur is audible, it is typically not holosystolic as the LV and LA pressures equilibrate before the end of systole—thus with no LV-LA gradient, the duration of MR is attenuated. Due to the aforementioned reason, the echocardiographic evaluation with color Doppler frequently underestimates the severity of MR. The diagnosis must be considered when the LV demonstrates hyperdynamic function in the presence of acute heart failure. Urgent transesophageal echocardiographic (TEE) evaluation is often needed in this setting to confirm the diagnosis as acute MR and papillary muscle rupture is generally poorly tolerated and is associated with a poor prognosis. Urgent surgical intervention should be performed to correct the MR [16••].

Chronic Degenerative Mitral Regurgitation

In its chronic stage, even severe MR may be well tolerated over a surprisingly long period, and patients may remain asymptomatic for many years. The primary clinical examination may provide the first evidence that relevant MR is present. Symptoms such as dyspnea and chest pain atypical for angina [17], signs of left and right-sided heart failure, and physical signs of severe MR should be addressed. A laterally displaced apical impulse, a systolic thrill, a loud holosystolic murmur, and a third heart sound (S3) may be indicative for severe MR. A dynamic mid-systolic to late systolic click is characteristic but not specific for a MVP. Cardiomegaly with LA enlargement as seen on chest X-ray and the presence of atrial fibrillation which occurs most commonly later in the course of the disease may also support the diagnosis. Although these clinical signs are important and helpful, they are not specific and therefore sole reliance on them to suggest corrective surgery is not recommended [16••, 18].

Imaging in the Evaluation of Degenerative MR

Echocardiographic imaging is the primary method to evaluate degenerative MR and other findings that predict prognosis and risk of complications. The echocardiogram should allow for a detailed analysis of all the structures of the MV apparatus, the determination of MR mechanisms, an assessment of MR severity and hemodynamic consequences, and reparability [19].

Description of Mitral Valve Leaflets

Carpentier [3] proposed a simplified nomenclature of the MV leaflets that has been widely adopted and that is extremely useful particularly for accurately describing and localizing anatomic lesions thereby facilitating the communication between physicians of different specialization who are involved in the management of MR. The MV is composed of two leaflets, a longer hemiellipsoid shaped anterior leaflet that is abbreviated as "A" with narrower base and a posterior leaflet (abbreviated as "P") which forms two thirds of the annular circumference but has a shorter leaflet length. The posterior leaflet is classified as being segmented into three scallops through small identations that are referred to as P1 (lateral), P2 (middle), and P3 (medial). Although the P2 scallop is usually the largest, there is considerable variability. The number of slits and scallops (up to six may be present) may also vary largely [20], and in some instances, the three scallops present as distinct leaflets with separate annular attachment of each. The segments of the anterior leaflet are labeled correspondingly as A1 (lateral), A2 (middle), and A3 (medial) even if a distinctive separation between the segments can not be clearly identified in most cases. At the two commissures (anterolateral and posteromedial), both leaflets are fused by a tissue rim of variable length (usually < 1 cm).

Classification of Mitral Valve Prolapse

Using two-dimensional (2D) echocardiography, MVP is usually defined as an abnormal systolic movement of the MV into the left atrium ≥ 2 mm past the level of the saddle-shaped mitral annulus in long-axis views [21]. According to this definition, a mild billowing of the body of the anterior leaflet in systole which is a physiological occurrence may be mislabelled as MVP. The recognition that the mitral annular plane has "saddle" shape led to the suggestion that the diagnosis of MVP should only be made in echocardiographic long-axis views. However, this approach does not take into account that only the segments A2 and P2 are displayed in long-axis views and prolapses located in other valve segments may remain undetected. In the current era of modern transthoracic echocardiography (TTE) and TEE, the shape of the MV annulus is negligible and any echocardiographic view may be used to diagnose MVP keeping in mind that mild billowing of the body of the anterior leaflet (i.e., < 5 mm above the MV annular plane) is a normal finding that may be even more pronounced in patients with small ventricles, longer anterior leaflets, and a dehydrated status. However, displacement of a free edge of a leaflet of any MV segment above the annular plane is clearly pathological irrespective of the echocardiographic plane.

The coaptation of the mitral leaflets is normally located in the LV below the level of the MV annulus (Fig. 3). It is suggested to define MVP when a displacement of the free edge of a leaflet above the MV annular plane is present at end-systole [22]. This may be further subclassified as billowing MV with free-edge prolapse or flail MVP. This condition is most commonly associated with chordal rupture, but extreme chordal elongation without rupture can also be seen in some patients. A flail MVP due to PM rupture following acute myocardial infarction is less common. The billowing MV with prolapse is generally associated with excess tissue, chordal elongation, and free-edge prolapse.

As the involvement of other valves such as the tricuspid (43.3%) and aortic (10%) is a common finding in patients with MVP, these valves should also be carefully assessed [23].

Imaging Modalities in the Evaluation of Degenerative MR

In most cases, TTE is sufficient to differentiate between a functional or degenerative mechanism of MR [24] and can provide crucial information on structural alterations of the MV apparatus and lesions, in particular, on mitral annular dimensions [19], myxomatous MV changes [16••], MVP and/or flail leaflet, calcifications, vegetations, and perforations. In identifying the exact location of prolapses, not only the 2D appearance should be assessed but also the origin and the direction of the accompanying MR jet with color Doppler which is typically directed towards the opposite direction in patients with unileaflet prolapse (anterior MVP is associated with a posteriorly directed MR jet and posterior MVP with an anteriorly directed jet). In patients with a bileaflet prolapsed, two MR jets may be identified, or in the case of symmetrical prolapses of both leaflets, a central jet may be present. 2D TTE also provides reliable information on the size and function of both ventricles, LA size, and peak systolic pulmonary artery pressure. In addition, it enables the examiner to define the degree of MR severity by using an integrative approach which includes multiple parameters recommended in current guidelines [16••, 18]. Three-dimensional (3D) TTE in conjunction with color Doppler has recently shown to be superior in quantifying MR severity when compared with conventional 2D methods especially in patients with multiple MR jets and a dilated left ventricle [25•].

Two-dimensional TEE using a systematic approach [26] is usually performed before a planned procedure (either surgically or interventionally) as it provides enhanced image resolution

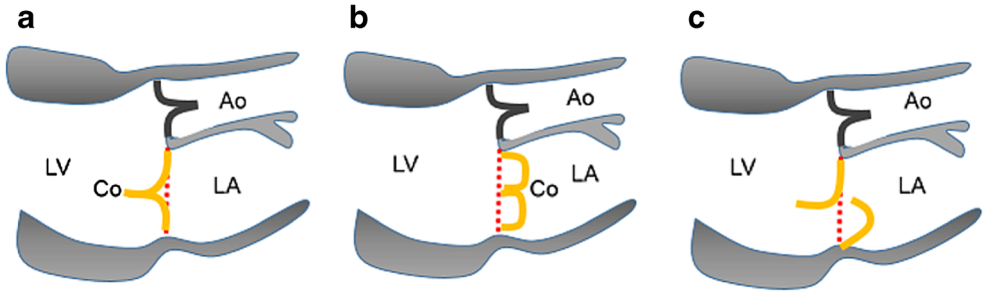

Fig. 3 Schematic to demonstrate the definition of prolapse taking the annular plane (*red dotted line*) as reference point in a long-axis parasternal view. **a** Normal coaptation is below the mitral annular plane; the body of the leaflets is not protruding into the LA). **b** Billowing with free edge bileaflet prolapse (the body of both leaflets protrudes into the LA, and the coaptation is above the mitral annular plane in the LA). **c** Flail mitral valve prolapse (the free edge of one leaflet is above the mitral annular plane, and no coaptation is present). Ao aorta, LA left atrium, LV left ventricle, Co coaptation

and is therefore advantageous in assessing morphological characteristics in more detail. Thus, the determination whether the valve can be surgically repaired requires valve replacement or is suitable for percutaneous repair that is improved. Exemplarly, eccentric MR jets can be better identified and matched with anatomical findings, and when TTE results are inconclusive in regard to MR severity, the assessment of pulmonary vein flow reversal may support the diagnosis of severe MR [18, 27].

In addition to 2D TEE, 3D TEE adds remarkable benefits in the assessment and visualization of the entire MV apparatus [19] by providing additional views thus allowing for a better morphological and quantitative evaluation than 2D TEE. It has been demonstrated that 3D TEE is superior in identifying valve segments [24], determining the exact morphology and pathology and the localization of lesions of the MV which correlated well with intra-operative findings (particularly regarding complex prolapses, flail lesions, and commissural lesions) [28–32], assessing dynamic changes of the mitral annulus [33], and detecting clefts, gaps, and perforations which are frequently missed by 2D TEE evaluation [28].

Exercise echocardiography may be useful to assess functional capacity, to reveal the dynamic component of MR (particularly in patients with ischemic MR or large prolapse/flail), and to grade MR severity during exercise [18]. The assessment of the contractile reserve under exercise may be useful for risk stratification and may help to optimize the timing of surgery in asymptomatic patients with severe MR [34]. In addition, the development of pulmonary hypertension with an increase of systolic pulmonary pressure > 60 mmHg under exercise provides a guideline indication for surgery [18].

In cases with suboptimal imaging quality rendered by echocardiography or inconclusive results concerning MR severity, cardiac magnetic resonance (CMR) imaging may be an alternative modality. Although experience in the assessment of MR is limited, it has some potential advantages over echocardiographic techniques. These include accurate determination of left and right ventricular volumes and ejection fraction [35], measurements of aortic flow volume and regurgitant volume, assessment of associated prolapse or leaflet restriction and in ischemic MR, comprehensive assessment of regional myocardial function, and viability in a single examination [36]. However, CMR imaging rarely permits adequate visualization of the chordal structures to identify ruptured or elongated chordae accurately. CMR is also not suited for visualization of annular or leaflet calcification which are important factors in determining the likelihood of successful MV repair [36].

Although only semiquantitative, a carefully performed LV ventriculogram by using the density of contrast to determine the amount of blood flow from the LV to the LA and hemodynamic measurements can add valuable information regarding the assessment of MR severity, global and regional LV function, and the need for surgery, particularly when echocardiographic findings are inconclusive or discordant [16••, 37]. Prior to an intervention or a surgical procedure, a coronary angiography is usually indicated to rule out associated coronary artery disease. Alternatively, computed tomography coronary angiography can be used as non-invasive imaging option to evaluate coronary anatomy in appropriately selected patients [38].

Assessment of Mitral Regurgitation Severity

According to current guidelines, the severity of MR should not be quantified by a single parameter. A multiparameter approach based on a comprehensive integration of color-flow Doppler and pulsed and continuous wave Doppler is recommended to adequately assess the degree of MR. Qualitative and semiquantitative parameters that indicate severe MR include [39] an abnormal MV morphology with prolapse, flail, or large coaptation defects; a large central jet or eccentric jet swirling and reaching the posterior wall of the LA; a dominant E-wave > 1.5 m/s in the absence of other causes of elevated LA pressure and of mitral stenosis; a dense, triangular shape of the continuous wave Doppler signal of the MR jet; a vena contracta width ≥ 7 mm (> 8 mm when averaged between apical four- and two-chamber views); a large convergence zone at a Nyquist limit of 50–60 cm/s; systolic flow reversal in the pulmonary veins; and a time velocity integral (TVI) mitralis/TVI aortic > 1.4. Quantitative MR assessment should be included in the evaluation as it allows

for the measurement of effective regurgitant orifice (ERO) area and regurgitant volume (RVol) (an ERO area ≥ 40 mm^2 and RVol ≥ 60 ml per beat indicate severe MR) and has important prognostic relevance [40]. The proximal isovelocity surface area (PISA) is the most frequently used method to calculate ERO and RVol. However, the PISA method has some important limitations the echocardiographer must be aware of. These include the following:

- Eccentric jets (e.g., inadequate acquisition of the continuous wave Doppler signal of the MR jet).
- MR jets for which the convergence zone is not hemispherical (e.g., due to non-circular regurgitant orifice area/wall constraint (Fig. 4)).
- Jets that are dynamic and not holosystolic (single-frame evaluation).
- Multiple jets (PISA is not validated for multiple jets).
- Inadequate when no clear delineation of the PISA radius is achievable.
- Inadequate when the precise location of the effective regurgitant orifice is not judgeable.
- Presence of atrial fibrillation.
- Large interobserver variability.

Additionally, new 3D methods (particularly the measurement of the 3D vena contracta area) may be helpful in the evaluation of degenerative MR when 2D echocardiographic quantification does not clearly suggests mild or severe MR [41].

Specific pitfalls in the assessment of degenerative MR should be mentioned:

1. MR that results from MVP is frequently eccentric in nature. An assessment of the jet area by using color Doppler will underestimate the true severity of MR.
2. When applying the PISA technique, effects of wall constraint on the proximal isovelocity surface area must be taken into account particularly in patients with large prolapses or flail leaflets [42] which may modify the appearance of the true hemispheric proximal convergence zone, thus leading to incorrect measurements of the PISA radius which is typically overestimated (Fig. 4). However, in such constraint, MR is most likely already severe, and clinical decisions are therefore usually not altered by an inaccurate overestimation.
3. In patients with MVP, the effective regurgitant orifice (ERO) and regurgitant volume may be dynamic and may vary during systole (Fig. 5). The ERO typically shows an increase in progression throughout systole. Regurgitant volume also increases initially but tends to decrease in late systole [43, 44]. In some patients, MR may even be confined to the end of systole. In this setting, color M mode and the continuous Doppler profile of the MR jet may help to determine the true duration of MR. When PISA is measured in mid-systole as it is traditionally done and as it is suggested in current recommendations [39], the grade of MR may be misjudged. When measurements for PISA are performed in still-frame images that are presenting the largest PISA during systole, the overall degree of MR will be falsely overestimated.

Hemodynamic Consequences of Acute and Chronic Degenerative MR

In case MR occurs acutely, the LA and an unadapted LV are acutely exposed to a large volume load. This leads to an immediate increase in LA pressure that is given back to the pulmonary circulation. Forward stroke volume and consecutively

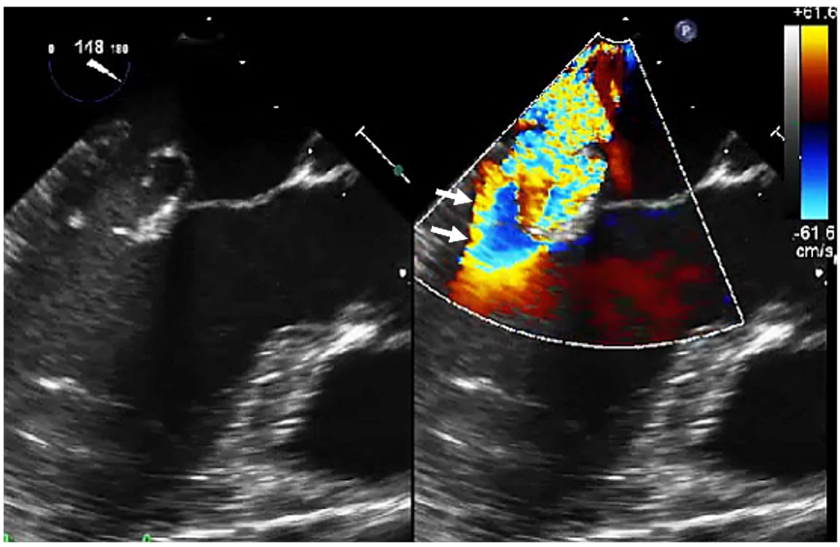

Fig. 4 Example of a proximal convergence zone that is constrained by the posterior wall. A mitral valve prolapse of the posterior mitral leaflet is seen without (left) and with color (right) Doppler in a long-axis transesophageal echocardiographic view. The proximal convergence zone is constrained by the posterior wall (*white arrows*) and is no longer truly hemispheric

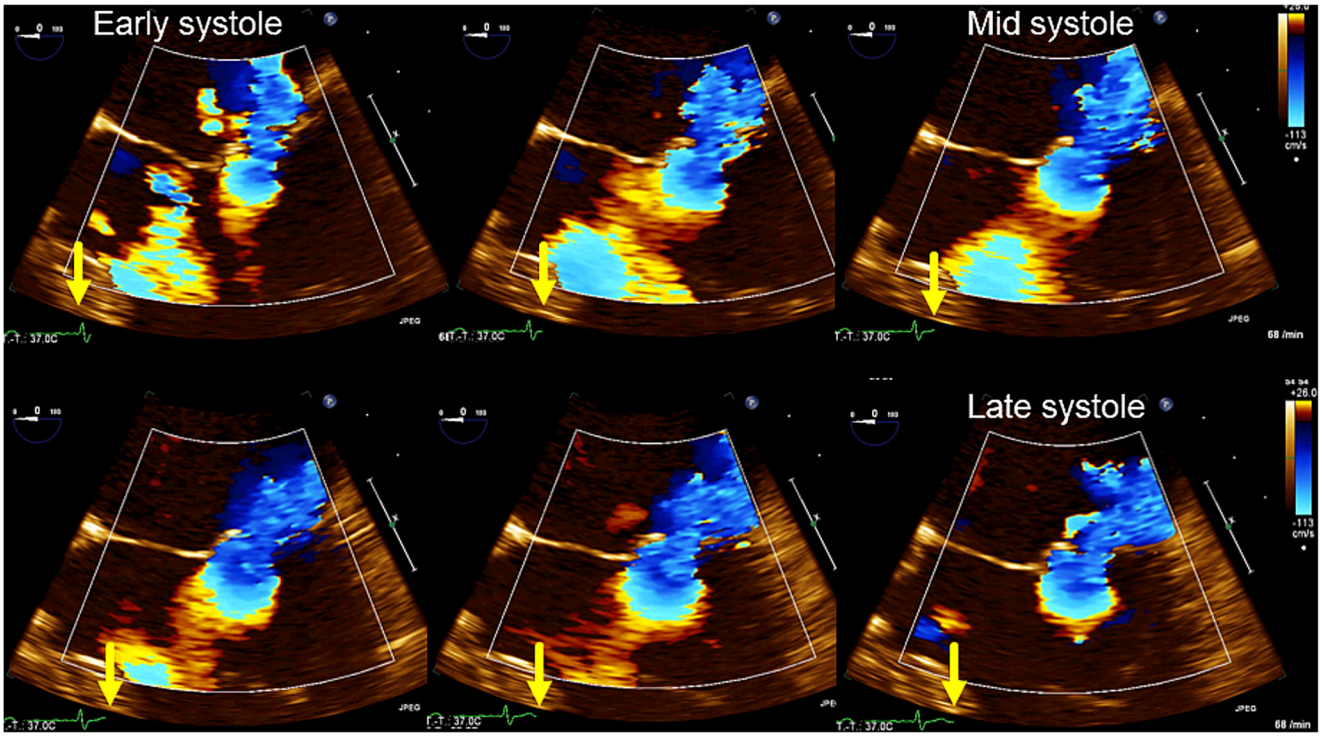

Fig. 5 Example to demonstrate the dynamic nature of the PISA (proximal isovelocity surface area) during systole in a patient with anterior prolapse and an eccentric jet towards the posterior leaflet. The smallest PISA is seen in early systole (top left) whereas the largest PISA is seen in the later systole (bottom middle). The *yellow arrows* indicate the time point during the cardiac cycle

cardiac output decrease as the blood is directed backwards into the lower pressure zone of the LA. This causes clinical symptoms like acute shortness of breath, pulmonary edema, or eventually pulmonary congestion. The short-term adaptation of the LV leads to an increased preload and thereby to an increase of total stroke volume via the Frank-Starling mechanism thus resulting in an increase in LV ejection. The end-systolic volume decreases as a consequence of the low resistance runoff of blood into the LA thus leading to a decrease in systolic wall tension. Provided that these compensatory mechanisms are successful in maintaining forward cardiac output and that the LA pressure can be lowered (e.g., by medial therapy), a translation towards a chronic stage of MR may occur [45].

In chronic degenerative MR, volume overload with an increased preload leads to ventricular enlargement which constitutes the major compensatory mechanism of the LV. The LV pumps the extra volume due to MR into the lower pressure zone of the LA thus causing LA enlargement. The LV usually remodels eccentrically with a large increase in LV dimensions and little or no increase in LV wall thickness. Diastolic function is typically preserved in this type of remodeling, and in early stages of the disease, LV contractility is also preserved. Afterload, the force opposing ventricular ejection, is normal in chronic MR patients with a normal or slightly increased endsystolic volume [46, 47]. In later stages of the disease, when remodeling progresses, afterload becomes abnormally high which may impede the unloading of the LV in systole.

The combination of an increased preload with normal afterload and initially preserved contractility results in higher LV ejection fraction levels than normal. Therefore, in chronic MR, an ejection fraction of about 70% has to be considered as "normal" whereas an ejection fraction less than 60% or the inability of the LV to contract to < 40-mm diameter at end systole [48] already indicates overt LV dysfunction and is associated with an impaired prognosis [49, 50, 16••, 51]. In asymptomatic patients with DMR and formally preserved LV function, 2D strain imaging (longitudinal strain) can reliably reveal subclinical LV dysfunction and thus may have influence on the timing of a corrective procedure [51].

Left atrial volume overload as indicated by an increase in LA diameter (≥ 40 mm[10]) and LA volume indices (≥ 40 ml/m^2 [52]) majorly impacts clinical outcome and predicts the occurrence of atrial fibrillation. Therefore, careful assessment of LA enlargement should be included in the assessment of DMR.

In case no clear signs of LA and LV volume overload are present in asymptomatic patients, the diagnosis of severe MR is doubtful particularly when considering recent studies that reported frequent overestimation of MR severity by echocardiography when comparing it with CMR [53]. In this context, the integration of LV end diastolic diameters (LVEDD ≥ 55 mm) in the assessment of chronic MR provided a sensitivity of 83% and specificity of 77% to predict concordance between echocardiography and CMR imaging. This finding underlines the importance of

Table 3 Typical echocardiographic changes seen in acute vs. chronic severe mitral regurgitation

Echo parameter	Acute MR	Chronic MR
LV size	Normal to ↑	↑↑
LV function	Hyperdynamic	Hyperdynamic to decreased
LA size	Normal	↑↑
PA pressure	Mildly increased	↑↑
PV flow	Systolic flow reversal	Diastolic dominant or systolic flow reversal
Continuous wave Doppler signal/color Doppler M mode	Not holosystolic	Holosystolic

MR mitral regurgitation, *LV* left ventricle, *LA* left atrium, *PA* pulmonary artery, *PV* pulmonary vein

integrating LVEDD measurements in the assessment of chronic MR as a key parameter [54].

The measurement of systolic pulmonary artery pressure (sPAP) should also be part of the echocardiographic evaluation of DMR. When a sPAP > 50 mmHg at rest is present, the risk of death and heart failure is nearly doubled after diagnosis, and in the case of pre-operatively existing pulmonary hypertension, the beneficial effects of MV surgery are diminished [55].

Hemodynamic consequences of MR must be carefully monitored by serial echocardiograms as they provide critical information which help to decide upon the best time point for a surgical or percutaneous mitral intervention. Echocardiographic findings in acute versus chronic severe MR are listed in Table 3. Without timely relief of the burden of LV and LA overload by surgical MR correction, patients may develop left heart failure, atrial fibrillation, and secondary pulmonary hypertension eventually with right heart failure.

Although natriuretic peptides are not part of current guidelines, they are associated with symptoms status, MR severity, and MR-induced or MR-independent LV dysfunction. The pulmonary artery pressure and brain natriuretic peptide (BNP) ratio has shown to be a powerful, independent, predictor of long-term mortality in patients under medical management [56•, 57]. Thus, it may become an integral part of the future clinical evaluations of MR.

Defining Reparability of the Mitral Valve

MVP is generally associated with excess tissue that allows for the possibility of repair. An accurate assessment of the exact location of the lesion and the extent of the disease is paramount to determine the likeliness of repair and the extent of surgical repair that is needed. The goal of MV repair is to restore a good surface of coaptation to ensure satisfactory function of the MV. MR resulting from a P2 prolapse or flail, for example, is generally amenable to surgical repair in nearly 100% [58•] of cases with very durable results. Extensive leaflet calcification is the major reason for failure of repair in this situation as it precludes leaflet resection. This is usually easily assessed by echocardiography. The implantation of neochordae and a ring is a newer approach but has limitations in patients with excessive and exuberant myxomatous degeneration [59]. A bileaflet lesion occurs more frequently in younger patient and is often associated with myxomatous changes of other valves. The severity of MR is often more dynamic [60]. However, successful repair can be performed in most cases. The presence of two MR jets or a central jet usually indicates true bileaflet prolapse. In patients with a severe posterior MVP, an apparent prolapse of the anterior leaflet can occur due to loss of the anchoring effect of the opposite posterior leaflet ("pseudo-prolapse" of the anterior mitral leaflet). The chordae tendinae of the anterior mitral leaflet are typically preserved in these cases, and repair is as likely as with isolated posterior MVP [61]. Barlow's disease remains a surgical challenge. However, a 4-year freedom from re-operation can be achieved in > 90% of cases by using different techniques of repair [62]. Prolapses of the anterior leaflet are generally the most challenging lesions to be repaired due to the "curtain-like" configuration and the missing segmentation. Additional chordal transfer is usually needed, and the results are less durable as with posterior lesions even if advanced surgical techniques increase the likelihood of repair [63, 64].

Conclusion

Degenerative mitral regurgitation is a common valvular heart disease in the industrialized world. We have reviewed the available data on how to assess acute and chronic degenerative mitral regurgitation. We have discussed the natural history, physical exam, and imaging. Specifically, imaging is described in detail using currently available transthoracic and transesophageal 2D and 3D echocardiography, as it is crucial in the management of patients with mitral regurgitation. Further, we have described the anatomic classification and indices of severity of degenerative mitral valve disease. It is important to not only document the severity of mitral regurgitation. Documentation of the valve morphology itself and the mechanism of the regurgitation are of equal importance. All factors combined are relevant for the optimal timing and the

type of therapy for the mitral regurgitation. Comprehensive assessment is essential for patient management, which may include watchful waiting, mitral valve surgery, or percutaneous repair/replacement.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Klein AL, Burstow DJ, Tajik AJ, Zachariah PK, Taliercio CP, Taylor CL, et al. Age-related prevalence of valvular regurgitation in normal subjects: a comprehensive color flow examination of 118 volunteers. J Am Soc Echocardiogr. 1990;3(1):54–63.
2. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet. 2006;368(9540):1005–11.
3. Carpentier A. Cardiac valve surgery—the "French correction". J Thorac Cardiovasc Surg 1983; 86(3): 323–337.
4. Enriquez-Sarano M, Freeman WK, Tribouilloy CM, Orszulak TA, Khandheria BK, Seward JB, et al. Functional anatomy of mitral regurgitation: accuracy and outcome implications of transesophageal echocardiography. J Am Coll Cardiol. 1999;34(4):1129–36.
5. Monin JL, Dehant P, Roiron C, Monchi M, Tabet JY, Clerc P, et al. Functional assessment of mitral regurgitation by transthoracic echocardiography using standardized imaging planes diagnostic accuracy and outcome implications. J Am Coll Cardiol. 2005;46(2):302–9.
6. David TE, Armstrong S, Sun Z, Daniel L. Late results of mitral valve repair for mitral regurgitation due to degenerative disease. Ann Thorac Surg. 1993;56(1):7–12 discussion 3-4.
7. Fornes P, Heudes D, Fuzellier JF, Tixier D, Bruneval P, Carpentier A. Correlation between clinical and histologic patterns of degenerative mitral valve insufficiency: a histomorphometric study of 130 excised segments. *Cardiovasc Pathol*. 1999;8(2):81–92.
8. Mills WR, Barber JE, Ratliff NB, Cosgrove DM 3rd, Vesely I, Griffin BP. Biomechanical and echocardiographic characterization of flail mitral leaflet due to myxomatous disease: further evidence for early surgical intervention. Am Heart J. 2004;148(1):144–50.
9. Kim S, Kuroda T, Nishinaga M, Yamasawa M, Watanabe S, Mitsuhashi T, et al. Relationship between severity of mitral regurgitation and prognosis of mitral valve prolapse: echocardiographic follow-up study. Am Heart J. 1996;132(2 Pt 1):348–55.
10. Avierinos JF, Gersh BJ, Melton LJ 3rd, et al. Natural history of asymptomatic mitral valve prolapse in the community. Circulation. 2002;106(11):1355–61.
11. Anders S, Said S, Schulz F, Puschel K. Mitral valve prolapse syndrome as cause of sudden death in young adults. Forensic Sci Int. 2007;171(2–3):127–30.
12. Chesler E, King RA, Edwards JE. The myxomatous mitral valve and sudden death. Circulation. 1983;67(3):632–9.
13. Sriram CS, Syed FF, Ferguson ME, Johnson JN, Enriquez-Sarano M, Cetta F, et al. Malignant bileaflet mitral valve prolapse syndrome in patients with otherwise idiopathic out-of-hospital cardiac arrest. J Am Coll Cardiol. 2013;62(3):222–30.
14. Aydin A, Adsay BA, Sheikhzadeh S, Keyser B, Rybczynski M, Sondermann C, et al. Observational cohort study of ventricular arrhythmia in adults with Marfan syndrome caused by FBN1 mutations. PLoS One. 2013;8(12):e81281.
15. Grigioni F, Enriquez-Sarano M, Ling LH, Bailey KR, Seward JB, Tajik AJ, et al. Sudden death in mitral regurgitation due to flail leaflet. J Am Coll Cardiol. 1999;34(7):2078–85.
16. •• Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2017;135:e1159–e1195. **Most current American guidelines.**
17. Alpert MA, Mukerji V, Sabeti M, Russell JL, Beitman BD. Mitral valve prolapse, panic disorder, and chest pain. Medi Clin North Am. 1991;75(5):1119–33.
18. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg Surgery 2012; 42(4): S1–44.
19. Lancellotti P, Moura L, Pierard LA, Agricola E, Popescu BA, Tribouilloy C, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). Eur J Echocardiogr. 2010;11(4):307–32.
20. Victor SNV. Definition and function of commissures, slits and scallops of the mitral valve: analysis in 100 hearts. Asia Pac J Thorac Cardiovasc Surg. 1994;3:10–6.
21. Levine RA, Triulzi MO, Harrigan P, Weyman AE. The relationship of mitral annular shape to the diagnosis of mitral valve prolapse. Circulation. 1987;75(4):756–67.
22. Shah PM. Current concepts in mitral valve prolapse—diagnosis and management. J Cardiol. 2010;56(2):125–33.
23. Ribeiro CL, Ginefra P, Albanesi Filho FM, Christiani LA, Quaresma JC, Gomes Filho JB. Prevalence of tricuspid and aortic valve prolapse in patients with mitral valve prolapse. Arq Bras Cardiol. 1989;53(5):251–5.
24. Ben Zekry S, Nagueh SF, Little SH, Quinones MA, McCulloch ML, Karanbir S, et al. Comparative accuracy of two- and three-dimensional transthoracic and transesophageal echocardiography in identifying mitral valve pathology in patients undergoing mitral valve repair: initial observations. J Am Soc Echocardiogr. 2011;24(10):1079–85.
25. • Heo R, Son JW, B OH, et al. Clinical implications of three-dimensional real-time color Doppler transthoracic echocardiography in quantifying mitral regurgitation: a comparison with conventional two-dimensional methods. J Am Soc Echocardiogr 2017. **Underlines the importance of new 3D methods to adequately quanify MR severity.**
26. Foster GP, Isselbacher EM, Rose GA, Torchiana DF, Akins CW, Picard MH. Accurate localization of mitral regurgitant defects using multiplane transesophageal echocardiography. Ann Thorac Surg. 1998;65(4):1025–31.
27. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr. 2003;16(7):777–802.
28. La Canna G, Arendar I, Maisano F, et al. Real-time three-dimensional transesophageal echocardiography for assessment of mitral

valve functional anatomy in patients with prolapse-related regurgitation. Am J Cardiol. 2011;107(9):1365–74.
29. Grewal J, Mankad S, Freeman WK, Click RL, Suri RM, Abel MD, et al. Real-time three-dimensional transesophageal echocardiography in the intraoperative assessment of mitral valve disease. J Am Soc Echocardiogr. 2009;22(1):34–41.
30. Agricola E, Oppizzi M, Pisani M, Maisano F, Margonato A. Accuracy of real-time 3D echocardiography in the evaluation of functional anatomy of mitral regurgitation. Int J Cardiol. 2008;127(3):342–9.
31. Macnab A, Jenkins NP, Bridgewater BJ, Hooper TL, Greenhalgh DL, Patrick MR, et al. Three-dimensional echocardiography is superior to multiplane transoesophageal echo in the assessment of regurgitant mitral valve morphology. Eur J Echocardiogr. 2004;5(3):212–22.
32. Tsang W, Freed BH, Lang RM. The role of 3-dimensional echocardiography in the diagnosis and management of mitral valve disease: myxomatous valve disease. Cardiol Clin. 2013;31(2):203–15.
33. Grewal J, Suri R, Mankad S, Tanaka A, Mahoney DW, Schaff HV, et al. Mitral annular dynamics in myxomatous valve disease: new insights with real-time 3-dimensional echocardiography. Circulation. 2010;121(12):1423–31.
34. Lee R, Haluska B, Leung DY, Case C, Mundy J, Marwick TH. Functional and prognostic implications of left ventricular contractile reserve in patients with asymptomatic severe mitral regurgitation. Heart. 2005;91(11):1407–12.
35. Pennell DJ. Cardiovascular magnetic resonance. Circulation. 2010;121(5):692–705.
36. Chan KM, Wage R, Symmonds K, et al. Towards comprehensive assessment of mitral regurgitation using cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2008;10:61.
37. Dujardin KS, Enriquez-Sarano M, Bailey KR, Nishimura RA, Seward JB, Tajik AJ. Grading of mitral regurgitation by quantitative Doppler echocardiography: calibration by left ventricular angiography in routine clinical practice. Circulation. 1997;96(10):3409–15.
38. Pontone G, Andreini D, Bertella E, et al. Pre-operative CT coronary angiography in patients with mitral valve prolapse referred for surgical repair: comparison of accuracy, radiation dose and cost versus invasive coronary angiography. Int J Cardiol. 2013;167(6):2889–94.
39. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2013;14(7):611–44.
40. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, Detaint D, Capps M, Nkomo V, et al. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. N Engl J Med. 2005;352(9):875–83.
41. Grayburn PA, Weissman NJ, Zamorano JL. Quantitation of mitral regurgitation. Circulation. 2012;126(16):2005–17.
42. Pu M, Vandervoort PM, Greenberg NL, Powell KA, Griffin BP, Thomas JD. Impact of wall constraint on velocity distribution in proximal flow convergence zone. Implications for color Doppler quantification of mitral regurgitation. J Am Coll Cardiol. 1996;27(3):706–13.
43. Enriquez-Sarano M, Sinak LJ, Tajik AJ, Bailey KR, Seward JB. Changes in effective regurgitant orifice throughout systole in patients with mitral valve prolapse. A clinical study using the proximal isovelocity surface area method. Circulation. 1995;92(10):2951–8.
44. Schwammenthal E, Chen C, Benning F, Block M, Breithardt G, Levine RA. Dynamics of mitral regurgitant flow and orifice area. Physiologic application of the proximal flow convergence method: clinical data and experimental testing. Circulation. 1994;90(1):307–22.
45. Gaasch WH, John RM, Aurigemma GP. Managing asymptomatic patients with chronic mitral regurgitation. Chest. 1995;108(3):842–7.
46. Wisenbaugh T, Spann JF, Carabello BA. Differences in myocardial performance and load between patients with similar amounts of chronic aortic versus chronic mitral regurgitation. J Am Coll Cardiol. 1984;3(4):916–23.
47. Corin WJ, Monrad ES, Murakami T, Nonogi H, Hess OM, Krayenbuehl HP. The relationship of afterload to ejection performance in chronic mitral regurgitation. Circulation. 1987;76(1):59–67.
48. Tribouilloy C, Grigioni F, Avierinos JF, Barbieri A, Rusinaru D, Szymanski C, et al. Survival implication of left ventricular end-systolic diameter in mitral regurgitation due to flail leaflets a long-term follow-up multicenter study. J Am Coll Cardiol. 2009;54(21):1961–8.
49. Enriquez-Sarano M, Tajik AJ, Schaff HV, Orszulak TA, Bailey KR, Frye RL. Echocardiographic prediction of survival after surgical correction of organic mitral regurgitation. Circulation. 1994;90(2):830–7.
50. Enriquez-Sarano M, Tajik AJ, Schaff HV, Orszulak TA, McGoon MD, Bailey KR, et al. Echocardiographic prediction of left ventricular function after correction of mitral regurgitation: results and clinical implications. J Am Coll Cardiol. 1994;24(6):1536–43.
51. Lancellotti P, Cosyns B, Zacharakis D, Attena E, van Camp G, Gach O, et al. Importance of left ventricular longitudinal function and functional reserve in patients with degenerative mitral regurgitation: assessment by two-dimensional speckle tracking. J Am Soc Echocardiogr. 2008;21(12):1331–6.
52. Messika-Zeitoun D, Bellamy M, Avierinos JF, Breen J, Eusemann C, Rossi A, et al. Left atrial remodelling in mitral regurgitation–methodologic approach, physiological determinants, and outcome implications: a prospective quantitative Doppler-echocardiographic and electron beam-computed tomographic study. Eur Heart J. 2007;28(14):1773–81.
53. Uretsky S, Gillam L, Lang R, Chaudhry FA, Argulian E, Supariwala A, et al. Discordance between echocardiography and MRI in the assessment of mitral regurgitation severity: a prospective multicenter trial. J Am Coll Cardiol. 2015;65(11):1078–88.
54. Rafique AM, Siegel RJ. Left ventricular size is critical for the echocardiographic assessment of chronic severe mitral regurgitation. J Am Coll Cardiol. 2015;66(13):1519–21.
55. Barbieri A, Bursi F, Grigioni F, Tribouilloy C, Avierinos JF, Michelena HI, et al. Prognostic and therapeutic implications of pulmonary hypertension complicating degenerative mitral regurgitation due to flail leaflet: a multicenter long-term international study. Eur Heart J. 2011;32(6):751–9.
56.• Clavel MA, Tribouilloy C, Vanoverschelde JL, Pizarro R, Suri RM, Szymanski C, et al. Association of B-type natriuretic peptide with survival in patients with degenerative mitral regurgitation. J Am Coll Cardiol. 2016;68(12):1297–307 **Underlines the importance of additional factors like BNP in the evaluation of MR which may have impaact on the timing of a procedure.**
57. Johl MM, Malhotra P, Kehl DW, Rader F, Siegel RJ. Natriuretic peptides in the evaluation and management of degenerative mitral regurgitation: a systematic review. Heart. 2017;103:738.1–744.
58.• Correia PM, Coutinho GF, Branco C, Garcia A, Antunes MJ. Surgical treatment of posterior mitral valve prolapse: towards 100% repair. J Heart Valve Dis. 2015;24(6):752–9 **underlines the excellent surgical results in patients with P2 prolapse**.
59. Perier P, Hohenberger W, Lakew F, Diegeler A. Prolapse of the posterior leaflet: resect or respect. Ann Cardiothorac Surg. 2015;4(3):273–7.
60. Mills WR, Barber JE, Skiles JA, Ratliff NB, Cosgrove DM III, Vesely I, et al. Clinical, echocardiographic, and biomechanical differences in mitral valve prolapse affecting one or both leaflets. Am J Cardiol. 2002;89(12):1394–9.

61. Cho L, Gillinov AM, Cosgrove DM 3rd, Griffin BP, Garcia MJ. Echocardiographic assessment of the mechanisms of correction of bileaflet prolapse causing mitral regurgitation with only posterior leaflet repair surgery. Am J Cardiol. 2000;86(12):1349–51.
62. da Rocha ESJG, Spampinato R, Misfeld M, et al. Barlow's mitral valve disease: a comparison of neochordal (loop) and edge-to-edge (Alfieri) minimally invasive repair techniques. Ann Thorac Surg. 2015;100(6):2127–33 discussion 33-5.
63. Lawrie GM, Zoghbi W, Little S, Shah D, Ben-Zekry Z, Earle N, et al. One hundred percent reparability of degenerative mitral regurgitation: intermediate-term results of a dynamic engineered approach. Ann Thorac Surg. 2016;101(2):576–83 discussion 83-4.
64. Bourguignon T, Mazine A, Laurin C, Bouchard D, Demers P, Pellerin M. Repair of anterior mitral leaflet prolapse: comparison of mid-term outcomes with chordal transposition and chordal replacement techniques. J Heart Valve Dis. 2016;25(2):187–94.